

THE KS PROJECT REPORT:

Current Issues in Research & Treatment of Kaposi's Sarcoma by Michael Marco with Martin Majchrowicz Forward by Susan E. Krown, M.D. TREATMENT ACTION GROUP (TAG) 200 East 10th Street 601 New York, NY USA 10003 212.260.0300 phone 212.260.8561 fax Eighteenth AIDS Clinical Trials Group Meeting Washington, D.C. 25 July 1994 Michael Marco works as a consultant for the Treatment Action Group (TAG) and heads its ONCOLOGY PROJECT. An art historian and a member of the AIDS activist affinity group The Marys, Michael sits on the ACTG Oncology Committee's KS and Lymphoma Working Group, the NCI's ECOG AIDS Committee, and the Memorial Sloan-Kettering Cancer Center-New York Hospital/Cornell Medical Center ACTU Community Advisory Board (CAB).

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The Treatment Action Group (TAG) fights to find a cure for AIDS and to ensure that all people living with HIV receive the necessary treatment, care, and information they need to save their lives. TAG focuses on the AIDS research effort, both public and private, the drug development process, and our nation's health care delivery systems. We meet with researchers, pharmaceutical companies, and government officials, and resort when necessary to acts of civil disobedience, or to acts of Congress. We strive to develop the scientific and political expertise needed to transform policy. TAG is committed to working for and with all communities affected by HIV.

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This report is dedicated to Andrew Zysman, M.D. 1955 - 1993 *

The numbers continue to climb, but final statistics are unimportant, especially to those who are unfortunate enough to have developed the disease. The important fact is that this cancer poses a very real and potentially lethal threat to segments of the gay culture. It is a menace that must be dealt with logically and quickly if we are to overcome it, and knowledge of the disease, its causes and effects, is our best weapon.

-- Douglas Mayfair "Gay Cancer", MANDATE, December 1981

Those ID docs lived their lives with 'find a bug, find a pill' mentality. They have never worked in a field such as cancer or leukemia where advances and successes are slow in coming and sometimes don't come at all. They look down on oncologists because we don't have a myriad of great success stories. But, now they are baffled because HIV has finally stumped them. Things are no longer so easy. There is no quick fix.

-- Anonymous NCI oncologist, 1994

The [mere] observation of patients with progressive KS in the setting of HIV infection is no longer acceptable.

-- Steven A. Miles, M.D. Kaposi's Sarcoma (In press), 1994

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FOREWORD

Men will find that they can prepare with mutual aid far more easily what they need, and avoid far more easily the perils which beset them on all sides, by united forces.

Spinoza, Ethics (1677)

We may affirm absolutely that nothing great in the world has been accomplished without passion. Hegel, Philosophy of History (1832)

An educated consumer is our best customer.

Sy Syms, Discount Store Advertisement (late 20th century)

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The report that follows is long, so I will be brief in my introductory remarks. What you are about to read (and I hope you will do that, despite its length) is the result of months of tremendous but well spent effort by its authors, who have combed the literature, consulted liberally with clinical investigators,

basic scientists and scientific administrators, and attempted a synthesis of science and policy as it applies specifically to Kaposi's sarcoma, and to the broader issues of HIV-associated neoplasia. Although I cannot endorse every interpretation that follows - this is, after all, a mixture of data (published and unpublished, and of varying quality) and editorial comment (the latter to be taken with a grain of salt) - I think it accomplishes the intended function of a TAG report, which is to stimulate awareness and change where it is needed. You will find in this report examples of tangible advances in understanding KS and improving its treatment, but you will also find examples of impediments to progress.

From my perspective, the three broad themes - the "take-home messages" - of this report are summarized in the three quotations that began this foreword:

(1) We need to be united in our approach to developing better treatments for KS. "We" means clinical investigators (of all sorts, not simply oncologists), basic scientists, primary caregivers, patients and their advocates, NIAID and NCI, among others. Rather than assuming the sometimes adversarial (or at least not always cordial) pose "we" have sometimes taken toward each other, perhaps we should begin thinking of KS, not each other, as the adversary.

(2) We need to be passionate to accomplish our goal: Passionate in our belief that nihilism about KS is unwarranted and in our belief that the effort, time and money needed to pursue the leads we have about KS pathogenesis (and the endurance to weather the inevitable setbacks we will suffer), will not only lead to more effective treatments for KS, but will also have important implications for the treatment of other diseases (including HIV).

(3) We need to educate the medical community and our "consumers" - the people with KS - about the significance of the disease, the options for its treatment, and the rationales underlying them. If we understand the early phase of KS development as a pathologic response to dysregulated cytokines and growth factors, rather than as a minor cosmetic problem to be treated only when it reaches its late florid phases, then there will be no dearth of volunteers for innovative, pathogenesis-driven clinical trials. Such trials, which are needed to move KS treatment forward, and which may ultimately lead to preventive strategies, have often been slow to accrue patients whose KS is at a stage when such interventions are, in my view, most likely to have a therapeutic impact. I can think of no other cancer or pre-cancerous condition for which patients are advised to defer therapy until the tumor is widespread and debilitating, yet this is done almost routinely for KS. Admittedly, the choice to defer or forego KS treatment may be appropriate for some patients because of other co-existing HIV-related problems, but as an overall strategy it defies logic.

Perhaps, as clinical investigators, I and my colleagues have failed to clearly present the logic and to educate our fellow physicians and prospective patients. Perhaps we have been so busy trying to get funded and playing the power game (an almost inevitable consequence of the war of egos that drives success in any field), that we have left behind some of the passion for science and finding cures that got us here in the first place. Perhaps reading this report will be a start toward sorting this all out.

Susan E. Krown, M.D.
INTRODUCTION

In October 1993, the National Institute of Allergy and Infectious Diseases (NIAID) published its HIV/AIDS Research Agenda. Only two pages were dedicated to

AIDS oncology research. NIAID stated that, "While advances have been made in the treatment of KS, no optimal or adequate long-term management options have been defined. There is no curative therapy for KS at the present time." (NIAID 1993).

There is no mention of the fact that AIDS-related malignancies -- with KS being the most common -- now complicate the lives of at least 40% of patients living with AIDS (Peters 1991). Recent evidence suggests that the incidence of KS, particularly in late-stage AIDS patients, may be increasing as more people survive OIs such as PCP and MAI, or avoid them altogether through the use of prophylaxis. Much of this progress with OIs only happened when activists, abetted by Congress, insisted that NIH increase the resources devoted to OI research. This must happen now if progress is to be made with KS and other AIDS-related malignancies.

There is a need for a comprehensive review of AIDS-related Kaposi's sarcoma, which deciphers current research and treatment taking place around this under-reported, under-treated and generally misunderstood AIDS-related malignancy.

Our initial research has been facilitated by the myriad of comprehensive KS review articles published over the past three years (Krown 1992 a; Tappero 1993 b; Miles 1994; Levine 1993). After analyzing these review articles we were forced to ask some crucial questions. The first was, "Is there really the need for another "kitchen sink" review that will merely footnote all the same studies and reformulate the same conclusions?" The answer to that was "no."

However, when we asked, "Isn't there a need to: 1) synthesize the various studies, as well as look for the most current follow-up data; 2) confer with researchers regarding the conclusions and problems with certain studies; 3) and query researchers on conflicting and sometimes ambiguous pathogenesis data (e.g., angiogenesis)?" The answer was "yes." Moreover, we eventually asked, "would it be beneficial to interview practicing oncologists, dermatologists, radiologists, and primary care physicians regarding their opinions on how KS has changed in the course of HIV disease over the past 10 years; when to treat and with what; ascertain what problems they might have with treating patients; and problems with the research establishment as a whole?" The answer to this last question was not only "yes," but it proved to be a motivating justification for a report on KS by treatment activists.

We were also challenged by the introductions to a number of protocols and public relations data from pharmaceutical companies claiming that their new compounds or reformulations (e.g., liposomal) was badly needed because current "standard-of-care" treatments were either marginally effective or too toxic. Such assumptions -- usually without supporting data -- concerning various therapies warranted investigation.

There is also incomplete and misleading epidemiological data claiming a lower incidence of people diagnosed with KS, and the wrongly held yet widely believed opinion that KS is rarely a cause of death in people with AIDS but merely a cosmetic annoyance that has "led in the minds of many physicians (and more that a few patients), to a sense of nihilism about treatment, and to the perception that Kaposi's sarcoma was somehow peripheral to the central concerns of the AIDS epidemic." (Krown 1993)

Recent data demonstrate that KS is not going away. Epidemiological data from major metropolitan cities such as New York and Los Angeles cite the reported cases of KS at 30+ % (Beral 1990). These numbers are low due to under-reporting and the fact that only a patient's first AIDS defining illness is reported. In

the MACS study, 49% of the men from Los Angeles were found to have KS (cutaneous and or visceral) at the time of autopsy (Ndimbie 1993).

Many of the myths and assumptions which have lead to this "sense of nihilism" are addressed in this report along with our analysis of existing published and non-published data. As treatment activists, our careers are not based on promoting or encouraging one treatment over another, and we have no loyalty to one group of physicians. We can do what publishing researchers and clinicians can't: call "foul" and point fingers when we believe people with AIDS are being done a disservice when not treated properly. And, it is our job to ask the questions that are not currently being addressed.

*

EXECUTIVE SUMMARY + RECOMMENDATIONS

Epidemic, AIDS-associated Kaposi's sarcoma (KS) is an unusual malignancy first noted in 1981 at the start of the global HIV pandemic. The epidemiology of KS is unusual in that it is mainly confined to a subset of the HIV-infected population, gay and bisexual men, suggesting that KS may be linked to an as-yet undiscovered infectious agent or cofactor other than HIV. While the etiology of AIDS-KS remains to be determined, its pathogenesis has recently been partially explained as the result of inflammatory processes in endothelial cells leading to spindle-cell formation, neoangiogenesis, edema, and ultimately, a multifocal, apparently non-clonal neoplastic disease. KS sometimes appears relatively early during HIV-associated immune dysregulation, and may be indolent in course. Later in disease, KS is more often found in visceral organs, and when found in the lungs may be fatal. Whether cutaneous or visceral, cosmetic or life-threatening, KS imposes a major burden on the quality of life of people with HIV, and may become life-threatening. Currently we lack reliable evidence about the incidence and severity of KS in all HIV-infected populations, but it appears to be becoming more common and more severe as people with HIV survive or avoid multiple opportunistic complications. Current standard-of-care treatments for KS remain incompletely validated and disappointing. While interferon alpha has shown limited anti-KS activity in people with relatively intact immune systems and CD4 counts over 200/mm³, progressive disease in persons with more advanced immunodeficiency is only imperfectly controlled with combination cytotoxic chemotherapies such as adriamycin, bleomycin and vincristine (ABV). Against the limited clinical utility of these approved agents must be set their toxicities, expense and inconvenience. Novel experimental approaches to the treatment of KS are now in preliminary studies, including liposomally-encapsulated anthracyclines, cytokines and their inhibitors, and several kinds of angiogenesis inhibitors. The safety, efficacy and optimal uses of these agents remain to be defined in well-controlled clinical studies. Current opinion among AIDS oncologists, infectious disease specialists, and primary care AIDS clinicians remains divided about when to initiate anti-KS therapy, what are the optimal regimens, and how best to integrate KS management into the spectrum of HIV primary care. Currently, research on the etiology, pathogenesis, epidemiology and treatment of KS remains inadequately supported by the National Institutes of Health (NIH). KS clinical trial programs remain ill-coordinated between multiple networks separately funded by the National Cancer Institute (NCI) and the National Institute of Allergy and Infectious Disease (NIAID). We recommend a series of new scientific initiatives and programs to resolve these problems and improve our understanding of and clinical management of AIDS-associated Kaposi's sarcoma, a disease which eventually afflicts over 30% of people with AIDS living in the United States.

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KS PROJECT RECOMMENDATIONS

1 THE NATIONAL INSTITUTES OF HEALTH (NIH) MUST ADD AN AIDS-RELATED MALIGNANCIES STUDY SECTION UNDER ITS DIVISION OF RESEARCH GRANTS (DRG), OR THE NATIONAL CANCER INSTITUTE (NCI) SHOULD CHARTER AN ONGOING AD HOC AIDS-ONCOLOGY STUDY SECTION.

2 NCI SHOULD PROVIDE MORE EXTRAMURAL FUNDING FOR AIDS-RELATED MALIGNANCIES.

3 THE NCI SHOULD PROVIDE FUNDING IN THE FORM OF SUPPLEMENTAL AWARDS TO AIDS CLINICAL TRIAL UNITS (ACTUs) TO CONDUCT AIDS ONCOLOGY TRIALS, BY SUPPORTING ON-SITE ONCOLOGY EXPERTISE AND NECESSARY ANCILLARY SERVICES.

4 THE AIDS CLINICAL TRIALS GROUP ONCOLOGY COMMITTEE SHOULD REMAIN AN AUTONOMOUS, SEPARATE COMMITTEE WITHIN THE ACTG.

5 ALL NCI COOPERATIVE CLINICAL ONCOLOGY GROUPS SHOULD SET UP AIDS COMMITTEES; THEY SHOULD FORM A JOINT UMBRELLA AIDS ONCOLOGY WORKING GROUP TO LIAISON WITH THE ACTG AND CONDUCT CROSS-NETWORK STUDIES.

6 NIH'S OFFICE OF AIDS RESEARCH (OAR) SHOULD WORK TO FOSTER COLLABORATION AND COOPERATION BETWEEN NCI'S COOPERATIVE GROUPS AND NIAID'S ACTG IN CONDUCTING LARGE-SCALE CLINICAL EFFICACY STUDIES TO FURTHER DEFINE THE STANDARD OF CARE AND DEVELOP NEW AGENTS FOR THE TREATMENT OF AIDS-RELATED MALIGNANCIES.

7 NCI SHOULD SUPPORT AN INITIATIVE TO TRAIN MORE AIDS ONCOLOGISTS.

8 OAR SHOULD SUPPORT THE NCI'S BYPASS BUDGET REQUEST TO PROVIDE FUNDS (THROUGH THE P20 MECHANISM) TO THEIR CANCER CENTERS FOR THE DEVELOPMENT OF NEW RESEARCH PROGRAMS FOCUSING ON AIDS-RELATED MALIGNANCIES.

9 OAR SHOULD SUPPORT THE NCI'S 1996 BYPASS BUDGET REQUEST FOR THE PROVISION OF FUNDS FOR PILOT PROJECTS AND FEASIBILITY CLINICAL AIDS ONCOLOGY STUDIES TO BE RUN THROUGH THE NCI'S CANCER CENTERS AND ACTUs.

10 NCI AND NIAID SHOULD ESTABLISH, AMONG EXISTING COHORTS (e.g., MACS OR ACTG, CPCRA), AND/OR AMONG NEW POPULATIONS, A PROSPECTIVE EPIDEMIOLOGICAL SURVEY OF THE INCIDENCE AND NATURAL HISTORY OF AIDS-RELATED MALIGNANCIES, WITH CENTRAL TISSUE AND SERUM BANKING, TO PROVIDE BETTER INFORMATION ON WHO DEVELOPS THESE COMPLICATIONS AND HOW THEY PROGRESS AND RESPOND TO TREATMENT.

11 OAR, IN COLLABORATION WITH NCI, NIAID, AND THE AGENCY FOR HEALTH CARE POLICY AND RESEARCH (AHCPR), SHOULD ESTABLISH A STATE-OF-THE-ART PANEL TO REVIEW CURRENT TREATMENT OPTIONS FOR AIDS-RELATED MALIGNANCIES (ESPECIALLY KS) AND RECOMMEND STANDARD-OF-CARE GUIDELINES, AS WELL AS IDENTIFY GAPS IN KNOWLEDGE WHICH COULD BE FILLED BY WELL-DESIGNED AND EXECUTED RANDOMIZED CONTROLLED STUDIES. A STANDARD OF CARE MUST BE ESTABLISHED SO THAT WE FINALLY KNOW WHAT IS THE OPTIMAL THERAPY FOR KS PATIENTS AT VARIOUS STAGES OF DISEASE.

12 THE NEW TREATMENT GUIDELINES SHOULD MAKE IT CLEAR THAT KS AND LYMPHOMA PATIENTS SHOULD BE REFERRED TO AN AIDS ONCOLOGIST FOR EVALUATION AND A DISCUSSION OF POSSIBLE TREATMENTS. "THE [MERE] OBSERVATION OF PATIENTS WITH PROGRESSIVE KS IS UNACCEPTABLE."

13 A MECHANISM NEEDS TO BE ESTABLISHED UP TO TEACH ONCOLOGISTS ABOUT AIDS AND HOW TO BECOME MORE INVOLVED IN BASIC AND CLINICAL RESEARCH .

14 PRIMARY CARE PHYSICIANS AND PATIENTS MUST ALSO LEARN MORE ABOUT THE CURRENT PATHOGENESIS OF AIDS MALIGNANCIES..

15 SERIOUS THOUGHT NEEDS TO GO INTO HOW WE GET PHYSICIANS TO REFER KS PATIENTS INTO CURRENT (AND THE NEXT GENERATION OF) ANTI-ANGIOGENESIS/CYTOKINE MODULATION TRIALS, AND OTHER NOVEL APPROACHES TO TREATING AIDS-RELATED MALIGNANCIES..

16 WE NEED TO STUDY WHETHER ANGIOGENESIS INHIBITORS AND CYTOKINE MODULATORS (MAYBE IN COMBINATION) ARE APPROPRIATE FOR PATIENTS WITH EARLY STAGE KS OR MAY PREVENT THE FORMATION OF NEW LESIONS. IN TIME, AFTER WE HAVE LEARNED MORE ABOUT THESE AGENTS, WILL WE BE AT THE POINT WHERE WE CAN SAY THAT THESE COMPOUNDS MIGHT BE EFFECTIVE AS PROPHYLAXIS FOR KS?

EPIDEMIOLOGY

Distribution

Kaposi's Sarcoma (KS) has an epidemiology unlike any other opportunistic infection (OI) or AIDS-related malignancy. As will be discussed later, the epidemiology of KS may provide some clues to the cause or one of the co-factors that leads to this disease. KS has a distribution that varies according to the method of HIV infection, sex, ethnicity, age, and residence of sexual partners.

Numerous epidemiological studies exist that provide additional pieces to this puzzle. However, while many conclusions can be strongly supported with additional studies, many issues remain controversial.

Kaposi's Sarcoma continues to be primarily a disease of homosexual/bisexual males. As HIV/AIDS has started affecting other populations, KS continues to be a greater risk among this population (Beral 1990; Selick 1987; Elford 1993; Rutherford 1990; Haverkos 1993). In the United States, KS is rare among those infected with HIV through heterosexual contact and even more rare among IVDUs, transfusion recipients, and hemophiliacs (Beral 1990; Rabkin 1990, 1992). Those who acquired HIV from heterosexual contact and had KS were more likely to be born in Haiti, other Caribbean countries, or Mexico/Central America (Beral 1990). One cohort study of hemophiliacs had only one case of KS, and that patient was also a homosexual living in New York City (Rabkin). Of extreme interest is the increase of KS among homosexual males who are not infected with HIV (Friedman-Kien 1990).

Geographic distribution of KS cases varies greatly in the US as well as Europe. The Multicenter AIDS Cohort Study (MACS) shows that patients living on or having sex partners from the West Coast, particularly in Los Angeles, a greater risk of KS (Armenian 1993). Out of 316 cases of KS, 52.9% were from Los Angeles, 19.9% from Chicago, 17.7% from Baltimore, and only 9.5 % from Pittsburgh. Rabkin has shown that the risk of KS is higher for those living in New York as opposed to Washington DC (Rabkin 1990). Beral et al. (Beral 1990) demonstrated that of the reported KS cases in the US, 3% were from Kansas, 6% from Iowa, 30% from California, and 31% from New York. This geographical distribution was found among all transmission groups with KS. Two Canadian studies support this hypothesis. A Canadian Surveillance study reported that KS was more common in cities that were considered primary epidemic centers such as Vancouver, Toronto, and Montreal (Schechter 1990). The Vancouver Lymphadenopathy-AIDS Group demonstrated that homosexual men were at a greater risk of KS if their sex partners were from Los Angeles, San Francisco, or New York (Archibald 1990). In

the UK, Beral et al. have shown that patients were at greater risk of KS if they had sex partners from the US or Africa as opposed to the UK.

Women are at a much lower risk of KS than men. Pathogenesis studies suggest that this may be due to hormonal differences (see pathogenesis). One study has shown that women who were infected with HIV from bisexual males as opposed to being an IVDU were at a 4 times greater risk of KS (Beral 1990). An update report supports this finding (Haverkos 1993). Other studies have not shown this strong association (Elford 1993; Lassoued 1991; Benedetti 1991, Serraino 1992).

Age also plays a role. KS is extremely rare in children and is more of a risk for those older than 15 years (Beral 1990). Beral has shown that it is common for children with KS to be born to Haitian women. An Australian surveillance study reported that the youngest case of KS was a 17 year-old homosexual male. They reported no children with KS. It has been reported that KS is more common among homosexuals between 25-44 years (Beral 1990) . One Canadian study suggests that KS was more common in the 1945-54 birth cohort of homosexual males (Schechter 1991).

Some studies have reported different KS risk among various racial groups. One surveillance study reports that the percentage of KS cases among whites and Hispanics was approximately twice that of blacks. However, this difference among racial groups was not consistent among the different HIV transmission categories (Beral 1990). In San Francisco, one study reports that KS was more common in White than Blacks or Hispanics (Reynolds 1993) while other studies of homosexual men report no racial differences (Lifson 1990; Haverkos 1993).

In Europe, epidemiological studies show similar distributions among people with HIV (Casabona 1991; Couturier 1991). KS appear to be more common in homosexual/bisexual males. However, one study showed that in Italy where most HIV infection is due to IVDUs, there is a greater proportion of heterosexuals with KS (Serraino 1992). One study showed geographic variances within Italy while another study showed no geographic differences within all of Europe. The Italian study mentions that it has a lower overall prevalence of KS relative to the United States. It was hypothesized that this difference may be due to a higher proportion of AIDS cases among IVDUs in Italy (70%) relative to the United States which has a higher proportion of homosexuals/bisexuals (Serraino 1992).

In summary, in the United States, KS is significantly more common among homosexual/bisexual males relative to other HIV transmission groups; is more prevalent in New York, Los Angeles, and San Francisco, areas considered the initial foci of the HIV/AIDS epidemic; rare among women unless they were infected with HIV from a bisexual male; extremely rare among children (less than 15 years) unless they were born to Haitian mothers; and conflicting data exists whether KS has a racial distribution. European and Australian studies show similar patterns in their respective countries. However, their studies have not collected enough data to demonstrate that women are at a greater risk of KS if they were infected with HIV from a bisexual male.

A Sexually Transmitted Disease?

Many epidemiologists hypothesize that the reason for the unusual distribution of KS among people with HIV/AIDS is that it is caused by sexually-transmitted agent (not HIV). This theory received new support after several known cases of HIV-negative homosexual men were reported to have what is now considered epidemic KS

(Kitchen 1990; Afrasiabi 1986, Friedman-Kien 1990; Lowdell 1989; Zucker-Franklin 1993; Castro 1992).

There are many other arguments in favor of KS being caused by an unknown sexually transmitted agent. Beral et al. (1990) have outlined these arguments. The high concentration of cases among homosexual men in the age group 25-44 parallels the current HIV/AIDS epidemic. Homosexual males are at a greater risk of KS than bisexual males. KS is extremely rare among children. The majority of children with KS were born to mothers with classic KS is endemic. And the two most compelling arguments that KS may be sexually transmitted are the geographic distribution and increased risk for women infected with HIV from bisexual males. It has been shown that KS is more common among those who either live, travel to, and have sex with in someone who lives in Los Angeles, San Francisco, or New York (Archibald 1990; Beral 1990). An increased risk of KS among women infected from bisexual males is an even stronger argument. Why is KS more common in this group?

Studies of homosexual/bisexual males have been conducted to determine the etiology and possible mode of transmission of the "KS agent." No etiologic agent has been discovered nor has there been any conclusive evidence on the possible mode of transmission. However, some interesting data has been collected that may provide us with some clues to the cause of KS. Some studies have suggested that KS may be associated with fecal contact through rimming, fisting, and anal-insertive sex (Beral 1992, Jacobson 1990, Darrow 1992, Archibald 1992) Other studies have not found an association between these sexual activities and an increased risk of KS (Lifson 1990, Elford 1993). More recent studies have suggested a combination of factors that suggest a greater risk of KS may be associated with a previous history of sexually transmitted disease and a greater number of sexual partners (Armenian 1993; Abrams 1990). In addition, reports of HIV-negative homosexual males with epidemic KS report similar findings (Friedman-Kien 1990; Zucker-Franklin 1993; Lowdell 1989).

The use of amyl nitrate (poppers), once considered one of the possible causes of AIDS, has also been implicated as a possible cause of epidemic KS (Haverkos 1985; 1990; Archibald 1992). This hypothesis has not been supported in other studies (Lifson 1990; Beral 1992). After 57 of the original 87 men interviewed for the Haverkos study were reevaluated, it was shown that KS was more closely associated with rimming and that there was no significant association with the use of poppers (Darrow 1992).

When analyzing the data involved in these epidemiological studies, one needs to keep in mind that several variables are usually being analyzed through some form of regression analysis. It is impossible to analyze these data to get a pure picture of exactly what variable or variables are involved. While using various statistical tools to control for confounding among variables may help to provide a clearer picture, isolating the effects of each variable independent of others is difficult. The lesson we may have learned from the various studies looking at the use of poppers is that there probably is not one variable associated with KS. The use of poppers may lead to particular behaviors that may be more associated with KS. In addition, it has been suggested that poppers may provide some biological mechanism that may facilitate the transmission of the possible KS agent (Archibald 1992).

It may be that there is no ONE agent that is associated with KS but a variety of agents or interactions. More specifically, KS may not be caused by a sexually transmitted agent but by the hyperactivation of the immune system. While no one agent has yet to be associated with KS, one theme has been very strong; in

homosexual men, KS is typically associated with a greater number of sexual partners, and a greater number of sexually transmitted diseases, which both lead to overactivation of an already overburdened immune system (Abrams 1990). KS may not be the direct result of one particular agent but the result of hyperactivation of the immune system (Robert C. Gallo, personal communication).

The two main issues that remain are:

* If an infectious agent (or a combination of agents) is associated with KS, this agent is unknown.

* If no agent is involved, and KS is the result of hyperactivation of the immune system, this hypothesis needs further attention.

Is KS Going Away?

Many researchers, oncologists, dermatologists, and primary care physicians, have reported that they are seeing much less KS than they did at the beginning of the AIDS epidemic. Several studies support the fact that the proportion of KS cases relative to other AIDS defining diseases has significantly decreased since 1981 in the United States as well as other countries (Selik 1987; Haverkos 1993; Beral 1990; Lifson 1990; Rutherford 1990; Elford 1993; Serraino 1992; Casabona 1991; Schechter 1991). In a cohort of 1,341 HIV-positive homosexual/bisexual men in San Francisco, Lifson et al. reported a decline of KS cases from 79% in 1981 to 25 % in 1989. Recent reports show that the percent of KS cases as an AIDS defining illness was as low as 9.9% in 1992 (Haverkos 1993). In most of these studies, it can be argued that the decline in cases of KS may be an artifact due to the method of data collection. Surveillance studies only collect initial AIDS defining diagnoses. As the AIDS definition has changed over time to allow for the reporting of other opportunistic infections and malignancies, the proportion of KS cases would naturally decrease over time.

In an attempt to compensate for the inability of the AIDS registries to collect all cases of KS, studies have been done to link AIDS registries with the cancer registries to determine the completeness of data collection within these registries. Reynolds et al. (Reynolds 1990) reported that only 72.3% of 1,330 reported KS cases appeared in both the San Francisco AIDS Registry and the California Tumor Registry between 1980-1986. Differences may be attributed to the fact that the AIDS registry required microscopic confirmation of KS while the CTR did not. Other differences noted were that private physicians' offices were more likely to report to the AIDS registry while hospitals and clinics were more likely to report to the CTR and the chances of only being reported to one or the other registry as opposed to both registries increased over time. This may be a sign that more private physicians or primary care providers were treating KS cases. Both registries showed a parallel increase in cases of KS during this time period. However, when the data from both registries were linked, there was an ever greater increase of KS cases. Reynolds et al. stated that these data may suggest an increase in the incidence of KS during this time period.

While not as sophisticated as the previous approach, the National Cancer Institute has also linked AIDS and cancer registries in San Francisco, the Bay Area exclusive of San Francisco, Los Angeles, San Diego, Orange County, Sacramento (which provided data on all other California counties), Florida, Metropolitan Atlanta, and New Jersey, to determine the completeness of KS case ascertainment. Cases were matched on social security number, name, and date of birth. When data collection was completed in November 1992, 10,350 cases of KS

were reported: 6,987 were reported to both registries, 1,935 were reported only to the AIDS registry, and 1,428 were reported only to the cancer registry. Among those reported to both registries, 1,209 (17%) had KS reported only to the cancer registry and other AIDS-defining diseases reported to the AIDS registry. Cote et al. (Cote: unpublished, 1993) reported that AIDS and cancer registries were 87% and 81% complete, respectively, for KS case ascertainment among people with AIDS. AIDS registry completeness was higher for men than women, and for whites than for non-whites. While there is some potential for both under and overestimating registry completeness through their method, the authors conclude that this is a successful and inexpensive method of providing more complete AIDS/KS case collection. Reynolds and Cote acknowledge, however, that some cases are not been reported to either registry.

Because AIDS surveillance data mostly collects the primary AIDS defining illnesses, a secondary diagnosis of KS would not be reported. In order to correct for this artifact, prospective cohort studies have attempted to analyze the incidence of KS as a primary or subsequent diagnosis among fixed populations of HIV infected individuals (Jacobson 1990; Archibald 1990; Munoz 1993; Reynolds 1993). In an analysis of the MACS population between 9/84 and 9/88, Jacobson et al. reported no systematic trend in the incidence of KS. In a population-based study in San Francisco, Reynolds et al. reported little or no change in KS incidence between 1980-1987. In another analysis of the MACS population between 1985-1991, Munoz et al. found an increase in the incidence of KS, which they attributed to progressive immunosuppression in this population. After adjusting for CD4 count, however, this analysis indicated a downward trend in the incidence of KS. The Vancouver Lymphadenopathy-AIDS study also reports a decreasing incidence of KS. However, similar to Lifson et al., Archibald et al. used the proportion of KS cases relative to opportunistic infections to describe the decreasing incidence of KS in this cohort.

Several hypotheses attempt to explain the decrease in the proportion of KS cases and the possible decrease in incidence of KS among people with HIV/AIDS:

Lack of reporting (Beral 1990; Jacobson 1990). Reporting of an AIDS diagnosis only records the index disease . If a patient later gets KS, this may not be reported.

Changes in behavior which include safer sex techniques as well as a decrease in number of sexual partners among homosexual males (Beral 1990; Jacobson 1990; Elford 1993). If KS is associated with a particular agent, a combination of agents, or the hyperactivation of the immune system associated with chronic enteric infections due to particular sexual activities, then safer sex techniques and/or decreasing the number of sexual partners may have an impact on the risk of KS among people with HIV.

While the proportion of KS cases relative to other AIDS defining illnesses and the true incidence of KS among people with HIV are debatable issues, the bottom line is that the prevalence of KS (the absolute number of KS cases) continues to rise as the number of AIDS cases continues to rise and people with HIV/AIDS live longer through the use of improved OI prophylaxis and treatments. Between 1981 and 1983, when KS accounted for 32.7% of all AIDS diagnosis, the actual number of KS patients was only 957. In 1992 when KS accounted for only 9.9% of the reported AIDS cases, the absolute number of cases was 4, 659 (Haverkos 1993). Due to underestimation in case ascertainment, both of these numbers are likely to be less than the true number of cases.

In a retrospective analysis of patient records of primarily homosexual/bisexual males at a hospital in the United Kingdom, Peters et al. (Peters 1991) have shown that while the reporting of KS as an index diagnosis has decreased from 30% to 20% from 1984-1989, the prevalence of KS has remained constant at around 35%. In addition, Peters et al. reported that while the deaths due to PCP have decreased from 46% in 1986 to 3% in 1989, deaths attributed to KS have increased from 14% to 32% between 1984 and 1989. The authors stated that in 1989, KS was the most common cause of death in this cohort. In an analysis of the MACS population, between 1984 and 1992, Hoover et al. (Hoover 1993) supported this data by showing that overall, 37.4% of AIDS cases in this cohort were diagnosed with KS prior to death. The MACS population of homosexual/bisexual males is similar to that of the Peters study.

What we have seen is controversy over whether or not the incidence of KS is declining. The reality is, while the incidence may or may not be decreasing, the prevalence of KS continues to remain high if not rising (Peters 1991; Hoover 1993). In addition, as people with HIV/AIDS are living longer, their risk of ever getting KS increases. As people become more immunosuppressed their presentation and prognosis changes. Patients are now developing extensive visceral KS and dying because of systemic disease (Peters 1991).

Has the Face of KS Changed?

Hoover et al. stated, "Many believe that Kaposi's Sarcoma is more localized and benign at higher CD4+ levels but becomes more invasive as T-cell function declines." This was demonstrated by the fact that in the MACS cohort between 1984 and 1992, the diagnosis of KS subsequent to an AIDS diagnosis almost doubled the hazard for death (Hoover 1993). Because 36% of all KS cases were reported as subsequent diagnoses, the author concluded that gay men presenting with an AIDS condition other than KS are at a significant risk for KS. It was also noted that a greater length of time from a non-KS AIDS-defining diagnosis to death was associated with a greater probability for later KS. While much more extensive than the Peters report, this data supports the increased risk and poorer prognosis of KS as people with HIV/AIDS live longer. Other researchers have seen similar patterns in their patient populations (Ronald Mitsuyasu, personal communication; Alexandra Levine, personal communication).

Autopsies performed on homosexual men with KS in the MACS study support previous reports that visceral KS may be going undetected (Ndimbie 1994). Of the 158 men autopsied, 46 had KS: Baltimore 12 (25.5%), Chicago 4 (28%), Pittsburgh 5 (11.4%), and Los Angeles with 24 (49%). Of the 46 case of KS, 8 (17%) had visceral, 10 (22%) had cutaneous, and 28 (61%) has cutaneous and visceral. 36 of the 46 cases had a visceral component. 4 (40%) of the 10 cases with cutaneous KS were reported as having KS as their AIDS defining disease. 19 (68%) of the 28 cases of cutaneous and visceral KS were reported as having KS as their AIDS defining disease. Only 1 (12%) of the 8 cases of visceral KS has KS as their AIDS defining disease. Even more interesting is that 5 (68%) of the 8 visceral cases were not detected until autopsy! Of all KS cases, the mean time in days from KS diagnosis to death was shortest for the visceral group (22 days), followed by cutaneous (312 days), and cutaneous and visceral (488 days).

Payne et al. (Payne 1990) reported that survival for AIDS patients diagnosed with KS between 1981 and 1987 decreased over time. This was explained by the possibility of more aggressive tumors or the presentation of KS later in the course of HIV illness.

In a study of cutaneous neoplasms among HIV-positive patients in the military, the most common neoplasm was KS. Smith et al. reported that while the majority of patients in their cohort were in early stages of disease, the majority of patients with KS were in later stages of HIV disease. In addition, KS was associated with poor survival.

One small study of KS in women also showed an association with low CD4 cells (less than 100), more aggressive disease, and poor survival (Lassoued 1991).

One study by Miles et al. suggests that after adjusting for CD4 number, hematocrit, number of KS lesions, and body mass index, there was an increase in survival for patients with KS over the past six years (Miles: unpublished data).

Comments

While reviewing the distribution of KS it may be easy to be convinced that KS is associated with an unknown agent, possibly transmitted sexually. However, why have we not found this agent? Is it a combination of agents? Is it related to particular behaviors? Is KS the result of a hyperactive immune system? Why do HIV-negative homosexual males get KS? Why does epidemic KS have epidemiology patterns not seen in endemic KS or in KS as a result of immune suppression due to organ transplants? Only additional studies will provide additional clues to the true cause of epidemic KS.

Is the incidence of KS truly declining? While many explanations exist for a possible decrease of KS incidence, the absolute number of cases of KS remains significant. In addition, while KS was once considered an early stage disease easily treated, this pattern may also be changing to a more aggressive disease with decreased survival.

Epidemiology Recommendation: Provide a coordinated and uniform mechanism to collect data on the true incidence and prevalence of KS as a primary and subsequent AIDS diagnosis. Conduct prospective, longitudinal studies to better assess the natural history of AIDS-associated KS. Improve outreach to primary care physicians to emphasize the importance of reporting KS diagnoses to AIDS and cancer registries.

ETIOLOGY + PATHOGENESIS

As the epidemiology suggests, many researchers have tested the hypothesis of several different etiologic agents with the hopes of finding one that is associated with KS. As sexually transmitted agents have been associated with other malignancies, it has been hypothesized that a sexually transmitted agent may be associated with KS.

To date the following viruses have been studied, without evidence for viral sequences in KS cells: HTLV-I, HTLV-II, HIV-1, HBV, HHV-6, EBV, CMV, HSV-1, HSV-2, papova and polyoma viruses (Salahuddin 1988; Marmor 1984).

Cytomegalovirus once seriously considered as a possible cofactor, has been ruled out due to the low prevalence of KS in intravenous drug users and a variety of other studies that could not confirm the that CMV infection was more common in people with KS (Marmor 1984; Salahuddin 1988).

Huang et al. (Huang 1992) suggested that Human Papilloma Virus-16 (HPV-16) may be associated with KS (92). Polymerase chain reaction was used to detect HPV DNA

fragments in tumor tissues. HPV DNA fragments were found in KS lesions from 11 of 69 homosexual men with HIV-related KS, in 3 of 11 HIV-negative homosexual men, and in 5 of 17 elderly men and women with classic KS. However, Biggar et al. (Biggar 1992) were unable to detect HPV in KS lesions. Using PCR and in situ hybridization, no evidence of HPV was found in 14 KS tissue samples from 3 homosexual men, 6 elderly people, and five HIV-negative individuals. In addition, Fugiwara et al. (Fugiwara 1993) were unable to detect HPV-16 DNA sequences in HIV-related and classic KS tissue samples. Researchers continue to search for etiologic agents. However, some feel that there is no one agent responsible for KS and that KS is the end result of a cascade of events resulting from hyperactivation of the immune system. These questions can only be answered through additional pathogenesis research. Is KS a True Malignancy?

This is an extremely integral question that, when or if it can be answered, can have some serious implications for the future management of this disease. This unanswered question has had implications on more than treatment choice. The inability to classify KS as either a malignancy or an infectious disease has had, and continues to have, implications for the funding and coordination of research efforts. While the National Cancer Institute (NCI) and the National Institute of Allergy and Infectious Diseases (NIAID) fund basic research and clinical studies, neither the NCI nor NIAID have taken the leadership role in the funding and coordination of these efforts. This same lack of leadership and responsibility is missing in treatment. As stated by Susan Krown, an oncologist in New York City, "Just as many infectious disease specialists feel that Kaposi's Sarcoma is a peripheral issue in AIDS, so too many oncologists feel that understanding and developing treatments for Kaposi's Sarcoma is not germane to the central issues of our specialty." (Krown 1993)

More questions can be asked than statements made about this hyperplasia. Markers of true malignancy such as clonality and/or clonal chromosomal abnormalities, have not been demonstrated (Levine 93). In the early stages of disease there is no one dominant cell line. As disease progresses and immunosuppression becomes more severe, the disease becomes more aggressive. One malignant cell line becomes dominant, chromosomal change occurs, and lesions may begin to take on a tumor-like behavior. In addition, the dependence of KS on a variety of cytokines and growth factors also suggests aspects of a true malignancy. Robert Gallo of the Laboratory of Tumor Cell Biology (LTCB) at the NCI suggests that as KS progresses into late stage disease, it begins to resemble a true malignancy (Robert C. Gallo, personal communication).

Robert Gallo's lab has successfully isolated an immortalized cell line, referred to as KS Y-1. This cell line is able to generate long lasting tumors and metastases in nude and SCID mice. This KS cell line shows the same phenotype in vitro as KS cell strains and can induce angiogenesis in vivo (Lundardi-Iskandar 1993).

Many questions remain regarding the classification of KS into any disease type. If KS is not a cancer than why does it respond to chemotherapy in systemic disease? If KS is a cancer than why does KS spontaneously regress in transplant recipients after immunosuppressive therapy has been stopped? No other cancer responds to the restoration of the immune system (Alvin Friedman-Kien, personal communication). The ability to answer these questions lies in pathogenesis studies. While we have gained a wealth of knowledge regarding the pathogenesis through the ability to culture KS cells in long term tissue cultures, we still do not know the cell of origin.

KS Cell of Origin: The Missing Link

Several studies have been conducted in order to determine the cell of origin of KS. Potential progenitors of the spindle-shaped KS cells are mesenchymal in origin. They have variously been reported to have characteristics of endothelial cells of vascular (Corbeil 1991) and lymphatic origin (Salahuddin 1988), smooth muscle cells (Weich 1991) and dermal dendrocytes (Huang 1993). Overwhelming evidence does not exist for any one specific cell type. Roth et al. suggested that due to the heterogeneity of the cultivated cells, KS tumors may be composed of spindle-shaped cells of various origins (Roth 1992). Growth Factors

The establishment of KS cell cultures in the laboratory has made it possible to study factors associated with the growth of KS cells. Nakamura et al. (Nakamura 1988) have successfully maintained long-term KS cell cultures using growth factors released by CD4 cells infected with retroviruses (HTLV-I, HTLV-II, and HIV-1). It was also noted that factors associated with KS cell growth were also associated with the growth of endothelial cells. However, this was not true for the reverse; factors associated with endothelial cell growth were not associated with KS cell growth. This suggests differing growth requirements for the different cells lines.

After KS cells have initiated cell growth from as yet undetermined factor(s), they have the capacity to sustain their own growth, as well as the growth of normal endothelial cells, fibroblasts and other cell types, and to induce new blood vessel proliferation (Ensoli 1989; Salahuddin 1988). These reports suggest that the growth of KS and other cells is maintained by paracrine and autocrine factors produced by retrovirus-infected CD4 cells and by KS cells themselves. Salahuddin et al. supported these findings by demonstrating the induction of KS cell proliferation in nude mice. Five days after being inoculated with cultured human AIDS-KS-derived cells, nude mice developed a transient angiogenic reaction, and developed lesions of mouse cell origin, histologically similar to human KS, at the site of inoculation.

Several cytokines and growth factors have been associated with the possible initiation and continued growth of KS cells and angiogenesis:

Fibroblast Growth Factors (FGFs) have been associated with angiogenesis. The expression of both FGF and FGF receptors has been demonstrated in cultured KS cells as well as in fresh biopsies (Li 1993). Li et al. reported that these findings suggest that FGF and FGF receptors play a role in the pathogenesis of KS. However, it is unclear whether this is due to their oncogenic and/or angiogenesis properties. These findings also support the paracrine and autocrine mechanisms that contribute to the development and growth of the KS cells. An in vitro study of antisense oligonucleotides against bFGF showed that they can block AIDS-KS cell proliferation in response to inflammatory cytokines produced by activated T-cells. This report suggests that inflammatory cytokines induce KS-cell proliferation through an increase of bFGF activity and that they may promote the expression of bFGF found in KS lesions (Samaniego 1993). Ensoli et al. reported on the use of bFGF antisense in nude mice injected with bFGF. This study showed that bFGF antisense was successful in blocking KS cell growth and inhibited the angiogenic activity of these cells such as the stimulation of normal endothelial cell growth, migration, and invasion. These effects were seen in a dose-dependent manner (Ensoli 1993 b).

Numerous studies have suggested a role for inflammatory cytokines such as IL-1, IL-6 and TNF-alpha, in the pathogenesis of KS (Barillari 1992; Miles 1990; Salahuddin 1988; Nakamura 1988). IL-1 has been implicated in indirectly inducing angiogenesis through working with cells of the immune system. IL-1 is induced in

monocytes and macrophages in HIV infected individuals. In addition it has been shown that like bFGF, IL-1 is also produced by KS cells, suggesting the continued proliferation of KS cells and mesenchymal cell types in an autocrine and paracrine fashion (Ensoli 1993 b).

IL-6 as well has been shown to act in an autocrine fashion in KS cell proliferation (Miles 1990). This was demonstrated by the reduction of IL-6 protein translation when an IL-6 antisense oligodeoxynucleotide was added. Proliferation continued when exogenous IL-6 was added. Using involved and uninvolved tissue from a patient with AIDS-KS, Miles et al. showed that IL-6 and IL-6 receptors were in great excess in the involved skin relative to the uninvolved skin. Miles suggests that the mitogenic activity of IL-1 and bFGF for AIDS-KS cells might be by inducing IL-6 production or altering IL-6 responsiveness of these AIDS-KS cells. This may be one reason for the variation in prognosis for patients with AIDS-KS. Since opportunistic infections increase cytokines such as IL-1 and TNF, the expression of these cytokines may be the reason why people with KS have rapid progression with concurrent opportunistic infections. While elevated IL-6 is not unusual in the absence of AIDS-KS, the expression of IL-6 receptors in endothelial cells is of interest in this study.

TNF has also been associated with KS pathogenesis. A study of skin biopsies from 6 patients with AIDS-KS showed that all 6 patients showed increased amounts of IL-6 and TNF in the epidermal cells of the tumor. Neither cytokine was found in the endothelial cells of the tumors. The authors were unsure of the significance of this finding.

A variety of other growth factors have been associated with the proliferation of KS cells through autocrine and paracrine mechanisms, including platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF) also known as vascular permeability factor (VPF) (Weindel), transforming growth factor (TGF), and granulocyte-macrophage colony stimulating factor (GM-CSF) (Ensoli 1994). TGF is an immunosuppressive cytokine that is released from PBMCs upon infection with HIV and was found to stimulate KS cell growth (Ensoli 1994).

It has been suggested that it is the above growth factors that lead to the angiogenesis involved in KS tumor growth. The question is which one or which combination of growth factors is involved.

While there are several growth factors involved in the proliferation of KS-spindle cells, there has, until recently, been no explanation for its association with HIV infection. Although it was once thought that HIV might play a direct role in causing KS, more recent studies suggest a more indirect role mediated by the HIV tat protein. Male transgenic mice developed KS-like lesions when tat was expressed (Vogel 1988). In addition, tat has been shown to stimulate the growth of KS cells as well as the growth of normal vascular (endothelial) cells after exposure to inflammatory cytokines (Barillari 1992). Farewell et al. suggest that tat mimics bFGF in the presence of activated endothelial cells (Farewell 1993). Ensoli et al. have shown that tat and bFGF act synergistically to induce KS-like lesions in mice, and have suggested a mechanism by which inflammatory cytokines (TNF, IL-1, and gamma-IFN), tat, and bFGF work in cooperation in the pathogenesis of KS (Ensoli 1993). These results suggest it may be useful to reinvestigate tat inhibitors against AIDS-KS.

Etiology + Pathogenesis Recommendations: Further explore the epidemiologic and pathogenetic determinants of AIDS-KS, and define whether or not an infectious agent or cofactor is involved. Further study epidemic KS incidence in HIV-negative gay and bisexual men. Further elucidate and confirm the contribution of

inflammatory cytokine pathways to the pathogenesis of KS. Foster new collaborative research projects among epidemiologists, immunologists and KS oncologists. Establish a national tissue and serum repository to provide access to clinical samples from HIV-infected persons at risk for and those developing AIDS-related neoplasms, and guarantee equitable access to extramural researchers to these valuable samples.

HISTOLOGIC AND CLINICAL FEATURES

Histogenesis

The cell of origin (histogenesis) for KS still remains controversial. KS is characterized by the proliferation of spindle-shaped cells ("KS cells", Ensoli 1991). The histogenesis of these spindle cells, however, is still undefined. Mesenchymal cells, vascular and lymphatic endothelial cells (Rutgers 1986; Way 1993) and smooth muscle cells (Weich 1991) have all been proposed as potential KS cell progenitors.

Most researchers contend that these spindle-shaped KS cells are considered to be the "tumor" element of the lesions, which are associated with slit-like vascular channels lined by endothelial cells, fibroblasts and inflammatory cells; the vascular channels extend themselves in the process of new blood vessel formation (neo-angiogenesis) in the early stage lesions. In the later stage of the lesions, neo-angiogenesis continues, but the KS spindle-cells now make up larger, three-dimensional tumor masses.

Two methods have been developed to study the histogenesis and pathogenesis of KS: 1) the establishment of long-term cell cultures derived from KS lesions; and 2) the development nude mice into which cultured KS-derived cells are injected.

Pathology

Three characteristic histologic stages have been described for cutaneous KS: patch, plaque and nodular. While some lesions appear to rise de novo as nodules (Susan E. Krown, personal communication), the patch stage is often the earliest pattern of KS lesions, which arise in the reticular dermis as a clinically macular (non-palpable) lesion (Gottlieb 1992). Patch stage lesions are characterized by a proliferation of small interweaving bands of spindle cells with irregular slit-like vascular channels surrounding normal dermal vessels and adnexal structures accompanied by a variable, inflammatory lymphocytic infiltrate (Tappero 1993 b).

In plaque-stage, KS there is expansion of the spindle-cell and vascular process. These spindle cells, now dispersed in the reticular dermis, are comprised within a network of reticular and collagen fibers (Levine 1993). Clinically, such lesions are palpable (i.e., they have depth).

Nodular-stage KS lesions are mostly composed of sheets of spindle cells with mild to moderate cytologic atypia, single cell necrosis, and trapped erythrocytes (Tappero 1993 b). The irregular, slit-like, vascular channels of the spindle cells tend to coalesce in larger tumor masses.

Clinical Features

AIDS-KS has a wide variety of clinical presentations. Lesions composed of various colors and shapes are usually defined as macules, papules, nodules or plaques.

Macular lesions are often innocuous looking, faint pink, red or purple, and small in size. At this stage they are usually asymptomatic. They are most commonly seen on sole, hard palate and tip of the nose.

Lesions on the trunk of a patients can start out as macules, but they are usually papular at presentation. When they are on the trunk, neck or the penis, they are frequently oblong and 1 to 2 cm in longest dimension (Tappero 1993 b). When lesions occur on the face they are most often round and less than 1 cm in size.

Papular lesions or plaques are often found in the distal extremities, whereas larger plaques with nodules frequently occur around the elbows and knees of patients. The plaques and nodules on the legs are often associated with painful edema. Lymphatic infiltration alters the course and dimension of cutaneous KS as well as cause extreme pain, maceration and ulceration. Lymphedema is also thought to be associated with a release of multiple cytokines which are central to the pathogenesis of KS.

Oral lesions are much harder to categorize and measure. Oral lesions are the first clinical manifestation in approximately 22% of patients with KS, and are seen in approximately 45% of patients who have concomitant skin lesions (Ficarra 1988). They are usually asymptomatic, but can produce obstructive symptoms such as difficulty in swallowing, loosening of teeth and pain.

Gastrointestinal tract lesions, which are usually asymptomatic, occur in almost 50% of patients with KS (Mitsuyasu 1993). They most commonly appear in the bowel, liver and spleen. They often appear as raised, red lesions and are not easy to biopsy because of their submucosal location.

Pulmonary KS is the most severe and life threatening form of AIDS-KS (Garay 1987). Dyspnea (difficulty in breathing) with or without fever and sometimes hemoptysis (coughing up blood) are the presenting symptoms of pulmonary KS. To definitively diagnose pulmonary KS, a transbronchial or open lung biopsy is necessary. Pulmonary lesions, however, are not usually biopsied because of the risk of bleeding. A chest radiograph can detect subtle, diffuse reticulo-nodular infiltrates and pleural effusion (fluid around the lung in the pleural space) (Mitsuyasu 1993).

STAGING AND RESPONSE

A discussion regarding KS staging and its use in assessing treatment response must occur before analyzing results from the various studies that have taken place for KS over the past 10 years.

Before 1989, there was no widely used and validated staging classification for Kaposi's sarcoma. It was not until July, 1988, that members of the AIDS Clinical Trials Group (ACTG) Oncology Committee came up with a comprehensive proposal for uniform evaluation, staging and response criteria for AIDS-related KS (Krown 1989). This is now standard for all ACTG KS trials. It has been suggested that the ACTG criteria "be used in all clinical trials in HIV-related KS if we are to build a consensus" (Volberding 1989). These staging and response criteria are not universally employed in non-ACTG KS trials.

Careful study of trials that pre-date 1988 indicate that at least three different staging classifications were being used (Krigel 1983; Mitsuyasu 1984; Vadhan-Raj, 1986). The very first, and now obsolete, four-stage KS classification proposed by Krigel and colleagues (Krigel 1983), took into account tumor extent (localized vs. general) and observed rate of progression. This classification was intended to stage patients with AIDS-KS along with those with classic and African KS. Most patients with AIDS-KS were, however, assigned to stages III or IV. Moreover, it did not take into account variables of immune status which appear to be important in AIDS-KS treatment response.

Mitsuyasu and Groopman's (Mitsuyasu 1984) four-stage system, specifically designed for AIDS-KS, was the first to stratify patients into two subtypes, A or B. Type (A) indicated the absence, and type (B) the presence, of "B" constitutional symptoms (unexplained fever, night sweats, more than 10% involuntary weight loss, or diarrhea persisting for more than two weeks); or opportunistic infections (OIs). Using this classification, Mitsuyasu not only noted a survival advantage in patients in tumor stages I and III, but also saw a marked survival difference when comparing KS patients with subtype (A) vs. subtype (B) (Mitsuyasu 1986).

The ACTG system went further to classify patients based on the clinical extent/placement of tumor (T), immune status/CD4 cell count (I) and assessment of HIV-related systemic illness (e.g., OIs/"B" symptoms/Karnofsky status) (S). Based on the composite score of the three categories, (T), (I) and (S), patients are scored as good risk (0) or poor risk (1). Thus, a patient with gastrointestinal KS, a CD4 count of 100, and no prior OIs or "B" symptoms would be staged T1, I1, S0.

Although patients are staged at entry into ACTG KS trials, they are not followed prospectively to determine survival. Five years after the implementation of this ACTG staging system, the ACTG Oncology Committee is now attempting a retrospective analysis of approximately 227 patients from past KS trials to determine the validity of their staging system. This will be an arduous task for the ACTG Oncology Committee because there is scant long-term follow up or survival data on most KS trial patients. This classification must be looked at prospectively to determine if the staging system is effective in determining treatment outcome and survival (Steven Miles, personal communication).

A group of Italian researchers recently completed a retrospective analysis of KS patients (reclassifying and restaging patients) using a staging system similar to the ACTG's T-I-S classification. They noted that (I) immune status/CD4 count, and (S) assessment of HIV-related systemic illness are accurate prognostic indicators of survival, but the extent of tumor (T) at baseline is not a major prognostic factor (Lawrence Kaplan, personal communication).

Krown and colleagues contended that scoring of responses in earlier clinical trials was "somewhat vague." (Krown 1989). Thus, attempting to make true comparisons of the efficacy of treatments based on clinical data before 1989 might be misleading.

While a complete response (CR) has generally been regarded as the disappearance of all lesions, past studies have not always specified their method for documenting a CR. For example, tumor biopsies were only conducted "in some patients" in the 1984 recombinant alpha-2 interferon trial conducted by Groopman and colleagues (Groopman 1984). A partial response (PR), which has generally been defined as 50% or more reduction in the number or size of lesions, was

often ambiguously worded in clinical trials from the early and mid 1980s. Volberding and colleagues (Volberding 1985), in their 1985 Vinblastine trial, never specified the criteria used for assessing the "significant" changes of lesion nodularity and pigmentation that would actually warrant a PR.

The ACTG's four separate response definitions for CR, PR, stable disease and progression were intended to ameliorate such ambiguity and vagueness. The "vagueness" is still present in some studies because: 1) making up a definition for response might make mediocre data look better; 2) people do not want to invest the time to actually use the ACTG response criteria or attempt to come up with something better. This vagueness was embarrassingly evident at the FDA's Oncologic Drugs Advisory Committee hearing on Vestar's NDA for Daunoxome in 1993. Vestar claimed that its research showed a 51% PR with Daunoxome for patients who were refractory or intolerant to standard chemotherapy regimens. The FDA, in its separate analysis of the data, lowered the PR rate to 18%. Humiliated by this separate data analysis, Vestar was then chided for rating patients with "breakthrough" lesions as partial responders. Ad hoc committee advisor Susan E. Krown, carefully explained that with breakthrough lesions, this "response to treatment cannot meet the definition." (The Pink Sheet, 1993)

In order to implement this ACTG staging and response criteria, a patient evaluation form was drafted to document the extent of the patient's disease. This form is completed at baseline and with each follow-up visit. In addition, a complete physical examination, including a chest x-ray, a biopsy for KS confirmation and a series of photographs should take place before the evaluation process begins. The evaluation process that occurs while the patient is on drug can be subjective.

Originally, Krown and colleagues (Krown 1989) suggested that the "exact number" of lesions not be counted, but be classified (range counting) into one of four categories: 1 = 0; 2 = 10 or less; 3 = 10 to 50; 4 = more than 50. However, with the commencement of ACTG 163, the Oncology Committee mandated that all lesions must be counted on a patient's body with 50 lesions or less. If the patient has over 50 lesions, then a designated area of the patient's body was to be selected (i.e., the back) where all of those lesions will then be counted.

There are some physicians who prefer the older range counting method and feel that it is adequate because it is "impossible to count the exact number of lesions -- especially when there are more than 25 -- on a patient's body." (Alvin Friedman-Kien, personal communication) Others maintain that it is possible to count lesions at each clinic visit, especially when there are fewer than 50 -- "We do this all the time," according to Susan Krown.

This will be one of the many crucial issues that the FDA's Oncologic Drugs Advisory Committee (ODAC) must realize if they are to rationally evaluate KS NDAs. Besides the response rates, ODAC needs to also consider quality of life, complications and toxicity when determining the efficacy and usefulness of the KS agent.

Prognosis and the Parameters Predictive of Response

In 1994, we now know that there are a variety of factors that help predict a patient's response to therapy. In a retrospective analysis of 688 patients with AIDS-KS at UCLA Medical Center from 1981 to 1990, Miles and colleagues were able to identify four baseline variables that best predicted survival: CD4 cell number, the volume of red cells (erythrocytes) in the blood, the number of KS lesions, and body mass index (Miles: unpublished data). Myskowski and colleagues

have also documented the location of a patient's lesions is a predictor of a patient's response to therapy. They also documented that a KS patient's CD4/CD8 ratio can predict survival (Myskowski 1988). Using this ratio as a prognostic variable for patients with KS as their first AIDS defining illness, Myskowski and colleagues reported: patients with normal ratios (> 1.7) had a median survival time of 49 months; those with ratios from 1.0-1.7 had 29 months; and those with ratios < 1.0 had 14 months.

Other factors that correlate with overall survival include past or present OIs, the presence of "B" constitutional symptoms and the extent of disease (Mitsuyasu 1986; Taylor 1986). Lesions which appear after the onset of an OI, or during an OI, follow a more aggressive course and may be difficult to treat (Buchbinder 1992; Donald Abrams, personal communication).

A host of other immunologic activation markers which include beta 2 microglobulin, neopterin, in vitro proliferative T-cell response, levels of endogenous interferon, and IL-6 level have all shown to have some prognostic value (Taylor 1986; Vadhan-Raj 1986; Krown 1991). Most recently, Martinez-Maza and colleagues (Martinez-Maza 1993) at UCLA documented that high levels of IL-6 were identified retrospectively in HIV positive patients 6 months to a year before they developed their first KS lesion.

With more conclusive pathogenesis research, it will be essential to measure cytokine levels (IL-6, IL-1, TNF, GM-CSF and alpha interferon) at baseline before initiating treatment of experimental KS therapies. If certain therapies are aimed at inhibiting various cytokines, which many do in vitro, then baseline and subsequent measurements from lesion biopsies may assist in detecting activity.

STANDARD OF CARE TREATMENTS

Treatment should be individualized based on the prognostic parameters and the desired effect of therapy. Many researchers believe that immediate treatment is not necessary at the first episode of KS with a few small lesions and that a "watchful waiting" period would be in order to determine the course of the disease (Levine 1993).

During this initial observation period, a biopsy confirmation is crucial for many reasons other than histological confirmation (Tappero 1993 b). First, a biopsy confirmation will undoubtedly be needed when a patient is later referred for radiation therapy, chemotherapy, or volunteers for a clinical trial. Secondly, a tumor biopsy is in order to avoid confusion with bacillary angiomatosis. Lastly, biopsy reports from pathology laboratories go into tumor registries which are major sources for compiling surveillance data and tracking disease trends.

If the patient has rapidly progressing KS, the physician should take notice and thoroughly check for previously undiagnosed OIs. Sometimes KS appears aggressive and is followed by the occurrence of OIs (Donald Abrams, personal communication).

However, if the patient begins with only a few lesions, this does not mean that a primary care physician should do nothing. The trauma and disfigurement of the KS lesion, a social stigma and constant visual reminder of one's HIV disease, can take a serious psychological toll on patients. Indeed, one clinician contends, "a patient's psychological distress may bear no relationship to the actual extent of cutaneous involvement by KS." (Schwartz 1992) Physicians must

explain to their patients the various courses the disease might take and assure them that there are various treatment options at the different stages that can be palliative, limit morbidity and possibly prolong survival. In fact, treating a patient with asymptomatic indolent lesions might be appropriate for some simply for its psychological benefit (Miles: in press).

Local Therapies

Cryotherapy

Liquid nitrogen cryotherapy is often used by dermatologists for the palliation of minor, yet cosmetically unacceptable lesions on the face, neck and hands. Cryotherapy has been shown to be safe and relatively inexpensive. Patients generally receive two freeze-thaw cycles of liquid nitrogen, administered with cryospray for 30 to 60 seconds in each cycle.

In 1991, Tappero and colleagues (Tappero 1991) from San Francisco General Hospital conducted a 20 patient, non-controlled, phase II efficacy and toxicity trial of liquid nitrogen for cutaneous KS. Complete responses in 80% of the treated lesions were obtained and lasted from six weeks to six months. The best cosmetic results were seen in macular and papular lesions less than 1 cm in diameter. Treatment was repeated at three week intervals, and on the average, patients received three treatments per lesion with a mean follow up time of 11 weeks. Minor pain and blistering did occur, but there were no secondary infections. In addition, a response to cryotherapy had no bearing on the patients' CD4 counts, presence of "B" constitutional symptoms, or previous treatment with chemotherapy. Patients with prior OIs, however, did not respond as well to therapy.

Cryotherapy does give some cosmetic benefit, but this is often accomplished by superficial scarring. The scarring results because the liquid nitrogen basically freezes/burns the lesions. Some patients might find this better than nothing at all, but they should realize that KS is often persistent in the deep reticular dermis of the treated lesion (Tappero 1993 b). Cryotherapy is also mainly recommended for fair skinned individuals because liquid nitrogen causes hypopigmentation leaving a flat, white scar (Krown 1992 a). This white scarring may be more noticeable than the original KS lesion itself for individuals with dark skin.

Because lesions usually blister and then form a crust, it has been strongly advised (Tappero 1993 b) that patients keep the treated site covered until well healed because HIV has been found in blister fluid (Supapannachart 1991).

Intralesional Cytotoxic Chemotherapy

Intralesional vinblastine has also proven to be an effective treatment for the palliation of minor lesions. Unlike liquid nitrogen, vinblastine can be used for bulkier lesions and symptomatic oral lesions.

Newman and colleagues (Newman 1988) conducted an uncontrolled, 15 patient trial in which they injected vinblastine into a total of 190 lesions. Each lesion was injected with 0.1 - 0.2 mg of vinblastine every two weeks. There was a complete resolution (flattening or depigmentation) of 25 lesions (13%) in 4 patients, a partial resolution of 149 lesions (78%) in 8 patients, and no response was seen in 16 treated lesions (8%) in 3 patients. Local pain from the injections was noted in all patients, and 90% had minor skin irritation.

Recommended doses of intralesional vinblastine for cutaneous lesions are: 0.1 mg (0.5 ml of a 0.2 mg/ml solution) injected per square centimeter of lesion; and for those not responding to 0.1 mg/cm², incremental doses to a maximum of 0.2 mg/cm² can be used (Tappero 1993 b).

Both studies -- and other practicing physicians -- have noted that while intralesional vinblastine is efficacious, there is often pain lasting one or two days after injection, and the post-inflammatory hyperpigmentation (brown spots) that occurs might be cosmetically unacceptable to light and fair skinned individuals (Timothy G. Berger, personal communication). Other toxicities not uncommon to intralesional vinblastine include a transitory flu-like syndrome, intense edema (swelling around the treated lesion), and erythema (blotchy red patches). Most recently, researchers warned against using intralesional vinblastine around thick hair-bearing sites such as the eyebrows and near the hairline because alopecia (baldness) might occur and also caution against intralesional use near large peripheral nerves to avoid mono-neuropathy (Tappero 1993 a).

Symptomatic oral lesions also respond well to intralesional vinblastine. Epstein and colleagues (Epstein 1989) completed a 10 person trial of intralesional vinblastine for KS of the palate. One lesion was treated while another lesion was used as a control. At baseline, most of the patients had concomitant oral infections, including hairy leukoplakia, candidiasis and ulcerated gingivitis.

Patients in this study received one or two intralesional injections of vinblastine (0.2 mg/mL, at 0.1 mL per 0.5 cm² of KS lesion). The mean reduction of the palatal lesion area after one or two treatments was 63%. All patients were noted to have responded to treatment. Four had a "significant" response, two had a partial response, and two had a "minor" response. There was increased size in seven out of the ten control lesions. There was no increase in the oral opportunistic infections. Mild to moderate pain was noted in all patients which lasted one or two days.

In a larger and more recent 42 patient non-controlled trial of intralesional vinblastine for oral KS, Epstein noted a greater than 50% reduction in the lesions of 74% of the patients (Epstein 1993). For patients not lost to follow-up, the mean duration of response was 4.25 months.

An alternative to intralesional vinblastine for oral KS may be the injection of 3% sodium tetradecyl sulfate (Sotradecol) which is commonly used in eliminating vascular lesions of the oral tissue (Goebel 1976). While this agent is only being used by a handful of physicians to treat oral KS, Drs. Lucatorto and Sapp of the School of Dentistry at UCLA recently published results of a preliminary study of injecting Sotradecol into oral KS lesions (Lucatorto 1993). In treating 15 lesions in 12 patients with one or two injections, they noted 8 complete responses and 4 partial response with no recurrence for as long as 18 months. Unlike intralesional vinblastine, initial injections of Sotradecol caused ulcerations in all treated lesions, but healing began by the middle of the second week. Best results were obtained in lesions that were 2.6 cm or less in size.

Lucatorto and colleagues are in the process of planning a comparative efficacy trial of 3% sodium tetradecyl sulfate (Sotradecol) vs. intralesional vinblastine for oral KS (Frank M. Lucatorto, DDS, MS, personal communication).

Intralesional Biologic Response Modifiers Tumor Necrosis Factor-alpha (TNF-alpha)

Initial in vitro studies of TNF-alpha demonstrated a vascular inhibitory effect on endothelial cells (Sat 1986) and also induced necrosis of solid transplantable tumors (Carswell 1975). TNF-alpha was then tried in the late 1980s as a therapeutic modality, both intravenously and intralesionally, for KS. Aboulafia and colleagues (Aboulafia 1989) at UCLA tested intravenous recombinant TNF-alpha in a five patient study. All five patients receiving TNF-alpha intravenously had some progression in their lesions. The noted toxicities were fatigue and arthralgia (pain in the joints).

Lesion reduction was seen in a 27 patient, double-blinded, randomized, placebo-controlled study of recombinant intralesional TNF-alpha conducted by Kahn and colleagues at San Francisco General Hospital (Kahn 1989). Each patient had one lesion injected with TNF-alpha and one lesion injected with saline as a control. Of 16 evaluable patients, 15 showed response (a reduction in the cross-sectional area of the TNF-injected lesion) to therapy compared with a 7% response in the placebo controlled lesions. Of the TNF-alpha treated lesions, there were 3 CRs, 5 PRs, and 8 minor responses. Because of the toxicities observed -- fever, rigors and chills -- and the lack of antitumor effects in non-injected lesions, the investigators said they doubted the usefulness of intralesional TNF-alpha as a treatment for KS.

Interferon-alpha (IFN-alpha)

Intralesional recombinant interferon-alpha is still considered an experiment treatment for cutaneous KS (Tappero 1993 b). In a 5 patient, placebo-controlled trial, Sullis and colleagues (Sulis 1989) injected 3 to 5 million units of recombinant IFN-alpha-2b three times a week for four weeks into skin and oral lesions. There was a complete resolution of all lesions treated, whereas no response was seen in the untreated lesions. It should be noted that two of the five treated patients had previously been receiving systemic IFN for four month with no results.

Laser Therapy Various kinds of laser therapy -- argon, carbon dioxide, and pulsed-dye (PDL) -- have been used for cutaneous and oral KS over the past years (Wheelard 1985; Tappero 1992). The moderate response rates achieved in treating AIDS-KS using these three types of lasers have never been acceptable in light of the cost and time consuming nature of the treatment. There have also been reports of infectious virus particles from laser smoke (Baggish 1991).

A recent 15 patient study of PDL conducted by Tappero and colleagues (Tappero 1992) at San Francisco General Hospital documented a complete or partial response of 44% (17 of 39) for treated lesions. There was an 18% response rate (7 out 39) for the untreated control lesions. After 12 weeks, all treated lesions recurred. Thus, the investigators concluded that PDL should not be recommended for AIDS-KS.

A new approach to laser therapy has come about with the use of photodynamic therapy (PDT) for AIDS-KS (Schweitzer 1990; Hebeda 1993). Safety and efficacy trials are currently underway at San Francisco General Hospital and Roswell Park Cancer Institute in Buffalo. The Buffalo group invented PDT 15 years ago and have been using it for a myriad of cancers.

Bernstein and colleagues (Bernstein 1994) at Roswell Park Cancer Institute recently completed a 10 patient, PDT pilot study. Of 6 evaluable patients, 5 had complete responses for a minimum period of 60 days. The remaining patient had a

"mixed" response and was retreated to a complete response for a period of 80 days. No significant toxicities or change in CD4 counts was noted.

Roswell Park is currently running a phase I/II trial which consists of injecting Photofrin, a light sensitizing chemical into the vein, waiting two or three days, then zapping the lesions -- which have a 5 fold retention of Photofrin over normal skin -- with an argon laser. They are observing significant response rates that are lasting up to 8 months in some patients (Thomas Mang, personal communication). At higher doses, the hyperpigmentation goes away and has shown beneficial, cosmetic results in facial lesions.

The San Francisco group is substituting Tin Etiopurin (SnEP2), a newer light sensitizing chemical, in place of Photofrin. They are trying to determine the optimal waiting time, after injecting Tin Etiopurin, to initiate laser therapy (Margaret Whitfeld, personal communication). It is important to stress that Photofrin and Tin Etiopurin make the skin extremely sensitive to light. Thus, exposed normal skin can develop a severe sunburn-like reaction.

Radiation Therapy

AIDS-KS lesions respond well to radiation therapy (RT) but response rates and time to remission are significantly less than those seen for classic KS. In 1981, Nisce and colleagues (Nisce 1982) at Memorial Sloan-Kettering in New York studied 20 patients with classic KS using 400 rads (100 rads = 1 Gy) of subtotal or total skin electron beam therapy once a week for six weeks and noted an 85% CR with a median duration of 48 months. The duration of remission seen in AIDS-KS can be as short as 6 months and as long as 3 to 4 years (Nisce 1993).

RT may be necessary and most beneficial for certain KS lesions on various parts of the body including: large KS tumors or plaques of the face, periorbital edema (swelling around the eyes) and lesions on the eyelid, lesions on or around the penis, and painful lesions on the weight-bearing areas of the body, such as the sole of the foot. RT is commonly used to reduce painful lymphadenopathy (swelling of the lymph nodes) and edema (swelling) on legs and the soles of their feet that inhibit mobility. While in agreement with using RT in these settings, some researchers warn against believing that RT is "the answer" for KS-associated lymphadenopathy and edema. Late complications of RT, include fibrosis, ulceration, and superinfection. Close monitoring of the areas is also recommended and crucial because the lymph nodes might be filled with KS or have an underlying infection, and over radiating might aggravate the edema and cause further fibrosis (Patrick Swift, personal communication).

Attempting to identify the best dosing regimen, Bernson and colleagues (Bernson 1990) studied 187 AIDS-KS patients at UCSF comparing 8 Gy in a single fraction (one dose) to 15 to 40 Gy in 5 - 10 fractions (doses over a period of time). Responses were defined as a complete flattening of a lesion or a decrease in the dimension of the lesion to at least 50% of the pretreatment size with decrease in pigmentation. There was a response to treatment in over 90% of the treated lesions with a median time to progression of 21 months. There was no difference in the response rates regardless of fractionation regimen used. The severe reactions, such as blistering and pain, which occurred with 17% of the treated fields were mostly seen in the smaller fractionated doses. The results from this study, and the results from another study in Amsterdam (de Wit 1990), have led some researchers to conclude that single fraction of 8 Gy is most effective for large areas because it is more time efficient, cost effective and limits severe reactions.

The treatment of symptomatic and asymptomatic oral lesions has been debated for a number of years. Nisce, who goes as far as saying, "RT of the oral mucosa had rather disastrous results," (Nisce 1993) was noted for advocating against using RT for oral KS (Lourdes Nisce, personal communication). The dead tissue that falls off after oral RT can cause severe pain and malnutrition because adequate normal tissue does not grow back quickly enough. It often takes 2 to 3 weeks to resume normal eating which can result in weight loss of 10% to 15% (Nisce 1993). Also RT of oral mucosal lesions often induces severe mucositis (Krown 1992 a).

Dr. Nisce has changed her mind about the use of RT for oral KS because of preliminary findings from a study she is conducting in which the inflamed oral lesions are premedicated with Oratec Gel (MGI-209), a topical benzocaine anesthetic (Lourdes Nisce, personal communication). Nisce has seen excellent results in the patients treated with MGI-209 before RT, and is then able to give daily low doses of 1.6 to 1.8 Gy until maximum doses of 25-30 Gy are reached. Patients are able to eat after treatments and there is no apparent weight loss (Nisce 1993).

Systemic Therapy

Interferons

Interferons have been extensively studied and used to treat AIDS-KS since the early 1980s (Krown 1983). We have learned more about interferons -- their effectiveness in certain patient populations, toxicity profile and possible use in combination with nucleoside analogues -- than any other anti-KS medication. Interferons became a logical therapeutic candidate to treat KS because early trials demonstrated its immunoregulatory, anti-proliferative and antiviral activity, (Borden 1981, 1982). Interferons can inhibit the replication of HIV in vitro (Poli 1989) and there is evidence that suggests interferons might inhibit lesion-associated angiogenesis (Sidky 1987).

IFN-alpha-2a (Roferon-A made by Hoffmann-La Roche) and IFN-alpha-2b (Intron A made by Schering-Plough) are approved by the Food and Drug Administration (FDA) for KS in patients with CD4 counts over 200/mm³. No other medication has been "specifically" approved for the treatment of KS. The two agents were reviewed by the FDA's Center for Biologics, and not by its Divisions of Antiviral or Oncologic Drugs.

It is difficult to compare the available data from the many interferon KS trials over the years due to the varying sizes of cohorts, the absence of uniform staging systems, the different preparations of interferons and the myriad of various dosing regimens (Rozenbaum 1990). Moreover, there has not yet been a large, randomized, placebo-controlled trial of IFN-alpha as a single agent for KS (Miles, in press). Except for one French study (Rozenbaum 1990) that followed patients from 1 to 6 years, follow-up on most trials has been short. Thus, we have little if no long-term efficacy data on the use of interferons for KS.

In most studies, IFN-alpha, as a single agent, given intramuscularly or subcutaneously in moderate to high doses (at least 20 million units per square meter body-surface area) has been shown to induce regression of KS lesions in roughly 30% of patients (Lane 1988; Real 1986; Evans 1991; de Wit R 1988). Response rates under 10% were seen with a low-dose regimen of 1.5-2.0 MU/m² (about 3 MU) (Real 1986).

In many of these trials, IFN-alpha response rates were higher for those patients who had CD4 counts of over 200, no previous OIs and no "B" symptoms (Lane 1988;

Evans 1991; de Wit 1988). A patient's CD4 count is undoubtedly the major predictor of IFN-alpha response. An IFN-alpha trial conducted by Lane and colleagues (Lane 1988) revealed that the 5 patients with over 400 CD4 cells had substantial reductions in tumors whereas none of the 7 patients with under 150 CD4 cells showed a response.

There is little published information on the duration of response with IFN-alpha. A study conducted by Real and colleagues (Real 1986) determined that the median response duration was 24 months for complete responders and 11.5 months for partial responders. In a long-term follow-up study (followed 1 to 6 years) of 120 AIDS-KS patients treated with IFN-alpha, Rozenbaum and colleagues (Rozenbaum 1990) concluded that the median survival time for all patients from onset of treatment was 794 days; 1,723 days for responders and 375 for non-responders. Both studies claim that "responders" (patients with a CD4 count of over 200 at baseline) to IFN-alpha had a greater probability of survival. Moreover, Evans and colleagues (Evans 1991) stipulate that even among patients with a CD4 count of over 200, those who responded to therapy (had a regression of their tumors) had a distinct survival advantage.

The FDA approved recommended dose of recombinant IFN-alpha-2a (intramuscularly or subcutaneously daily) as a single agent is 36×10^6 U daily. And for IFN-alpha-2b, the recommended dose is 30×10^6 U/m² subcutaneously three times a week.

IFN-alpha has also been noted for its toxicities which include: a "flu-like" syndrome characterized by myalgia, fever, fatigue and chills, anorexia, weight loss, nausea, diarrhea, confusion, hematological toxicities such as neutropenia and anemia as well as elevated liver enzymes (Pluda 1993 a). These symptoms are germane to IFN-alpha treatment for KS but might be exacerbated by overlapping or undiagnosed OIs. These symptoms can sometimes be reduced (or eliminated) by gradual dose-escalation, or in some cases, a temporary discontinuation of treatment and subsequent dose reduction (Krown 1992).

Interferon with Nucleoside Analogues

Zidovudine (AZT) alone is not an effective drug for the treatment of KS (Valentine F, et al., unpublished ACTG 001 data; Lane 1989; de Wit 1989). Even though AZT induced a significant rise in CD4 cells, there were few or no tumor responses (de Wit 1989). Possible reasons for AZT's lack of efficacy on tumor regressions are (1) AZT might not suppress HIV replication sufficiently to inhibit the release of the many cytokines involved in tumor growth and (2) various co-factors other than HIV play a more substantive role in the pathogenesis of KS (Krown 1992 a).

In vitro studies, however, have demonstrated a synergistic suppression of HIV replication when IFN-alpha and AZT were combined (Hartshorn 1987) as well as a synergistic antiviral activity in mice infected with a murine retrovirus (Ruprecht 1987, 1990). These findings gave rise to several clinical trials evaluating this combination.

Phase I and II combination AZT/interferon alpha trials which demonstrated response rates between 40% and 50% (Kovacs 1989; Krown 1990; Fischl 1991) were substantially higher than those seen with high dose IFN-alpha alone. A significant percentage of patients with CD 4 counts below 200 (as high as 30%) responded, and for the first time, low dose IFN-alpha (under 20 million unit) demonstrated antitumor activity. Because of the overlapping myelotoxicities of these agents, it was no surprise that neutropenia (as high as 57%) (Kovacs 1989) was the major dose limiting toxicity.

The use of colony stimulating factors (G-CSF and GM-CSF) has helped to considerably lessen the neutropenia seen when IFN-alpha and AZT are used in combination (Scadden 1991; Krown 1992 b). One study conducted by Scadden and colleagues (Scadden 1991) administered GM-CSF to 19 of the 26 patients (66%) who developed an absolute neutrophil count (ANC) below 1,000 ml. (This is not so shocking considering patients were receiving a high dose of 1,200 mg a day of AZT.) All patients who went onto GM-CSF had a prompt ANC increase, but there was no difference in tumor response or CD4 count for those who went onto GM-CSF versus those who didn't. Krown and colleagues (Krown 1992 b) noted that GM-CSF helped maintain the patients' ANCs. The major side effects were "flu-like" symptoms including malaise, fever, and fatigue. These non-hematologic toxicities prevented major dose increases of IFN-alpha and AZT.

Most oncologists -- in every day practice -- use G-CSF over GM-CSF to ameliorate the neutropenia caused by IFN-alpha. Although G-CSF's effects have never been proven in an IFN-alpha clinical trial, oncologists prefer it because of the impression that "flu-like" symptoms from GM-CSF and IFN-alpha combined are sometimes too overwhelming for patients (Susan E. Krown, personal communication).

IFN-alpha is currently being studied in combination with ddI. ACTG 206 is testing ddI with low dose (1 MU) or moderate dose (10 MU) IFN-alpha-2b. The principal Investigator noted that responses are being seen when 1 MU daily of IFN-alpha-2b is used in combination with 200 mg of ddI twice a day (Susan E. Krown, personal communication).

More recently, studies have concluded that interferon may in fact alter certain cytokines and growth factors involved in the pathogenesis of KS. Fidler and colleagues (Fidler 1994) found the IFN-alpha and IFN-beta decrease bFGF in cultured tumor cells at the protein and message level. Tilg and colleagues (Tilg 1993) have demonstrated that IFN-alpha increases the circulating levels of the IL-1 receptor without an increase in IL-1 in the plasma of healthy patients and those with chronic hepatitis C. IFN-alpha can also reduce the accumulation of mRNA of TNF-alpha and IL-6 and thus interrupt their autocrine production in hairy cell leukemia and B-chronic lymphocytic cells (Heslop 1990).

Systemic Chemotherapy

There are many myths and truths about systemic chemotherapy for the treatment of KS. Many of the preconceptions people have about chemotherapy are based on the experiences in generally older, sicker people who received high dose chemotherapy (often different agents) without the benefit of colony stimulating factors. It should be noted that the various cytotoxic (cell killing) chemotherapeutic agents used -- as single agents or in combination -- to treat KS have been around longer than AIDS and have been used for many years to treat the myriad of cancers.

It took oncologists a few years to understand what the safe and efficacious doses were for patients with HIV. Hence, patients with KS early on in the epidemic were receiving doses of chemotherapy that were highly toxic (Alvin Friedman-Kien, personal communication). It is now 1994. Oncologists who treat the various AIDS-related malignancies now know -- and basically tend to agree on -- the doses that are safe and efficacious for each cytotoxic agent used to treat KS.

For patients with widespread cutaneous or visceral KS, systemic (whole body) treatment with cytotoxic agents is the treatment of choice (Miles: in press).

Excellent response rates with manageable side effects have been seen with various single agent regimens or combinations of: vincristine, vinblastine, doxorubicin (adriamycin), bleomycin and etoposide (VP 16). Having these agents to choose from has led oncologists, such as Steve Miles, to proclaim, "the [mere] observation of patients with progressive KS in the setting of HIV infection is no longer acceptable." (Miles: in press).

As with most other treatment options for KS, it is difficult to compare the advantages of one cytotoxic agent over another because randomized, controlled trials have not been conducted and most did not use a uniform response or staging criteria (Krown 1992 a; Miles: in press). There are two reasons for this: 1) researchers fully understand that it would be unethical to attempt -- and impossible to recruit patients for -- a placebo-controlled trial for patients with symptomatic, visceral KS; 2) most of these single agent and combination cytotoxic agent KS trials were completed and published before it was standard practice to use the 1989 ACTG staging and response criteria.

In a 38 patient non-randomized, non-controlled, dose-escalating, intravenous vinblastine study, Volberding and colleagues (Volberding 1985) noted a 30% response rate; one complete response, nine partial responses, 19 with stable disease, and 9 who progressed. Administered once weekly at a starting dose of 4 mg. (median dose of 6 mg), the median time to response was 5 weeks with a median response duration of 13 weeks. The hematological toxicities were minor and some nausea was noted. 30% of the patients developed OIs during the trial.

Single agent vincristine is also sometimes used to treat symptomatic cutaneous and visceral KS, particularly in patients with low platelet counts. Intravenous vincristine was studied in 23 patients in an open, non-controlled trial conducted by Mintzer and colleagues (Mintzer 1985). Of 18 evaluable patients, 11 (61%) obtained a partial response and 7 had a "minor" response to therapy. The median duration of the partial responders was over four months. The major toxicity reported was peripheral neuropathy, which required dose reduction in 6 patients and a discontinuation of treatment in 2 patients. 5 patients developed OIs during the trial.

Studies of vinblastine (2-4 mg) alternating weekly with vincristine (2 mg) have been conducted to attenuate the toxicity of each drug. Kaplan and colleagues (Kaplan 1986) developed an alternating weekly vinblastine (0.1 mg/kg) and vincristine (2 mg) regimen for their study that modified doses for myelosuppression or peripheral neuropathy. Of 21 evaluable patients, they noted: one complete response, eight partial responses, seven patients with stable disease, and five with progressive disease. The median time to response was 13 weeks with a median response duration of over nine months. Six patients required dose modification due to peripheral neuropathy. Hematologic toxicity was minimal.

Lassoued and colleagues (Lassoued 1990) used single agent bleomycin either intramuscularly or intravenously to treat 60 patients in an uncontrolled trial. 30 patients received 5 mg/day intramuscularly for 3 days every 2 or 3 weeks, and 30 patients received bleomycin by slow continuous infusion (6 mg/m²/day for 4 days every four weeks). 40 of the patients also received AZT (200-1200 mg/day) in combination with bleomycin. 29 (48%) achieved a partial response and 18 (30%) had stable disease. No significant differences were seen in response rates when comparing the intramuscular and intravenous routes of administration. 23 (38.3%) of the patients died while on the study. Toxicities consisted of fevers, mild myelosuppression and some cutaneous toxicity.

A 1992 open, non-controlled, French study (Caumes 1992) evaluating the efficacy of intramuscular bleomycin on mucocutaneous KS in 70 patients noted a 74% overall response rate; two complete responders and 50 patients achieving a partial response. Using 5 mg/day for three consecutive days every two weeks, the median time to treatment response was 4 weeks, but the median time to relapse was 10 weeks.

Adriamycin (doxorubicin) has shown some efficacy used as a single agent. ACTG 006 was a phase II trial (Fischl 1993) of Adriamycin given intravenously to 53 chemotherapy naive patients at weekly doses of 15 mg/m². Of 50 patients evaluable for tumor response, there were 5 (10%) partial response, 32 patients (64%) had a "minor response", 12 patients (24%) had no change, and one patient (2%) progressed. Response duration was short, ranging from 4 to 14 weeks. The major toxicity, seen in 71% of the patients, was moderate to severe neutropenia. 18% of the patients had to discontinue therapy because of severe neutropenia.

Etoposide (VP-16) has also shown some efficacy and is often used because it can be taken orally. Laubenstein and colleagues (Laubenstein 1984) studied intravenous etoposide (150 mg/m² for three days every four weeks) on 41 chemotherapy naive patients with limited KS and no prior OIs. Response rates were high (12 CR and 19 PR), however, neutropenia and gastrointestinal toxicities were common and alopecia (baldness) was observed in all patients.

A 29 patient, phase I, dose-escalating, oral VP-16 trial (ACTG 110) was recently completed. Of 25 patients evaluable for response, 9 patients (36%) achieved a partial response, 14 (56%) had stable disease, and 2 patients (8%) progressed (Josephine Paredes, in press). The major toxicity was mild to moderate neutropenia. Peripheral neuropathy, nausea, and alopecia were also documented.

Very little efficacy data exists on the use of 4'-epirubicin for the treatment of KS. One phase II study of 4'-epirubicin (Shepherd 1991) in 26 patients with poor-risk noted an overall 42.3% response rate (1 CR and 10 PR) with a median time to relapse of 22 weeks. The dose-limiting toxicity was neutropenia.

Combination Chemotherapy

Combination chemotherapy regimens can be tailored for each patient individually to enhance efficacy and reduce toxicity. In an attempt to test the efficacy and toxicity of single agent versus combination therapy, Gill and colleagues (Gill 1991 c) conducted a randomized study of 61 patients comparing low-dose adriamycin alone (31 patients) versus adriamycin, bleomycin and vincristine (ABV) (31 patients). 29 patients were evaluable for response in the Adriamycin arm as were 24 patients from the ABV arm. An overall response rate of 88% was obtained in the ABV arm; 9 (38%) complete responses and 12 (50%) partial responses. The Adriamycin arm yielded a lower overall response rate of 48%; one (3%) complete response and 13 (45%) partial responses. The median survival was 9 months for both arms. Neutropenia occurred in 34% of the patients receiving Adriamycin and in 52% of the patients in the ABV arm.

19 of the 31 patients who failed or did not respond to Adriamycin alone were able to roll-over into the ABV arm or receive BV. Four of the eight patients receiving BV responded, as did nine of the 11 patients receiving ABV.

To avoid the myelotoxicity associated with Adriamycin, G-CSF is now frequently used to bolster a patient's ANC. The use of G-CSF has led some oncologists to believe that "neutropenia is a thing of the past." (Donald Northfelt, personal communication)

The use of a BV combination regimen is also considered a safe and effective alternative for those patients who can not tolerate Adriamycin. Gompels and colleagues (Gompels 1992) completed a retrospective case analysis studying bleomycin (30 mg over an 18 hour infusion) and vincristine (2 mg) (or vinblastine if peripheral neuropathy developed) in 46 chemotherapy naive patients with poor risk factors (72% had previous OIs and all had CD4 counts under 200). 26 patients (57%) achieved a partial response, 16 (35%) had stable disease and 4 (9%) progressed. The mean duration of response was only 2 months and survival was 8 months from start of therapy. Peripheral neuropathy was observed in 13 (28%) of the patients.

A non-randomized study conducted by Ireland-Gill and colleagues (Ireland-Gill 1992) compared ABV versus BV in 99 patients. 30 patients received BV and 69 received ABV. The BV arm had an overall response rate of 76% (7 CRs, 16 PRs) compared with a response rate of 81% (20 CRs, 36 PRs) for patients who received ABV. While high response rates were seen, most patients relapsed 2 months after treatment was stopped. The median survival time for these patients was just under one year.

28 out of the 99 patients underwent pulmonary function testing while on study to ascertain if cumulative doses of bleomycin induced pulmonary dysfunction. Investigators noted that there was significantly greater decline in the carbon monoxide diffusion capacity (DLCO) in patients who received more than 100 cumulative units of bleomycin. While none of these patients (who had received cumulative doses between 10 and 313 units of bleomycin) developed clinically significant pulmonary toxicity, investigators still concluded that any patient receiving over 100 cumulative units of bleomycin should have their pulmonary functions closely monitored.

Combination cytotoxic agents yield the most promising results for patients with pulmonary KS. Gill and colleagues (Gill 1989) evaluated several drug regimens (A versus BV versus ABV) in 20 patients with pulmonary KS. The 10 patients receiving ABV had an overall 80% response rate (4 CRs, 4 PRs); the 3 patients receiving BV had a 100% response rate (3 CRs); and the 7 patients receiving single agent Adriamycin only had a 14% response rate (1 PR). Out of the 20 patients, the median survival for the 12 responders was 10 months (range three to 31+ months) versus 6 months for the 8 non-responders. (It is important to note that 6 of the 8 non-responders were receiving only single agent Adriamycin.)

Gill and colleagues noted that pleural effusion (fluid surrounding the lungs, in the pleural space) and a CD4 count below 100 were the most significant predictors of shorter survival. It is also interesting that the DLCO level in patients increased while on study which was not the case in the later trial conducted by Ireland-Gill.

The median survival of 10 months (for responders) for patients in this trial is significantly higher than previously seen in other trials. In an older systemic chemotherapy trial of patients with pulmonary KS, Garay and colleagues (Garay 1987) noted a median survival of 6 months. And, in a trial that administered either radiation, IFN-alpha, or chemotherapy to 11 patients with pulmonary KS, Meduri and colleagues (Meduri 1986) only noted a median survival of 3.8 months.

Many researchers have hoped that IFN-alpha would be suitable for maintenance therapy after cytotoxic chemotherapy. At least two studies (Gill 1990, 1991 a) have shown that IFN-alpha did not provide additional antitumor effect or prolong

response duration. IFN-alpha's lack of activity here should not be surprising considering these patients' studied mostly had a CD4 count of less than 200 and prior OIs.

GM-CSF and G-CSF have become an adjunctive part of various cytotoxic regimens to ameliorate neutropenia. Trials have been conducted -- primarily with GM-CSF -- to determine whether such agents can limit neutropenia and allow patients to receive full doses of cytotoxic agents on schedule. In a phase I trial conducted by Gill and colleagues (Gill 1992), GM-CSF at a dose of 250 mcg/m² produced a cyclic increase in granulocyte counts in patients receiving ABV. At doses of 500 mcg/m², however, GM-CSF induced fever, fatigue and diarrhea.

Such toxicities have not been found with G-CSF. It may be possible to increase the maximum tolerated doses of ABV if G-CSF can prevent neutropenia without inducing additional non-hematologic toxicities (Miles, in press). In a recent trial of DOX-SL (liposomal encapsulated doxorubicin) (Sandor 1993), G-CSF was administered to 24 of the 33 patients whose ANC dropped below 1,000. G-CSF boosted the ANC back up, and the rate of bacterial, viral and fungal infections was also significantly reduced: 18 infections in 106 cycles with G-CSF (17%) vs 35 infections in 120 cycles without G-CSF (29%) (p < 0.05).

Combination Chemotherapy with Nucleoside Analogues

Most trials evaluating the combination of single agent cytotoxic therapy and AZT have noted adequate responses but high hematologic toxicity. There are studies evaluating the efficacy and toxicity of AZT with combination cytotoxic agents, however, few have been published. Rarick and colleagues (Rarick 1990) in a 12 person trial of BV with varying doses of AZT (400 mg a day or 800 mg a day) noted an 83% response rate (4 CRs, 6 PRs). The investigators noted that the 400 mg/day dose of AZT (compared with 800 mg/day) was as active and less toxic.

Preliminary results from a phase I/II trial of ABV with ddI or ddC (ACTG 163) (Mitsuyasu 1993) revealed that toxicities are minor with the nucleoside analogues (and probably due to ABV therapy). From the first phase of the trial, which accrued 29 patients (15 ddC and 14 ddI), two complete responses and 13 partial responses have been achieved so far. Complete results will be available in late 1994 or early 1995.

EXPERIMENTAL TREATMENTS FOR KAPOSI'S SARCOMA

There are more experimental drugs for KS in clinical trials in 1994 than ever before. Some trials are looking at IFN-alpha and cytotoxic agents -- usually in combination with AZT, ddI and ddC. Others are more novel approaches, such as cytokine and immune modulators, angiogenesis inhibitors, currently approved cytotoxic agents used in other cancers, and liposomally encapsulated anthracyclines.

It is up to patients -- and their physicians -- to determine if they want to use standard regimens to treat their KS or volunteer for a clinical trial. Many of these compounds seem appealing and some have even shown activity. Patients, however, must realize that most of these compounds are in phase I or II of their development. Long term efficacy and toxicity findings are, of course, not available.

Liposomal Formulated Anthracyclines

DOX-SL (DOXIL) (Liposome Technology Inc.)

DOX-SL is a liposomal formulation of doxorubicin (Adriamycin). Unlike most conventional liposomes -- tiny spheres composed of durable and primarily biodegradable lipid membranes -- DOX-SL is a trademark "Stealth" liposome that is surrounded by long chains of polyethylene glycol (PEG). These PEG coated chains alter the surface of the liposomes, thus shielding them from phagocytosis (engulfment) by the immune system. Thus, these Stealth liposomes are able to travel through the bloodstream for a prolonged period of time and deliver their contents directly to the site of disease. It is hoped that this liposomal encapsulations will be able to deliver DOX-SL more effectively.

DOX-SL is currently in three separate trials for KS. LTI's randomized phase III trial (protocol 30-10), DOX-SL versus ABV has accrued roughly 130 patients and another 100 are needed for adequate statistical power. Patients must have at least 25 mucocutaneous lesions and/or the development of 10 or more a month. Also, patients with just visceral disease and at least 2 assessable cutaneous lesions are also eligible. Patients who have had prior anthracycline therapy (doxorubicin) are not eligible.

DOX-SL is also available, through protocol 30-12, to patients who have failed or are intolerant of prior cytotoxic therapy. All patients who have completed six courses (at two week intervals) of DOX-SL or ABV in 30-10, also roll-over into 30-12, where all will receive DOX-SL. To date, approximately 300 patients are in this trial.

Data from 50 or so patients from LTI's non-randomized, DOX-SL trial, 30-12, will be part of the DOX-SL NDA, to be submitted to the FDA in mid 1994, for approval in KS patients who have failed or are intolerant of standard cytotoxic therapy. LTI plans to go to the FDA to expand the initial, salvage indication, to include first-line chemotherapy with DOX-SL, after 30-10 is completed. LTI plans to close 30-12 to enrollment in mid-1994. Future salvage patients may be able to obtain DOX-SL through a planned Treatment IND, if the FDA permits this.

Results from DOX-SL phase I and II trials demonstrate that it is safe and yields higher response rates than those reported with single agent doxorubicin (as seen in ACTG 006 conducted by Fischl and colleagues) (Fischl 1993). Northfelt and colleagues (Northfelt 1993) in their phase I trial noted that DOX-SL has a half-life in the blood of over 40 hours compared to free doxorubicin, which only has a half-life of less than 5 minutes. Moreover, DOX-SL was present in KS lesions at concentrations 5 to 11 times that after the same dose of free doxorubicin, and was also present at 10 to 20 times higher concentration in KS lesions than in normal skin (Northfelt 1994).

Results of various open phase I/II and II/III trials were released at the IX International Conference on AIDS in Berlin. Response rates (ambiguously and subjectively defined) for DOX-SL, as high as 70%, were reported at doses of 10-20 mg/m² given every two weeks (Goebel 1993; Jablonowski 1993). Many patients in these trials had progressive disease and had previously taken other cytotoxic agents.

Toxicities included mild to moderate neutropenia, alopecia and anemia. Most trials allowed for G-CSF which raised patients' ANC and allowed them to stay on drug. Cardiac toxicity, which has been seen with free doxorubicin at cumulative doses of over 500 mg/m² in other cancers, was not noted in these trials (George Tidmarsh, LTI, personal communication). Because of toxicity, intercurrent illness or tumor progression, however, most KS patients do not stay on

doxorubicin long enough to receive cumulative doses of over 500 mg/m². Patients in the DOX-SL trials have not yet received cumulative doses near 500 mg/m², so further monitoring will be warranted for those on maintenance.

Most recently, preliminary results on 48 patients from DOX-SL 30-12 indicated a 66.7% partial response rate (Thommes 1994). The mean duration of this partial PR was approximately 83 days.

If DOX-SL is approved, many researchers believe that oncologists will try DOX-SL in combination with BV (Jamie Von Roenn, personal communication). This is a logical substitution to standard ABV if DOX-SL's response rates (from the current trials) are higher and than those previously seen with doxorubicin and/or less toxic. Ronald Mitsuyasu, along with members from the KS Working Group of the ACTG Oncology Committee developed a concept sheet for a DOX-SL trial (DOX-SL vs. DOX-SL with BV) to ascertain how DOX-SL might be used most effectively (considering the toxicities) on chemotherapy naive patients.

Patients will get DOX-SL on either arm and will receive -- if necessary -- G-CSF to avoid neutropenia. This study also helps LTI because they only have to supply the drug and will not have to foot-the-bill for the extensive data monitoring. If the ACTG's Adult Review Group approves the concept sheet, this trial should be up and running by late 1994 (Jamie Von Roenn, personal communication).

Daunoxome (Vestar)

Daunoxome is liposomal-encapsulated daunorubicin. Unlike DOX-SL with its PEG coating, Daunoxome is a conventional liposome. Phase III randomized trials of Daunoxome versus ABV are open and actively recruiting patients at approximately 11 centers around the country. So far, approximately 200 patients have received drug and another 50 are needed (Michael Ross, Vestar, personal communication). Vestar also set up a salvage protocol, which unfortunately is ongoing at only 7 sites in major US cities, for patients who have failed on at least one cytotoxic agent.

A phase I pharmacokinetic study conducted by Gill (Gill 1991 b) revealed that Daunoxome has a half-life of approximately 2 hours compared with free daunorubicin which has a half-life of approximately 3 1/2 minutes. Data from their phase II trial was also delivered at the Berlin AIDS conference. From a 25 patient Phase II study of Daunoxome (40 mg/m² every two weeks), Chew and colleagues (Chew 1993) reported: one complete response, 20 partial responses, and one with a stable disease. Toxicities noted were mild nausea and neutropenia. G-CSF was needed in six of the 25 patients to raise the ANC.

What the company believed to be promising response rates from this trial and others (Presant 1993), led Vestar to submit an NDA to the FDA for approval of Daunoxome for KS patients who are either refractory or intolerant to standard chemotherapy. Vestar's application, with data on approximately 50 patients, of whom 39 were deemed evaluable, was from open-label, uncontrolled, Daunoxome trials (40 mg/m² every two weeks). The patients included in the data package were selected because they had failed or were intolerant of prior chemotherapy regimens (Michael Ross, Vestar, personal communication).

The FDA's Oncologic Drugs Advisory Committee on June 17, 1993 rejected Vestar's NDA on the basis of insufficient data (The Pink Sheet, 55: 21 June 1993). Vestar, in its analysis of the data, reported a 51% partial response rate. The FDA, in a separate analysis (but still using the protocol's response criteria), lowered the response rate to 18%. The discrepancy centered around definition of a

partial response. Vestar's partial responses were often based on the "measure of flattening" instead of "reduction in the number or surface area." (Pink Sheet) Moreover, many of the patients had "breakthrough" lesions (i.e., developed new lesions as others regressed), or their responses did not last for the required 4 weeks.

Treatment activists and noted oncologists felt that both Vestar and the FDA handled the ensuing events poorly. Vestar should have had cleaner data and should have followed the response definitions. On the other hand, the FDA could have notified Vestar (during the 3+ months when they had the data) as to the discrepancies found in their analysis of the data. Vestar might not have come and the fiasco could have been avoided.

Angiogenesis Inhibitors

Angiogenesis -- the process of forming new blood vessels -- is a natural phenomenon that takes place during certain physiologic processes such as wound healing or during a woman's reproductive cycle. Outside those circumstances, angiogenesis can be pathological. Evidence now suggests that Kaposi's sarcoma might not be a "true" malignancy (a clonal proliferation of genetically altered cells), but a dysregulation of angiogenesis. In fact, spindle cells (KS cells) that have been cultured -- as well as injected into nude mice -- respond to and secrete a number of cytokines (growth factors) including basic fibroblast growth factor (bFGF), vascular endothelial cell growth factor (VEGF), platelet-derived growth factor (PDGF), granulocyte macrophage colony stimulating factor (GM-CSF), IL-1, and IL-6 (Ensoli 1989; Nakamura 1988). Some of these cytokines secreted by spindle cells are thought to induce a proliferation of endothelial cells (neovascularization) that lead to the poorly organized vascular formulations found in the initial stage of KS lesions.

While many researchers believe these cytokine and growth factor produce this neovascularization which leads to the formation of new KS lesions, not all agree as to their exact mechanisms of action. Robert Gallo and his colleagues contend that KS begins with an HIV-associated inflammatory process of activated T cells, which secrete IL-1, IL-6, TNF, GM-CSF and gamma Interferon. These cytokines, in turn, induce endothelial cells to proliferate and transform into spindle-shaped KS cells that comprise the initial KS lesions (RC Gallo, personal communication). The KS spindle cells secrete large amounts of bFGF, VEGF, and PDGF -- as well as becoming responsive to Tat -- which create an ongoing cycle allowing new lesions to appear. It is felt that angiogenesis is central to the pathogenesis of KS. As Sam Broder said, "The blood vessels are the tumor."

Because solid tumors need a blood supply to grow and spread, scientific research has looked into ways to "starve" solid tumors to prevent this abnormal blood vessel development. This angiogenesis research has led to the development of a new class of compounds called angiogenesis inhibitors. Three such compounds, Tecogalan (SPPG, DS-4152), TNP 470, and recombinant human Platelet Factor 4 (rPF4) are currently in phase I safety and efficacy trials for patients with KS and various cancers.

These compounds have only been tested in a small number of patients with KS and have mostly induced a lessening of KS-associated edema and some minor activity on existing lesions. Many researchers feel that angiogenesis inhibitors might be most effective in preventing new lesions from occurring rather than affecting preexisting lesions (Pluda 1993 a). If this is true, these drugs might be optimal for maintenance therapy after systemic chemotherapy.

Tecogalan (SP-PG: Daiichi)

Tecogalan is an angiogenesis inhibitor that was isolated from a low molecular weight fraction of a sulfated polysaccharide that originates from the bacterium *Arthrobacter*. Tecogalan is thought to inhibit the binding of bFGF to the endothelial cell, thus inhibiting bFGF-stimulated migration and proliferation. Gallo and colleagues showed that Tecogalan, administered to "nude" mice (special immunodeficient mice) inoculated with AIDS-KS spindle cells, "led to a degeneration of newly formed vascular lesions." (Nakamura 1992).

Four sites are actively recruiting patients for a phase I dose-escalating pharmacokinetics and safety trials of intravenous Tecogalan. Thus far, no serious toxicity has been seen, except for prolonged APTT (activated partial thromboplastin time) which normalizes shortly after the end of infusion. Prolongation of the infusion time of a single dose of Tecogalan decreases the prolongation of APTT. Some patients also noted fever and chills after dosing, but such symptoms are ameliorated with meperidine (Demerol) and acetaminophen (Tylenol). Initial assessments of Tecogalan in the uncontrolled phase I trials suggest a decrease in KS-associated edema (swelling) and possible lesion reduction in some patients (Gill 1994).

There is no specified CD4 range for these trials, but patients must have at least 5 cutaneous lesions and no evidence of symptomatic visceral involvement. Sites require 24 hours of hospitalization for monitoring and pharmacokinetics during initial dosing. Subsequent doses will be given on an outpatient basis.

TNP-470 (AGM-1470: Takeda Chemical Ind., Ltd.)

TNP-470 is an analogue (a closely related chemical) of fumagillin which is a naturally secreted product of the fungus *Aspergillus fumigatus fresenius*. Fumagillin was originally found, in the 1940s, to have some effect against amoebas, but was toxic in animals. In 1990, Ingber and colleagues found that fumagillin and its synthetic analogue, TNP-470, exhibited potent activity against endothelial cells and inhibited the growth of solid tumors without side effects when injected into mice. TNP-470 was found to be less toxic in animals and 50 times more potent in vitro than its fumagillin parent (Ingber 1990). Yarchoan and colleagues at the National Cancer Institute (NCI) also found that TNP-470 inhibited spindle cells in KS cell lines (Robert Yarchoan, personal communication).

Administration of extremely high doses given by bolus injection every other day induced small hemorrhages in the brain, lungs, heart and retinas of dogs. However, the drug was better tolerated when given as an infusion. Hence, initial clinical testing favored a one hour infusion starting at low doses.

In preliminary results from an NCI phase I study of TNP-470, given intravenously for one hour every other day in a dose-escalating schema, Pluda and colleagues reported a lessening of edema, activity on existing tumors and a decrease in the development of new lesions with no dose-limiting toxicities (Pluda 1993 c).

This trial, like the four-site study by the ACTG (20 - 50 mg/m² IV weekly), is actively recruiting patients. There is no CD4 level requirement for these dose-escalating trials. Patients with pulmonary KS are excluded from the NCI trial, and patients with pulmonary and/or symptomatic visceral KS are excluded from the ACTG trials.

Recombinant Platelet Factor 4 (rPF4: Repligen)

rPF4, purified from genetically engineered *Escherichia coli*, has been found to inhibit endothelial cell proliferation and migration (Maione 1990). Miles and colleagues found that rPF4 also inhibited the proliferation of cultured AIDS-KS cells in a dose dependent manner (Miles 1991).

In the initial phase I/II safety and preliminary efficacy trial, rPF4 was injected into one KS lesion while another control lesion was injected with saline. Six of the 12 patients injected with rPF4 demonstrated an anti-KS effect, the only toxicity being mild erythema (redness around the lesion) in approximately 20% of the patients (Kahn 1993). More recently, preliminary data was released from an ongoing intralesional rPF4 trial with seven evaluable patients (Staddon 1994). From the seven patients who had one lesion injected with rPF4, there were 2 CRs, 2PRs, 2 with stable disease and 1 with progressive disease. There were no CRs and only one PR noted in the non-injected, proximal and distant control lesions. Investigators noted that while the drug seems active, "intralesional dosing appears suboptimal to achieve systemic levels."

There are three Phase I/II trials currently underway and actively recruiting patients for rPF4 at different sites in the country. The trials differ on the how rPF4 is administered: intralesionally, subcutaneously, and intravenously. The duration of these dose escalating trials is a maximum of eight weeks to assess responses and toxicity. In the intravenous study, there are two arms: one for patients with CD4s below 200 and another for those with over 200 CD4s. Patients with cutaneous and visceral KS are eligible. The intralesional study excludes those with pulmonary KS. Patients receiving prior systemic chemotherapy are excluded from the subcutaneous study.

Cytokine Modulation

Recent insight into the role of cytokines in the pathogenesis of KS lesions has suggested that inhibitory strategies, aimed at inhibiting the production or action of cytokines, might be used to treat KS. As with the angiogenesis inhibitors, the various cytokine inhibitors now in phase I and II trials have been tested on very few KS patients. Almost all of the published articles on their supposed effectiveness and possible mechanisms of action are from in vitro data from various KS cell lines.

Tumor Necrosis Factor (TNF) Inhibitors

Over the past few years there has been a great deal of discussion surrounding TNF's role in the pathogenesis of primary HIV infection. Elevated serum TNF-alpha levels increase with advancing stage of HIV infection (Lahdevirta 1988). TNF-alpha has also been demonstrated to enhance HIV replication in chronically infected T-cell and macrophage cell lines when administered alone (Wright 1988).

Many researchers also believe that blocking TNF or its effects might inhibit the development of KS. TNF not only causes the proliferation of KS cells, but it also increases IL-6 levels and alters its expression in normal endothelial cells (Parkash Gill, personal communication). There are in fact, at least three different ways of blocking and or interfering with TNF: 1) by using a drugs such as pentoxifylline, thalidomide (and maybe Tenidap, made by Pfizer) that "decrease the production" of TNF; 2) by using a monoclonal antibody to "neutralize" TNF; 3) modulating the circulating TNF by "blocking" it from the receptor of the cell (Steven A. Miles, personal communication).

Pentoxifylline (Trental: Hoechst-Roussel)

Pentoxifylline (Trental), a methylxanthine (caffeine) derivative is an FDA approved drug used to treat intermittent claudication. When used in cancer patients, Dezube and colleagues found that pentoxifylline decreased TNF-alpha RNA levels in monocytes (Dezube 1990). Pentoxifylline has also been found to inhibit HIV-1 replication in infected human peripheral blood mononuclear cells (Fazely 1991).

Because pentoxifylline was found to decrease production of TNF, it was studied in KS patients in a phase I/II dose-escalating trial. In a UCLA trial that enrolled 12 patients (6 patients with a CD4 count above 200 and 6 patients with CD4 counts below 200), there were 3 responder; 1 CR and 2 PRs (Ronald Mitsuyasu, personal communication). These were from the over 200 CD4 group. Investigators do not believe that Hoechst-Roussel has any further plans for its clinical development in KS.

Recombinant Soluble TNF Receptor (r hu TNFr:Fc : Immunex)

Soluble TNF receptors might be beneficial by blocking TNF from binding to TNF receptors on KS spindle cells. rhu TNFr:Fc is a dimer of two molecules of the p80 TNF receptor linked by the Fc portion of immunoglobulin (Dower 1990). It binds TNF alpha and beta with high affinity. While it has no direct effect on KS cells, it is believed that it will block the effects of TNF, because the soluble receptor will act as decoy receptor and may prevent TNF from binding to the cell.

Miles and colleagues at UCLA are beginning a phase II placebo-controlled trial of rhu TNFr:Fc for KS patients. Walker and colleagues at the NIH are using rhu TNFr:Fc in a phase I/II trial in patients with HIV. In the UCLA 12 week safety and efficacy trial, patients will be randomized to receive either 125 micrograms/m², subcutaneously twice weekly for 12 weeks or a placebo. Up to 40 patients will enroll. At least half of the enrolled patients will have a CD4 count above 200. The patients with over 200 CD4 cells will not be eligible if they have had a prior OI and the patients with below 200 CD4 cells will not be eligible if they have uncontrolled concurrent OIs.

Response rates with the soluble TNF receptor might only be about 30% (as was noted in the UCLA pentoxifylline study). This may be because only a third of KS patients probably have a TNF-driven mechanism (Steven Miles, personal communication). However, the TNF receptor might also prove beneficial for other HIV-associated conditions such as wasting syndrome.

Interleukin-4 (IL-4, Schering-Plough)

Studies have shown that interleukin-4 (IL-4) is a potent inhibitor of IL-6 secretion by monocytes in vitro (te Velde 1990; Miles 1992). IL-4 has also been shown to suppress the growth of myeloma cells in vitro by blocking endogenous IL-6 production (Herrmann 1991). Tepper and colleagues (Tepper 1989) conducted studies of malignant cells transfected with IL-4 cDNA that were introduced into tumor-bearing mice. Growth inhibition was noted in a variety of tumor types, including plasmacytoma, mammary adenocarcinoma, transformed fibroblast cell lines, a melanoma and sarcoma cell line.

The only toxicity seen in monkeys was cardiac toxicity. At extremely high doses (50 micrograms per kilogram per day), all ten monkeys died of multifocal myocardial necrosis. However, when monkeys were given 5 micrograms per kilogram per day, no cardiac toxicity was seen.

An ACTG dose-escalating phase I/II trial of recombinant IL-4 is in progress and actively recruiting KS patients. ACTG trial 224 is currently being conducted at UCLA with Steve Miles and at New England Deaconess Medical Center with David Scadden. A separate trial of IL-4 at USC is being conducted by Parkash Gill and has a few spots left for patients. All patients on this study must be receiving some form of antiviral therapy for at least 21 days prior to starting treatment. Patients with active OIs will be excluded. Group 1 will have under 100 CD4 cells. If they tolerate the treatment for 12 weeks, then group 2, with CD4 counts from 100-500, will start treatment.

Giving IL-4 to HIV-positive patients was controversial when this study was being planned because some believed that IL-4 might increase viral load. Researchers such as Gene Shearer of the NCI told Steve Miles that IL-4 was probably the worst thing you could give to an HIV-positive patient (Steven A. Miles, personal communication), because IL-4 is thought to shift the balance of CD4 cells from TH1 type (cytotoxic) towards TH2 type (immunoglobulin producing).

Now that IL-4 has been given to a handful of patients in both the ACTG trial and 17 patients in the USC trial, just the opposite has occurred. IL-4 has not show much activity on KS lesions. There has been only 1 PR in the UCLA trial and only 1 PR in the USC trial. (Steven A. Miles, personal communication; Parkash Gill, personal communication). However, Miles has seen "significant decreases" in patient's p24 antigen levels. Decreases in patients' p24 levels have also been seen by Parkash Gill and by Lawrence Kaplan, who is using IL-4 in a lymphoma trial.

Soluble Interleukin-1 Receptor (IL-1r, rhu IL-1R: Immunex)

IL-1 has been shown to play a major role in the pathogenesis of HIV (Fauci 1993) as well as HIV associated KS. IL-1, a pro-inflammatory cytokine, acts as an autocrine growth factor for smooth muscle cells and induces the secretion of Platelet derived growth factor (PDGF) (Dinarello 1991). IL-1 has also been shown to increase production of TNF and IL-6 from peripheral blood mononuclear cells (Granowitz 1992). In vitro, IL-1 has been shown to stimulate the growth of KS cells (Nakamura 1988). It has thus become evident that by blocking IL-1, you might be able to stop its autocrine effects as well its effect on increasing IL-6 secretion. One possible way of blocking IL-1 is with the use of a soluble receptor that would act as a decoy receptor and prevent both IL-1 alpha and beta from binding to the surface of the cell. rhu IL-1R is the soluble extracellular portion of the human type I IL-1 receptor (Dower 1989). It binds tightly to IL-1 beta and IL-1 alpha. While it has no effect on basal proliferation rates of KS cells, it can completely abrogate the IL-1 specific induction of proliferation (Steven A. Miles, personal communication).

Susan Krown at Memorial Sloan Kettering Cancer Center in New York has begun a phase I/II safety and efficacy trial of a soluble recombinant human IL-1 receptor for HIV positive patients with or without KS. This 8 week trial of subcutaneously administered soluble rhu IL-1R is currently recruiting patients with less than 300 CD4 cells.

Interleukin-2 (IL-2, Leukine, Chiron)

Intravenous IL-2 is being studied for KS in a small phase II trial at the NIH. This trial is part of the larger continuous IL-2 infusion trial that is currently under way at the NIH in HIV-positive patients.

Part of the rationale for testing IL-2 in KS patients resulted from the dramatic increase in CD4 cells seen by Kovacs and colleagues (Kovacs 1993) in their 8 patient trial of IL-2. Kovacs hopes IL-2 will show activity in patients with KS lesions who are also at risk for other OIs (Joseph Kovacs, personal communication).

This trial, with a target accrual of ten patients, has two arms: one for patients with over 200 CD4 cells and another for between 100 and 200 CD4 cells. Patients will receive IL-2 as a continuous infusion (18 million units for five days) as well as AZT, ddI, or ddC. Patients need to be on an antiretroviral because of the risk that IL-2, by stimulating T cell proliferation, will increase viral load.

Roswell Park Cancer Center is also running a phase II trial of IL-2. In this trial, for patients with KS and non-Hodgkin's lymphoma, IL-2 is administered at low doses by injection every day for one to three months.

CD8 Cell Expansion + IL-2 (Applied Immune Sciences)

CD8 cell expansion with the infusion of IL-2 has shown a hint of some anti-KS activity in clinical trials conducted by Klimas and colleagues (Klimas 1992, 1993). Two patients who had KS in a six-person phase I trial (Klimas 1992) had a response to therapy. One patient had a 70% regression of tumor size and number of lesions. The other patient had a partial resolution of oral and facial lesions but no change in his visceral lesions.

In a later KS-specific trial of 10 patients (6 had completed treatment and were evaluable), Klimas and colleagues (Klimas 1993) reported 5 partial responses. (Responses, however, were defined "by an overall reduction of greater than or equal to 25% in tumor load.")

In a separate analysis of that trial (with 8 patients who had completed treatment and were evaluable), AIS, using ACTG response definitions, claims there was 1 CR and 3 PRs (Annemarie Moseley, AIS, personal communication). The only toxicities noted by investigators were "flu-like" symptoms attributed to IL-2.

Kahn and colleagues completed a similar trial of CD8 expansion with IL-2 and recorded only 1 CR. AIS said they believed the reason for the discrepancy in the results between the two identical trials was: Klimas' patients had lower CD4 cell counts (between 50 and 150). Hence, CD8 expansion with IL-2 works better on KS patients with a less intact immune system (Annemarie Moseley, AIS, personal communication).

CD8 expansion is not being studied in any current KS trials. AIS says that they want to finish compiling the Klimas and Kahn data before deciding what KS patient population they should study. All Trans-Retinoic Acid

Retinoids -- derivatives of vitamin A -- are a class of drugs that have been widely used to treat various skin conditions. They also have immunomodulatory effects, including enhancement of lymphocyte and macrophage functions (Pluda 1993 a).

Warrell and colleges (Warrell 1991) reported clinical activity when all-trans retinoic acid was administered to patients with acute promyelocytic leukemia. All-trans retinoic acid has also exhibited anti-angiogenic activity in the chick embryo chorioallantoic membrane assay system (Oikawa 1989). Additionally, Sidell

and colleagues (Sidell 1991) have found that retinoic acid inhibited the growth of a myeloma cell in vitro via down-regulation of IL-6 receptors. Gill and colleagues, however, found that this might not be the case in KS (Parkash Gill, personal communication). They have found that TRA down-regulates IL-6 (not the receptor) in vitro.

In an oral TRA trial (2 mg/kg) of seven patients conducted by Bonhomme and colleagues (Bonhomme 1993), one patient had a "significant response", two had a partial response, three remained stable, and one progressed. Duration of response was short, with patients experiencing new lesions shortly after discontinuing treatment. Toxicities included dry skin, myalgia, and headaches.

Disconcerting results were seen in a 14 patient trial of oral TRA conducted by Von Roenn and colleagues (Von Roenn 1993). Of the first 6 patients who received a high dose of TRA 175 mg/m² every day for approximately 32 days, 5 showed rapid KS progression. Rapid progression was not seen at lower doses. There could be a differential, dose-dependent effect on KS (Pluda 1993 a).

In a trial with topical TRA in eight KS patients with less than 100 CD4 cells, Bonhomme and colleagues (Bonhomme 1991) noted partial remission in seven patients. Clinical responses were based on change of color, and size of the lesions.

Presently, there are four different oral TRA trials -- two as a single agent and two dose-escalating in combination with varying doses of IFN-alpha. Two of the trials are closed and two others (one with Robert Yarchoan at the NCI and one with Susan Krown at Memorial Sloan-Kettering) are still open and accruing patients.

Gill and colleagues have seen a number of partial responses in their dose escalating trial (Parkash Gill, personal communication). Gill mentioned that it took a mean time of 22 weeks to actually see the responses. In fact, a few patient initially had mild exacerbations of their lesions, but went on to respond many weeks later. Moreover, the majority of the patients who responded had fewer than 100 CD4 cells. The toxicities he has noticed were mild, including headaches, ringing in the ears, dry skin and elevated triglyceride levels.

Another retinoid that might work on KS, 13-cis retinoic acid, in a topical and oral formulation, has been developed by Ligand Pharmaceuticals. The UCLA group is planning to start a trial in the next few months (Steven Miles, personal communication). This retinoid binds to different retinoid receptors than TRA.

Taxol (Paclitaxel: Bristol-Myers Squibb)

Taxol is a drug derived from the bark and needles of the pacific yew tree. Recently approved by the FDA for breast cancer, Taxol has also shown anti-cancer activity in ovarian and non-small cell lung cancer. In a lung cancer study by Murphy and colleagues (Murphy 1993), an overall 24% response rate was noted with one patient achieving a complete response. Some of the toxicities noticed in other trials, included mild neutropenia, anemia, alopecia and peripheral neuropathy (Taxol, package insert).

Taxol is also being tested in a dose-escalating phase II trial for KS patients at the NCI. The trial is open and currently recruiting patients with KS. Patients receive Taxol over a three hour infusion once every three weeks. Patients with symptomatic pulmonary KS and those who have previously received more than one cycle of cytotoxic chemotherapy are excluded.

Preliminary results, according to Robert Yarchoan, principal investigator for the study, demonstrate that Taxol is causing lesion reduction (Robert Yarchoan, personal communication). Of 8 evaluable patients who have received Taxol at low doses, 5 have achieved partial responses. Alopecia, mild fatigue, rash and chills have been the observed toxicities.

Graveyard

The number of advances in the pathogenesis of KS led to the development of compounds which had promise of antitumor activity. Although some compounds seem to work in vitro, they have shown no antitumor effects in KS patients, and they have been toxic. Below, are two compounds that have been studied in KS clinical trials without evidence of efficacy. While some of these compounds might be resurrected for other HIV complications, they are no longer being studied specifically for KS.

TAT Inhibitor (Hoffmann-LaRoche)

The Tat protein, made by HIV inside of infected cells, has been shown to increase the proliferation of KS spindle cells (Ensoli 1990), and to upregulate TNF expression. Tat proteins are secreted into the bloodstream and apparently bind to and activate KS spindle cells, forming an ongoing cycle for the proliferation of KS lesions (Robert C. Gallo, personal communication). Vogel and colleagues demonstrated that HIV Tat, under the control of the HIV long terminal repeat, could induce KS-like lesions in nude mice when transfected into mouse embryo cells (Vogel 1988).

A trial was designed for KS patients using Hoffmann-LaRoche's Tat inhibitor (Ro-24-7249). This was the same Tat inhibitor used in the HIV trials (ACTG 213) that proved, after months of speculation and hype, to be ineffective, and possibly harmful. Two centers enrolled 22 patients at the 600 mg dose. There was an exacerbation of KS lesions in some patients, and a great deal of central nervous system toxicity was seen (Ronald Mitsuyasu, personal communication).

Pentosan Polysulfate

Pentosan polysulfate has been shown to inhibit bFGF (basic fibroblast growth factor) and FGF-like dependent tumor growth in vitro and in vivo (Wellstein 1990, 1991). Pentosan polysulfate was also found to inhibit the formation of tumors in nude mice and inhibit the growth of Kaposi's sarcoma spindle cells in vitro (Nakamura 1992).

These findings led researchers to believe that pentosan polysulfate might work as an angiogenesis inhibitor for patients with KS. In a 16 patient phase I trial of pentosan polysulfate, given systemically or intralesionally, conducted by Pluda and colleagues (Pluda 1993 b) at the NCI, the investigator noted that no "significant antitumor responses" were observed in any of the patients.

CURRENT OPINIONS IN KS FROM PHYSICIANS, CLINICIANS + RESEARCHERS

25 oncologists, dermatologists, radiation oncologists, primary care physicians and laboratory researchers who have worked on AIDS-related KS for over 10 years were interviewed by telephone or in person. They were all asked about their work to get an idea about the current state of KS research. Many were asked about articles they have published over the years concerning various studies which

provide the basis for current treatments used on patients with KS. They were all asked three questions about several of the myths and truths surrounding KS treatments as well as three basic questions: 1) "How has the course of KS changed from the beginning of the AIDS epidemic to 1994?"; 2) "What do you feel the standard of care treatment should be for patients with KS?"; and 3) "What are some of the problems you have with the current state of KS research?"

Specific comments from those interviewed are unattributed. The assurance of anonymity allowed individuals to relate sensitive issues that they will not discuss publicly.

I. THE MYTHS AND TRUTHS ABOUT CHEMOTHERAPY

A majority interviewed talked about the use of cytotoxic agents for KS. Many blamed treating physicians for spreading myths about various cytotoxic agents, telling their patients that their immune system was "too shot" to handle cytotoxic agents even though some have such wide-spread symptomatic cutaneous KS with horrible edema that prevented their mobility. A. "Is there any proof that cytotoxic agents deplete your immune system?"

Most could not come up with clear-cut proof or cite studies in which cytotoxic agents actually depleted patients' CD4 cells. Many cited studies that showed that various cytotoxic agents caused severe neutropenia, anemia, and even peripheral neuropathy.

One oncologist noted that a patient's CD4+ cells can and do drop when receiving cytotoxic agents, but this usually correlates with a falling white blood cell count. He said, however, that cytotoxic agents do not have an effect on a patient's CD4 percentage.

Some even hark back to an early ABV pilot study conducted by Gill and colleagues at USC (Gill 1990) in which 23 of the 33 patients developed OIs, 17 of which were PCP. PCP prophylaxis was not required in this study. This caused many to demand PCP prophylaxis on all subsequent chemotherapy trials.

B. "Where did these ideas about the risk outweighing the benefits of Chemotherapy come from?"

One primary care physician noted that patients are afraid of chemotherapy because of horrible anecdotes about cancer patients losing all their hair, looking like ghosts and throwing their guts up. He has had to tell patients that these myths/anecdotes were from cancer patients in their 50s, 60s and 70s who had prostate or breast cancer. He often says, "Yes, we have seen horrible side effects in women with breast cancer and men with prostate cancer in their 60s and 70s, and if you feel like an elderly man or women, then chemo is not for you."

One oncologist mentioned that the patients who come to see him say that they "want to try everything in the book" before using any chemotherapy. In accordance with their wishes, this oncologist uses various other standard treatments and or immune modulators. When they don't work and patients finally go on to use single or combination cytotoxic agents, they often see results and don't feel as bad as they thought they would. He says, "They yell at me for wasting their time and not initially being more persuasive."

One primary care physician also went as far as to say that oncologists are "trigger happy" when it comes to giving chemotherapy. He will not recommend chemotherapy unless his patient has symptomatic pulmonary KS.

Another physician explained that cytotoxic agents now used to treat KS have been around for a number of years and oncologists learned how to use them when treating various cancers in the 1970s. However, when KS started to surface in New York, oncologists used the doses they were "familiar with" which were way too much and proved to be extremely toxic if not deadly. (For example, Adriamycin was often administered at 40 to 60 mg/m² on cancer patients, but studies have now proven that the maximum tolerated dose of Adriamycin on young men with AIDS-KS is probably 10 to 20 mg/m².) He recalls an event in the early 1980s, in which he was observing an AIDS patient who had just died. The oncologist turned to him and said "Look, there are no more lesions." He said, "Yes, but he is also dead."

Some oncologists mentioned that fellow oncologist also follow truisms that were handed down from early cancer days, such as "The maximum cumulative dose of bleomycin that should be given to a patient is 300 mg/m²," and "The maximum cumulative dose of Adriamycin given to a patient ranges from 450 to 550 mg/m²." Many believe this is not the case for young men with KS -- nor has it been clinically proven for KS -- and this information came from cancer studies in the 1970s (Pascual 1973; De Lana 1972). C. In 1994, how can cytotoxic agents be used in KS patients so that they might not cause so many toxicities?

A majority of those interviewed, especially the oncologists, felt that the use of GM-CSF and G-CSF will help in preventing neutropenia which is caused by Adriamycin and other cytotoxic agents. While GM-CSF has been studied in many ACTG trials (and others) in combination with single agent and combination cytotoxic agents, its toxicities appear to be greater than those of G-CSF, although both appear relatively equivalent when it comes to ameliorating neutropenia. The tendency is to use G-CSF, rather than GM-CSF, because it does not cause the "flu-like" toxicities that have been seen with GM-CSF.

In fact, anecdotal information from ACTG 094 (ABV + AZT + GM-CSF) is that 20 mg/m² of Adriamycin was the maximum tolerated dose. The objective of the study was to see if patients could tolerate up to 40 mg/m² of Adriamycin and BV when administered 10 mcg/kg of GM-CSF. This never happened because the dose of GM-CSF had to be dropped from 10 mcg/kg to 5 mcg/kg to 2.5 mcg/kg because of the continual flu-like toxicity noticed with GM-CSF. Thus, neutropenia was never ameliorated because a 2.5 mcg/kg dose of GM-CSF was not potent enough.

Others noted that Epogen, which wasn't around in the 1970s or 1980s, is now extremely helpful for preventing severe anemia. And even though extreme nausea is not often seen with low doses of cytotoxic agents used on KS patients, Zofran is a new drug that works for ameliorating nausea.

Various agents that have been approved recently for prophylaxis against OIs (PCP and MAI) are now mandated in most protocols. Most believe this should be standard practice for any HIV positive patient with a CD4+ cell count of under 200, but note that a patient with raging KS might either have an underlying, undetected OI or become more susceptible.

Another oncologist mentioned the fact that patients receiving cytotoxic agents in the late 1980s were also taking 1,200 mg of AZT a day, which might have contributed to the neutropenia and anemia. Now, the AZT dose is usually less than a half, and some patients eschew nucleosides for various reasons.

This fact was echoed by another oncologist who is involved in the ACTG 163 trial (ABV + ddI or ABV + ddC). While he mentioned that results have been impressive, there is still some toxicity seen with ddI and ddC. He believes that if a patient is truly late stage with pulmonary KS, they might be better off sticking just with ABV and holding off for a while on their nucleosides.

One oncologist, however, related that if a patient comes to see him with extreme, uncontrolled KS, the first thing he likes to do is put them on an antiretroviral. This uncontrolled KS, he says, is probably due to a flurry of HIV activity with rapidly declining CD4+ cells. He feels that usually the antiretroviral will calm things down. It will, of course, not take away existing lesions, but might stop the explosion.

II. HOW HAS THE PATIENT POPULATION WITH KS CHANGED OVER THE PAST 10 YEARS?

Most all who were interviewed believed that the patient population with KS has changed over the past 10 years. They seemed to all agree that patients with KS in the early 1980s often had CD4+ cells between 200 and 400 and even higher. Now days most patients seen by many of the various physicians have a CD4+ cell count below 200 and often under 100.

A. What are some of the reasons patients now appear to develop KS at lower CD4+ counts than earlier in the epidemic?

A good many believe that KS is not only a function of HIV immune dysregulation, but that co-factors and some type of infectious agent is responsible for certain individuals -- most notably homosexuals -- getting KS. Most contend that this co-factors or infectious agent was usually sexually transmitted through oral-fecal transmission, and some hold to the poppers myth. The patients with HIV who got KS were probably very sexually active gay who were either getting the "KS agent" or chronic immune stimulation from rimming or unprotected anal sex with a man who had this infectious agent. Thus, when HIV was being transmitted through sex, sometimes this infectious agent was also being transmitted.

This hypothesis was based on the presumption that this group of men infected each other in the late 1970s and early 1980s. Hence, this cohort had HIV, their KS sprouted early on because of the infectious agent -- with or without an intact immune system -- and now most all of them are dead.

Now, however, this different population of men may not be engaging in rimming or exposing themselves to a population who had this infectious agent.

There are also those who don't believe the oral-fecal/infectious agent analysis. Many just believe that the course of HIV has evolved over the past ten years, and didn't know, or care to guess, why patients now seem to develop KS as a late-stage disease.

One oncologist does not believe in the infectious agent analysis. He says that if it were true, and all the people with this infectious agent have died, then why is the prevalence of KS still the same? He pointed to current MACS cohort epidemiological data which shows an high ongoing incidence of KS in the HIV-infected population.

Some felt that the reason was simple: 1) There are drugs patients have been taking to cure other OIs and prophylaxis for OIs. Since they are not getting PCP or dying from PCP, as were many in the 1980s, and because patients can prophylax

for and treat MAI, then there is more time in which to develop KS. 2) Since patients are not getting these other OIs, whose inflammatory complications may have triggered KS, patients may not be as susceptible to early KS. 3) Early AIDS patients died quickly from PCP or another OI, so, of course, they never had KS, early on or later. 4) Anti-retroviral therapy now keep patients CD4+ cell count up. Patients with high CD4+ cells are not as likely to develop KS. Patients were not taking these drugs in the 1980s and their CD4+ dropped rapidly and they, in turn, developed KS.

One oncologist didn't really have an answer, but related that unlike all other OIs, "KS is a totally unpredictable disease." He said that a patients may have a few lesions early in the course of their disease and they have gone away. After a few months and maybe even sometimes years, the same patient will suddenly get 16 new lesions.

There were also those that were not sure if patients who now develop KS have a lower CD4+ cell count. These doubts came from a few oncologists and radiation oncologists. They believe that there are probably KS patients out there with CD4+ cells of 200 to 400, but primary care physicians are "hiding them" and don't refer patients to them, as they did in the 1980s.

A few oncologists reported that it is too often the case that they only see KS patients with advanced disease who have low CD4+ cells. This angered those oncologists who would have liked to have established some sort of a relationship with the patients and start treatment, instead of getting a patient with 17 CD4+ cells and horrible edema that prevents their mobility. One oncologist proclaimed that up to a third of the patient who come for treatment are self-referred because their primary care physicians have chosen to ignore their KS or tell them they are too weak for chemotherapy. Some primary care physicians balked at the assertion that they are "hiding" patients with KS. They noted that they don't always feel the need to refer patients to an oncologist. A few noted that since they are the patient's primary care physician, and they know the treatments available for the various stages of KS, they can administer injections of Velban (vinblastine), liquid nitrogen and even IFN-alpha. One admitted to administering cytotoxic agents (without a chemotherapy certified nurse) to patients who need it.

Another mentioned that some patients are reluctant to go to an oncologist because they only trust their primary care physician and having to go to an oncologist makes them think they have cancer. Having HIV and admitting they have a malignancy -- a "cancer" -- is often more than a patient is ready to deal with.

III. STANDARDS OF CARE

It was expected that most of those interviewed felt that the treatments they were providing were safe, effective and part of the standard of care regimen for KS at various stages of the disease. It is also important to note that those interviewed have been treating patients for a number of years, have published widely and are considered the experts in their respective fields. Those interviewed also practice in major cities (New York, San Francisco, Los Angeles, Chicago) where there is a much higher incidence of KS. Oncologists, radiation oncologists, dermatologists, and primary care physicians from small cities or rural areas, who have not seem much KS and might not know exactly how to treat KS, were not interviewed or consulted. Thus, no one gave "crack-pot" or "scary" answers on how to treat a patient with KS.

The use of liquid nitrogen for freezing small, indolent lesions was often recommended and rarely contested. Most said that it should be done when the

lesion is in its early stage and relatively small. Some mentioned that hypopigmentation results after therapy so this might not be acceptable for darker skinned patients. Primary care physicians felt that they can administer therapy and there is no need to refer patients to a dermatologist for liquid nitrogen.

The use of Velban (intralesional vinblastine) was problematic for many who were interviewed. Some mentioned the price of Velban as being an issue. One said, "Velban is dirt cheap." Another said, "Velban is expensive. Doctors make a lot of money off Velban because you can charge for Velban as a chemo drug and you also get to charge for each injection. Every time you inject Velban, that's more money."

Some oncologists had trouble with Velban being used so widely and on patients who have 20 to 50 lesions. One had trouble with dermatologists who choose to inject Velban into a patients with numerous lesions. This oncologist chided, "Just because you inject one lesion, doesn't mean that the other 20 on the leg are going to go away. Doesn't the patient or doctor notice the scarring from the [intralesional] Velban? A dose or two of intravenous bleomycin might be able to clear them all away."

One primary care physician, however, said, "Some patients demand numerous injections of Velban. They will deal with the pain over taking chemotherapy. I have to try real hard to tell them that we probably aren't getting anywhere, and chemotherapy might be the answer."

There was often some disagreement about how and when to treat oral KS lesions. Most thought that oral lesions should not be treated unless they are highly symptomatic, causing a loosening of the teeth or interfering with eating. When they are, some recommended injections of bleomycin, Velban, liquid nitrogen or surgical incision.

One thought that the oral lesions should be treated right away, because if you stop that lesion, you might prevent other lesions by interfering with cytokine proliferation.

Most physicians, but not the radiologists, believe that radiation therapy can be harmful for oral lesions because of severe confluent mucositis and salivary gland dysfunction.

Radiologists said that radiation therapy is effective on highly symptomatic and hard to reach oral lesions, but that the patient should be on an anti-fungal drug and probably Acyclovir before and during treatment. One noted that a single field dose of 8 Gy is effective, followed by smaller, fractionated doses. Another mentioned her pre-treatment of the lesions with topical Oratect gel that allows her now to treat lesions without the usual side effects.

Many believe that IFN-alpha is useful for patients who don't want or are not ready for systemic cytotoxic agents. IFN-alpha as a single agent was not recommended mostly because treating physicians aren't seeing patients with over 200 CD4+ cells. Some even said that single agent IFN-alpha was "obsolete." There are those who feel comfortable, and claim to see results, using IFN-alpha in combination with nucleosides. One oncologist mentioned that although IFN-alpha might not be for all patients, he has not seen "anything as useful as IFN for totally making lesions disappear. When it works it really works." Most everybody agreed that cytotoxic therapy (as a single agent or in combination) must be used for symptomatic visceral KS. While many are not happy with certain toxicities,

they noted that there are many agents to choose from. Some thought that administering a few doses of single agent cytotoxic therapy was warranted for problematic cutaneous KS.

Most oncologists are thankful for having G-CSF for dealing with myelotoxicity that accompanies cytotoxic therapy. "Now, with the use of G-CSF," mentioned one oncologist, "neutropenia might no longer be an issue." One oncologist, however, thought that G-CSF was being overused in some cases, and that he has heard about patients going on to G-CSF with an ANC above 2,000.

Almost all agreed on two issues surrounding cytotoxic agents: 1) even though response rates are high, the duration to relapse is often short; and 2) there needs to be something that can be used after cytotoxic therapy for maintenance therapy.

There are those that hope that some of the new angiogenesis inhibitors (Tecogalan, TNP-470, rPF4) will be that maintenance therapy. Some believe that this class of agents now in clinical trials, or others that may come along, will be the "answer" for treating KS instead of chemotherapy. And, even if these angiogenesis inhibitors don't take away existing lesions, many feel that they will help in preventing new lesions from occurring. One physician doesn't feel that any "one" will do it, but that it may have to be a combination of these or one of the angiogenesis inhibitors with an immune modulator.

There are also those who are excited about DOX-SL and Daunoxome. Some believe that they will be more effective than ABV. Many believe that these liposomal anthracyclines will be effective in combination with B and V. Others are not sure if they will be more effective than ABV, but they bet that they will probably be less toxic. A few oncologists giving DOX-SL to patients who have been on other cytotoxic regimens say that their patients are "grateful" and "feel much better" after taking DOX-SL than when they were on other cytotoxic regimens. Others report a mixed bag of results, some partial responses and some progressive disease.

THE TSURIS AND MISHIGOS OF AIDS MALIGNANCY RESEARCH There are a number of problems with how AIDS malignancy research is carried out, including the basic funding mechanisms, the clinical trials systems and the overall lack of support from those who know AIDS and those who know oncology.

Let's look at AIDS-Kaposi's sarcoma (KS) research as a microcosm for AIDS-related malignancy research. There are only a dozen or so researchers doing work on the pathogenesis of KS. There are two sites on the west coast: Steve Miles and O. Martinez-Maza at UCLA; and Parkash Gill, Shuji Nakamura, and Syed Zaki Salahuddin at USC. On the East coast there are Alvin Friedman-Kien and Yao Huang at NYU; and Bob Gallo's NCI funded Laboratory of Tumor Cell Biology (LTCB), which includes top researchers such as Barbara Ensoli and Yanto Lunardi-Iskandar. Except for some other researchers, including Judah Folkman (Harvard), Philip Browning (Vanderbilt), Theodore Maione (Repligen Corp.), and Jonathan Vogel (NCI), that's about it.

Problems with Basic Research

To investigate the problems with funding this research, we need to back up and look at 1) the basic funding mechanisms for AIDS related malignancies within the NIH (RFAs, RFPs, RO1s, RO3s, UO1, etc); and 2) who is reviewing these grants (i.e., one of the seven AIDS study sections of the NIH's Division of Research

Grants (DRG) or special review committees from selected NIH institutes); and 3) if there are qualified oncologists and immunologist on these committee or elsewhere who can actually judge the scientific relevance of these applications?

Unsolicited ROIs that deal with AIDS-related malignancies -- or AIDS in general -- go to the one of the seven AIDS study sections in the DRG. These seven AIDS study sections are: 1/A) Immunology; 2/B) Epidemiology; 3/C) Molecular Virology; 4/D) Pre-clinical Drug development; 5/E) HIV/OI clinical trials; 6/F) Behavior Research; 7/G) Neurology. It is up to Marcel Pons, Ph.D., to decide which of the seven study sections will review the grant applications. Pons must also decide which NIH institute will have the jurisdiction (and must come up with the funds) for the specific application. Pons also happens to be the Scientific Review Administrator (SRA) for study section 3/C. The SRA of the study section must designate primary and secondary reviewers for each grant application, assess conflicts of interest, ensure the grant application was filled out properly and decide if outside AD HOC experts (there is a long list of them) will be needed. to review a specific application. Members can be borrowed from certain study sections if he/she has some expertise that will be helpful for another section's review.

Pons believes that he is qualified to decide which study section a grant application should go to. He also said that it makes his job easier if the PI writes a cover letter and asks that his/her grant go to study section X and for what reason. Pons, however, says that only 20% of the PIs specifically ask to be reviewed by a certain study section.

Pons said that he usually places an AIDS-related malignancy grant in either Immunology (1/A), Molecular Virology (3/C) or sometimes in OIs/clinical trials (5/E). According to Pons, these three sections have oncologists, immunologists, and virologists who are up to date on the problems in the pathogenesis, histogenesis and clinical research of KS and other AIDS-related malignancies.

When asked if he felt there was a need for an eighth study section set up specifically to review AIDS-related malignancy grants, Pons said, "NO." He felt that it would be too difficult to get oncologist who not only knew AIDS malignancies, but also virology, immunology and basic chemistry. He also said that there was no need because there were not that many AIDS-malignancy grants that came into the DRG anyway.

A well known Midwest oncologist who sits on one of the study sections says that there is no need for a separate study section. He says that there will be separate ad hoc AIDS-malignancy study section set up for the late summer to look at on the etiology of AIDS-related malignancies. Here, he is obviously talking about a special study section/review committee for Ken Cremer's recent NCI RFA on the etiology of AIDS malignancies. This RFA grant review has nothing to do with the DRG except for the initial data entry. After that, it will go back to the NCI where they will set up their own special review committee. I was asking Dr. Midwest whether an eighth study section needed to be developed for reviewing unsolicited ROIs, R29s and applications in response to program announcements.

In fact, when asked about his study section, he felt that there were about two truly qualified experts who understood AIDS-related malignancy grants. When I asked about the lack of oncologists in his and other study sections, he told me that there were "several immunologists on our committee who were more familiar with cytokines and interleukins [and their role in the pathogenesis of KS and lymphoma] than most oncologists.

He also felt that while AIDS malignancy grants fared just as well as other HIV grants in his study section, he said that if an expert in crystallography of RT submitted a grant it would be looked at favorably and probably score well "as opposed to something in KS where nobody has done a lot in any extramural NIH lab. It's [the grants we get] all people coming into the field developing studies of KS based on previous experiences." He is basically saying that work done at any extramural NIH Lab (which basically means all other labs outside Gallo's LTCB) has not come up with anything new. Has he not read studies or seen abstracts in the past five years from the USC, UCLA and NYU labs? And yes, these labs, as well as other researchers might be doing work based on previous work, but don't we need some confirmatory studies and real answers (instead of guesses) about the pathogenesis and histogenesis of KS? Gallo, Yarchoan, Miles, Gill, etc. all say they don't know the complete answer and their pathogenesis models often differ. Funding some of these basic science studies in KS, and even some clinical trials may help solve some of these ambiguities. Dr. Midwest did make one relevant point and that was: "the issue is not the study section [their expertise], if there is money." What he meant by that was the fact that the NCI (where most of the KS and Lymphoma grants go) has a payline for RO1s at the 15th percentile and a payline for R29s at the 27th percentile. That means that if the grant in question does not fall within that percentile by ranking, it won't be funded. Another study section member from AIDS & Related Research Study Section (ARRS) 1/A (Immunology) believes that grants applications for AIDS-related malignancies are evaluated fairly. As an immunologist, he did admit that there were only a few oncologists or practicing clinicians who might be familiar with the many aspects of AIDS-related malignancies and actually treat patients. He also said that a grant's fate is often in the hands of the study section member who is picked as the primary reviewer. If the primary reviewer does not comprehend all aspects of the grant or understand its scientific merit, then the grant application is in jeopardy. As one of the top AIDS immunologists in the world, he contends that being on a study section is a long-term commitment for which most people have no time. Thus, some of the best AIDS researchers and clinicians won't ever become study section members. When asked why many of the KS grants (from 1990-92) involving the study of angiogenesis which went to his study section were turned down and critiqued so poorly, he said that these grants in question involved cytokines (IL-6, IL-1, TNF, etc.) and that there wasn't the degree of understanding of cytokines back then as there is now. Even if a grant is turned down at the DRG level because of a poor score or it did not make the payline, there are still ways this grant might be funded. There are exceptions to the general rules for grant funding. But are they for real? There is something called "Special Pay." Roy Wu, a grants officer at the NCI's Cancer Therapy Evaluation Program (CTEP) said that if some of the grants that first come to the NCI (after being sent over from Marcel Pons at the DRG) don't make that 15th percentile, then the NCI program director can ask that the grant be funded "Special Pay." The program director can pick out grants of high priority and submit them to the director of their division (there are 4 scientific Divisions and 1 Division of Extramural Activities within the NCI) where he/she will prioritize and defend them in the executive committee and at National Cancer Advisory Board. There are also "Shannon Grants," named after James Shannon, Director of the NIH from 1955 to 1968. Shannon grants turn into R55s from RO1s and R29s that did not make the payline. Each NIH institute can pick a small number of RO1s and R29s that did not make the payline that they find worthwhile and interesting and submit them to the Office of the Director (OD) of the NIH where they are reviewed. The OD will prioritize the requests from the different institutes. The Big question is: How many AIDS malignancy grants that did not make the payline get funded either through NCI's "exception to the payline" or through "Shannon grants?" A separate granting mechanism is the PO1 (program project grant). These are integrated, multi-component grants with a

minimum of three projects. They are supposed to involve both basic and clinical science. The PI who applies for these grants would need a clinic and labs. Dr. Wu said that he likes these, but very few PIs are submitting POIs. Some researchers, however, who believe that POIs are even harder to get funded than ROIs. There are also U01s that the NCI issued. U01s are cooperative agreements. The ACTG, for example, is a U01. An institute solicits the U01 and the grantee works with the institute staff in implementing these grants. The most current example of a U01 is the Tissue Bank U01 from Ellen Feigal at Cancer Therapy Evaluation Program (CTEP). Unlike contracts, the institute does not dictate projects to the cooperative agreement awardee.

Wu also said that there is an unwritten agreement between the DRG and the NCI that involves multi-institutional clinical trial grant applications. These multi-institutional grants are sent straight to the NCI where they will convene a separate review committee. For example, if a PI from Dana Farber writes a clinical trial protocol that involves University of California at San Francisco and Memorial Sloan-Kettering Cancer Center, this grant will be solely reviewed by a committee assembled by the NCI.

Wu also remarked that he did not think the DRG AIDS study sections fully understand AIDS malignancy grants. He contends, "I have been saying that these grants don't do well in the DRG for the past eight years. I have been bucking the system. I am thought of as a trouble maker over at the DRG."

Harold Varmus, the NIH Director, has recently commissioned an NIH-wide review panel called the Clinical Research Study Group (CRSG) to review the DRG's granting trends. The CRSG has been assembled from intramural and extramural NIH clinicians and researchers. The CRSG is mainly analyzing and comparing scoring on clinical grants vs. basic science grants and they are finding that clinical grants don't do well. They have found that the basic science grants usually receiving better scores.

Jeanne Ketley, Chief of the Clinical Science Review section at the DRG is acting as the Executive Secretary for the CRSG. Ketley reported to me that this group has met three times. Her minutes from the first meeting of the CRSG state:

The CRSG was formed because increased competition for NIH research funds has led to a degree of anxiety and concern in the scientific community of the grant review process, And, [there have been] many requests for new DRG study sections. It is important to remember here that the CRSG is not solely focussing on AIDS, but all unsolicited, extramural clinical research grants funded by the NIH. The fact that Varmus et al. set up the CRSG and believe that all is not well at the DRG does give those who have been complaining about the funding mechanism of AIDS-malignancy research something to go on. It seems as though AIDS activists and AIDS oncologists are not the only ones unhappy with the DRG study sections. However, our claim is that there is a lack of understanding in both the basic and clinical science of KS and AIDS-lymphoma.

The rejected basic and clinical science KS grants that I have reviewed (either deemed not worthy of further consideration or their scores were too high to put them within the pay line) have all been quite interesting for a number of reasons: 1) many of them dealt with the various cytokines and growth factors that we believe are involved in the pathogenesis of KS; and 2) the questions that the grants posed (some in 1991, '92 and '93) still have not been answered -- and probably won't be answered.

Below is a synopsis of six grants ("pink sheets") that were not funded from three of the leading KS researchers. This information is from their DRG "pink sheets" with paraphrased critiques from the study sections.

Grants 1 and 2 were studies of IL-6's role in the pathogenesis of KS. Grant 1 also involved in vitro experiments on four compounds that may downregulate the production of IL-6. Grant 3 was to study the in vitro and in vivo effects of all-trans retinoic acid. Grant 4 was for funding to establish of a center (an AIDS Malignancy Network) for the treatment of patients with KS which would also conduct clinical trials on novel anti-KS agents and serve as a tissue bank. Grant 5 was to conduct a phase I/II clinical trial of liposomal encapsulated doxorubicin (LED) on patients with KS. Grant 6 was to analyze the mechanism of fibroblast growth factor (FGF) 3 gene activation in KS and to develop antisense, monoclonal antibodies and angiogenesis agents to determine their inhibitory KS effects in vitro and in vivo.

The critiques and comments were unfortunately misguided for all of these grants. The generalized critiques/comments were:

These experiments will tell us nothing new about the pathogenesis of KS. There is no need for a confirmatory experiment. There is not enough preliminary data confirming the applicant's hypothesis. Reservation concerning the applicant's KS cell line or an objection for the need to develop new cell lines for in vitro KS studies. A skepticism as to the relevance of any of the compounds that were to be tested.

Problems with Treatment

There is still general confusion as to who is "specifically qualified" to treat patients with AIDS-related malignancies. Should oncologists be the only ones allowed to treat KS or should infectious disease doctors and primary care physicians attempt to treat their patients with KS?

Nobody knows if KS is a "true" malignancy (clonal proliferation) or if it is a dysregulation of angiogenesis in HIV + individuals. Even the semantics of this question can be damaging. This centers around the term "true" malignancy (meaning cancer/meaning life threatening/meaning bad). If physicians want to say that KS is not a "true" malignancy, this leads to a sense of ambivalence concerning treatment and comments such as, "Well if it's not a true malignancy it can't be that bad and therefore why would there be why should there be the need to treat it?"

Would an oncologist with no understanding of AIDS be able to adequately care for an individual with KS? Isn't it important that a treating oncologist be well versed in important aspects of the other complications of his/her patient's HIV disease?

Why are there so few oncologists who have a basic understanding AIDS? And why are so few AIDS oncologists capable of doing basic and clinical research.

Problems with Clinical Research:

The ACTG Oncology Committee vs. the ACTG vs. the NCI

It seems to be a sad truth that the ACTG Oncology Committee has very few friends in the hierarchy of the ACTG and also within the general oncology world. The ACTG Oncology committee has and continues to be heavily invested in the

treatments for patients with HIV-related malignancies. These oncologists specialize in AIDS unlike the vast majority of their fellow oncologists. Hence, they don't fit in with the traditional oncology groups. There is little interest in the study of AIDS-related malignancies in the general oncology research community, and the oncology/cancer conferences devote little time or effort to AIDS-related malignancies. Thus, these ACTG AIDS oncologists and others like them have chosen to live and work in the world of AIDS. But why are they the black sheep within the AIDS research community?

The ACTG is made up primarily of infectious disease doctors who have been used to having it easy for many years. As one NCI oncologist noted:

Those ID docs lived their lives with a 'find a bug, find a pill' mentality. They have never worked in a field such as cancer or leukemia where advances and successes are slow in coming and sometimes don't come at all. They look down on oncologists because we don't have a myriad of great success stories. But, now they are baffled because HIV has finally stumped them. Things are no longer so easy. There is no quick fix.

The Oncology Committee has had to battle with the Executive Committee to get concept sheets approved. In March of 1990, the Executive Committee attempted to cancel all four of the Oncology Committee's high priority trials. Susan Krown (the Chair), Alexandra Levine (the co-Chair), and Ronald Mitsuyasu (the past Chair) of Oncology Committee had to fight like hell to save 3 of their 4 trials.

More recently the Executive Committee has chided the Oncology Committee for slow and low accrual to its various studies. Are these members of the Executive Committee not aware of the overall problem in accruing for all ACTG trials and for their own lack of support for Oncology trials? that fundamentally goes back to them? Many of the members of the Executive Committee are the head PIs at some of the largest ACTUs in the country. Michael Lederman (Case Western), Peter Frame (University of Cincinnati), Michael Saag (University of Alabama), Henry Balfour (University of Minnesota), and Ruy Soeiro (Albert Einstein) have not entered one patient on an ACTG Oncology protocol nor have they registered for any oncology trial at their site. Their ACTUs don't have oncologists to conduct these trials and there obviously is no committed money to hire one. They surely must realize the fact that a lack of committed funds for oncology trials makes it impossible to court a qualified AIDS oncologist. Having trained AIDS oncologists at only a limited number of sites around the country will result in even the most compelling oncology trial to be slow in its accrual.

It is also the unfortunate truth that the Oncology Committee has been stuck with doing uninteresting -- yet nuts-and-bolts -- trials with old cytotoxic chemotherapy drugs and only moderately effective antiviral agents. Why is that? Because we don't have better treatments yet, and we need to know how to use the mediocre ones we do have. In the late 1980s and early 1990s we already had identified the common chemotherapy drugs active against KS. But questions had to be answered such as: 1) Were single agents effective enough or did we need to use them in combination? 2) What dose/s would be most effective with the least toxicities in this patient population? 3) Could we mitigate toxicities while maintaining or improving efficacy? There was also IFN-alpha to consider with the same list of questions. Additionally, KS patients (as well as all AIDS patients) were inundated with the concept that antiviral therapy was crucial for their survival. Whatever one thinks of AZT, ddI, or ddC, we must realize that there are thousands of KS patients on these drugs. This led to further questions such as: 1) Is combining antiviral therapy with cytotoxic agents and IFN-alpha beneficial or harmful? 2) Will the synergy we see with some of these

combinations in vitro result in enhanced clinical benefit? 3) What doses of both drugs can be used safely in combination? Are there overlapping toxicities? Can we administer IFN-alpha and AZT even knowing that they are both myelosuppressive? How extreme is peripheral neuropathy with vincristine and ddI or ddC?

Suffice it to say, the Oncology Committee has answered a great many of these questions, but there are still a number of questions that have not been -- and need to be -- fully answered in KS therapy, such as: * Optimal treatment for early (cutaneous) KS * Optimal treatment for early visceral KS * Second-line treatment for cutaneous KS * Second-line treatment for visceral KS * Salvage therapy for refractory KS * Role of newer agents, e.g., angiogenesis inhibitors, cytokine inhibitors with or without standard treatment

Over the last few years, however, things have changed. We have learned more about the pathogenesis of KS in the past 2 1/2 years than we have during the entire epidemic previously. Basic science research into the pathogenesis of KS has suggested possible etiologic mechanisms for KS and why KS develops in some HIV+ people and not in others. These findings have suggested several new agents which might be effective in controlling KS and even inducing regression of existing lesions. There is now the possibility that some cytokine inhibitors (soluble receptors of IL-1 and TNF, IL-4) and angiogenesis inhibitors (Tecogalan, PF4, TNP 470) might have activity either alone or in combination. Some of these agents down regulate IL-6 and TNF in vitro, but how they will work in humans has yet to be evaluated. Only time will tell. The group needs time and resources. Time is needed to run to run phase I through phase III clinical trials. An effective clinical trials network is needed to run these trials. If the ACTG does not survive or the Oncology Committee is discarded, who's is going to run these trials?

Various other studies also require an "AIDS" clinical trials network. A natural history study is needed to establish the natural history of KS and lymphoma in AIDS. We also need a cancer surveillance study that would tell us how, when, how many and why some HIV+ patients develop KS, lymphoma, or other neoplasias. The ACTG is the perfect place to do these studies. The Oncology Committee with the assistance and resources of the NCI has such the follow up study planned with CS252. CS252 will investigate the cancer consequences of HIV infection and its treatments, including the incidence, spectrum of disease and risk factors of cancer development in HIV. Such a study is crucial in light of the fact that over 25% of HIV+ patients in large antiviral trials (ACTG 019, ACTG 196, and Concorde) developed an AIDS-related malignancy as their AIDS defining endpoint. In fact, 23% of the deaths in ACTG 196 were cancer related.

THE NCI'S AIDS-MALIGNANCY EFFORT

The NCI also plays a complicated role in this dilemma. Their intramural staff which includes effective and dedicated individuals such as: Sam Broder and Judy Karp; Bob Gallo and his Lab; Bob Yarchoan and Hiraoki Mitsuya; Ellen Feigal, Jim Pluda, and Roy Wu at CTEP have made important contributions to AIDS and AIDS-related malignancies. Gallo's laboratory has been in the forefront of the KS pathogenesis research. Various divisions at the NCI have worked hard at putting out broad based RFAs on AIDS-related malignancies. Intramurally, the NCI has -- and continues to -- conducted well designed small phase I/II trials for KS and lymphoma.

At the urging of TAG (and prominent KS researchers), the NCI has also consented to organize and fund a KS Workshop in April 1995. This workshop -- which is

overdue and badly needed -- will assemble the leading KS researchers and clinicians for presentations of current data, discussions on the pathogenesis, epidemiology, natural history, and therapy of KS.

JOHNNY COME LATELY? NO, JOHNNY'S NOT HERE YET.

Extramurally, the NCI has dropped the ball by not creating official AIDS committees within their many cooperative groups (Southwest Oncology Group, Cancer & Acute Leukemia Group B, Gynecological Oncology Group, Radiation Therapy Oncology Group, etc.). With the exception of Eastern Cooperative Oncology Group (ECOG), no other cooperative group has an official committee to review possible AIDS malignancy protocols or expedite a protocol through with the appropriate staff. While there are a few qualified AIDS oncologists floating around in these cooperative group, there is no unified structure. Interestingly enough, it is Jamie von Roenn, current Chair of the ACTG Oncology Committee, who is also the Chair of ECOG's newly formed AIDS committee. Von Roenn has the experience in AIDS, KS, lymphoma and knows what it takes (who to work with or have as consultants) to run an AIDS malignancy trial. She either needs to be cloned or serve as a role model for other cooperative groups. This lack of a cohesive AIDS effort within the cooperative groups is a fundamental problem for the NCI. The cooperative groups -- for all of their years of existence during the AIDS epidemic -- have never worked together by signing onto and completing an AIDS malignancy study. Individually, some of these groups have done several AIDS lymphoma trials. Funding for these trials, however, mostly came from the AIDS Lymphoma Network. It is only now that these cooperative groups will jointly start a CNS lymphoma trial. This trial which will test combination cytotoxic agents followed by radiation is the cooperative group's first trial solely dedicated to the treatment of an AIDS malignancy. That's a milestone. Another milestone involving this trial is the NCI and the ACTG working together by both signing onto this protocol, which will help with broad based patient accrual and hopefully will lead to a sharing of resources. This is the right step, but it comes far too late.

The NCI once believed that they alone could and should conduct phase I through III AIDS malignancy clinical trials without the ACTG. During 1992, there were a number of meetings between intramural and extramural staff of the NCI and the ACTG Oncology Committee with other NIAID staffers. Many of these meetings (AIDS-Lymphoma Network, NCI-NIAID Meeting on AIDS malignancies, Task Force on AIDS Malignancies, and the NCI Strategy Meeting on AIDS Malignancies) brought both institutes together to share knowledge, discuss the pooling of resources, and basically discuss the current state of AIDS-KS and lymphoma. Unbeknownst to ACTG Oncology Committee members, the NCI considered themselves as the ones who should "lead the effort in the fight against AIDS-related malignancies."

Much of this might have been due to the existence of the NCI's AIDS Lymphoma Network which ultimately involved many of the best researchers and clinicians from the ACTG and elsewhere. Publically, the NCI was mentioning that they should be the ones to conduct future AIDS-lymphoma trials. Their master plan was to subsume all of the activities of the ACTG Oncology Committee. This however, was not publicized. The ACTG Executive Committee was outraged when they learned of this possible coup. The outrage was that both DAIDS and the NCI colluded in this without a word to the Executive Committee or the Oncology Committee.

Three things resulted from this controversial aborted coup:

1 The ACTG Oncology Committee was saved from extinction. 2 A lack of trust developed between the ACTG and the NCI. 3 The Task Force on AIDS Malignancies was established as window dressing.

In the end, it simply looked as a rude and aggressive plan on the part of the NCI. However, what is most perplexing is the question that was never really addressed: Did the NCI actually think that they could suddenly assume all AIDS malignancy trials in their ill prepared and AIDS-inexperienced cooperative clinical trials networks? If their cooperative groups were already on board and had a number of experienced AIDS oncologists to activate AIDS-KS and lymphoma protocols, then the coup would not have seemed so pointless. But to disband the present system, albeit somewhat flawed, without a better, functioning system to take its place is asinine and detrimental to people with AIDS.

Do AIDS-KS patients need to be involved in an aids clinical trials network? Are there resources they can get that they won't get elsewhere?

Yes! And for many reasons. Knowing that patients with AIDS have a 30% or greater chance of developing an AIDS-related malignancy later on in their illness (usually when their CD4s drop below 100) means that KS and lymphoma are not going to be their first OIs. They will often be under the care of a primary care physician or an infectious disease doctor who might be associated with an ACTU. While on an AIDS clinical trial (say an ACTG study), they might develop an AIDS-related malignancy and could easily be funneled into an existing oncology protocol. Having this patient in an ACTU that offers oncology trials ensures the patient better access to needed drugs, helps with accrual to important studies, and beefs up the trial network's data bank.

Setting aside the debate as to whether KS is a "true" malignancy, these patients have HIV-- a complex immunodeficiency virus we still don't fully understand. To insure proper care of these HIV infected patients on AIDS malignancy studies, there will often be the need for consultation from specialists in HIV infection and OIs these patients have and will develop. With the knowledge regarding pathogenesis factors (the role of cytokines, etc.), we now have on AIDS-related malignancies, it has become more apparent that AIDS oncologists must interact with AIDS immunologists in the development of certain protocols.

There is also the need for a comprehensive AIDS research agenda in this world of limited funding. The OAR must insure that various NIH Institutes work together with the ACTG to pool resources, to share data, to share patients and to better distribute funding. With the upcoming recompetition and resultant reorganization, the NIAID's ACTG will no longer be able to exist in a vacuum. It will be virtually impossible with only a \$68 million RFA. The NCI and the National Heart Lung and Blood Institute (NHLBI) both have nascent AIDS malignancy efforts. In the future, all three institutes (plus others) must evaluate their efforts to ensure that they are not duplicating certain functions. The NCI and the NHLBI should assess their budgets to determine if giving supplemental funding to the NIAID's ACTG Oncology Committee might be more opportune than commissioning RFAs that might not answer relevant questions. If the NCI and NHLBI choose not to, then the OAR should reduce portions of their budgets and allocate the funds to NIAID's ACTG AIDS-related malignancy efforts.

For example, the NCI's \$700,000+ RFA CA-93-10, Clinical Trials in AIDS Malignancies, distributed approximately \$70,000 each to 11 grantees to conduct pilot or small phase I and II clinical trials of novel therapies. However, giving \$700,000 to the ACTG as supplemental funding for Oncology studies would have been more opportune and cost efficient. In fact, certain ACTUs would be

able to hire oncologists at major sites that should be registering for oncology trials but aren't because there is no oncologist on staff nor funding to hire one.

This \$700,000 distributed widely for "novel" trials in AIDS malignancies is an excellent idea, but it makes more sense to give the money to the one and only existing AIDS clinical trials network that conducts AIDS-related malignancy trials which is incredibly underfunded. While the ACTG Oncology Committee is currently conducting "novel" phase I/II trials of biological modifiers and angiogenesis inhibitors, they are also still attempting to answer old questions that are essential to establishing the basic standards of care. Clinical trials must first determine how best to utilize existing therapies before we go monkeying around with a myriad of experimental compounds. Thus, having supplemental funding would help answer questions, provide more trial sites for patients over a wider geographic area of the country, and in turn, help with the sluggish accrual of most oncology trials.

KS PROJECT RECOMMENDATIONS

1 THE NATIONAL INSTITUTES OF HEALTH (NIH) MUST ADD AN AIDS-RELATED MALIGNANCIES STUDY SECTION UNDER ITS DIVISION OF RESEARCH GRANTS (DRG), OR THE NATIONAL CANCER INSTITUTE (NCI) SHOULD CHARTER AN ONGOING AD HOC AIDS-ONCOLOGY STUDY SECTION.

2 NCI SHOULD PROVIDE MORE EXTRAMURAL FUNDING FOR AIDS-RELATED MALIGNANCIES.

3 THE NCI SHOULD PROVIDE FUNDING IN THE FORM OF SUPPLEMENTAL AWARDS TO AIDS CLINICAL TRIAL UNITS (ACTUs) TO CONDUCT AIDS ONCOLOGY TRIALS, BY SUPPORTING ON-SITE ONCOLOGY EXPERTISE AND NECESSARY ANCILLARY SERVICES.

4 THE AIDS CLINICAL TRIALS GROUP ONCOLOGY COMMITTEE SHOULD REMAIN AN AUTONOMOUS, SEPARATE COMMITTEE WITHIN THE ACTG.

5 ALL NCI COOPERATIVE CLINICAL ONCOLOGY GROUPS SHOULD SET UP AIDS COMMITTEES; THEY SHOULD FORM A JOINT UMBRELLA AIDS ONCOLOGY WORKING GROUP TO LIASON WITH THE ACTG AND CONDUCT CROSS-NETWORK STUDIES.

6 NIH'S OFFICE OF AIDS RESEARCH (OAR) SHOULD WORK TO FOSTER COLLABORATION AND COOPERATION BETWEEN NCI'S COOPERATIVE GROUPS AND NIAID'S ACTG IN CONDUCTING LARGE-SCALE CLINICAL EFFICACY STUDIES TO FURTHER DEFINE THE STANDARD OF CARE AND DEVELOP NEW AGENTS FOR THE TREATMENT OF AIDS-RELATED MALIGNANCIES.

7 NCI SHOULD SUPPORT AN INITIATIVE TO TRAIN MORE AIDS ONCOLOGISTS.

8 OAR SHOULD SUPPORT THE NCI'S BYPASS BUDGET REQUEST TO PROVIDE FUNDS (THROUGH THE P20 MECHANISM) TO THEIR CANCER CENTERS FOR THE DEVELOPMENT OF NEW RESEARCH PROGRAMS FOCUSING ON AIDS-RELATED MALIGNANCIES.

9 OAR SHOULD SUPPORT THE NCI'S 1996 BYPASS BUDGET REQUEST FOR THE PROVISION OF FUNDS FOR PILOT PROJECTS AND FEASIBILITY CLINICAL AIDS ONCOLOGY STUDIES TO BE RUN THROUGH THE NCI'S CANCER CENTERS AND ACTUs.

10 NCI AND NIAID SHOULD ESTABLISH, AMONG EXISTING COHORTS (e.g., MACS OR ACTG, CPCRA), AND/OR AMONG NEW POPULATIONS, A PROSPECTIVE EPIDEMIOLOGICAL SURVEY OF THE INCIDENCE AND NATURAL HISTORY OF AIDS-RELATED MALIGNANCIES, WITH CENTRAL

TISSUE AND SERUM BANKING, TO PROVIDE BETTER INFORMATION ON WHO DEVELOPS THESE COMPLICATIONS AND HOW THEY PROGRESS AND RESPOND TO TREATMENT.

11 OAR, IN COLLABORATION WITH NCI, NIAID, AND THE AGENCY FOR HEALTH CARE POLICY AND RESEARCH (AHCPR), SHOULD ESTABLISH A STATE-OF-THE-ART PANEL TO REVIEW CURRENT TREATMENT OPTIONS FOR AIDS-RELATED MALIGNANCIES (ESPECIALLY KS) AND RECOMMEND STANDARD-OF-CARE GUIDELINES, AS WELL AS IDENTIFY GAPS IN KNOWLEDGE WHICH COULD BE FILLED BY WELL-DESIGNED AND EXECUTED RANDOMIZED CONTROLLED STUDIES. A STANDARD OF CARE MUST BE ESTABLISHED SO THAT WE FINALLY KNOW WHAT IS THE OPTIMAL THERAPY FOR KS PATIENTS AT VARIOUS STAGES OF DISEASE.

12 THE NEW TREATMENT GUIDELINES SHOULD MAKE IT CLEAR THAT KS AND LYMPHOMA PATIENTS SHOULD BE REFERRED TO AN AIDS ONCOLOGIST FOR EVALUATION AND A DISCUSSION OF POSSIBLE TREATMENTS. "THE [MERE] OBSERVATION OF PATIENTS WITH PROGRESSIVE KS IS UNACCEPTABLE."

13 A MECHANISM NEEDS TO BE ESTABLISHED UP TO TEACH ONCOLOGISTS ABOUT AIDS AND HOW TO BECOME MORE INVOLVED IN BASIC AND CLINICAL RESEARCH .

14 PRIMARY CARE PHYSICIANS AND PATIENTS MUST ALSO LEARN MORE ABOUT THE CURRENT PATHOGENESIS OF AIDS MALIGNANCIES..

15 SERIOUS THOUGHT NEEDS TO GO INTO HOW WE GET PHYSICIANS TO REFER KS PATIENTS INTO CURRENT (AND THE NEXT GENERATION OF) ANTI-ANGIOGENESIS/CYTOKINE MODULATION TRIALS, AND OTHER NOVEL APPROACHES TO TREATING AIDS-RELATED MALIGNANCIES..

16 WE NEED TO STUDY WHETHER ANGIOGENESIS INHIBITORS AND CYTOKINE MODULATORS (MAYBE IN COMBINATION) ARE APPROPRIATE FOR PATIENTS WITH EARLY STAGE KS OR MAY PREVENT THE FORMATION OF NEW LESIONS. IN TIME, AFTER WE HAVE LEARNED MORE ABOUT THESE AGENTS, WILL WE BE AT THE POINT WHERE WE CAN SAY THAT THESE COMPOUNDS MIGHT BE EFFECTIVE AS PROPHYLAXIS FOR KS? REFERENCES

Aboulafia D, Miles SA, Saks SR, et al.: Intravenous recombinant tumor necrosis factor in the treatment AIDS-related Kaposi's sarcoma. *J Acquir Immune Defic Syndr* 2:54-58, 1989.

Abrams D: The relationship between Kaposi's sarcoma and intestinal parasites among homosexual males in the United States. *Journal of Acquired Immune Deficiency Syndromes* 3(suppl.1):S44-S46, 1990.

Afrasiabi R, Mitsuyasu RT, Nishanian P, et al.: Characterization of a distinct subgroup of high-risk persons with Kaposi's sarcoma and good prognosis who present with normal T4 cell number and T4:T8 ratio and negative HTLV-III/LAV serologic test results. *American Journal of Medicine* 81:969-973, 1986.

Archibald CP, Schechter MT, Craib KJP, et al.: Risk factors for Kaposi's sarcoma in the Vancouver lymphadenopathy-AIDS study. *Journal of Acquired Immune Deficiency Syndromes* 3 (suppl. 1):S18-S23, 1990.

Archibald CP, Schechter MT, Le TN, et al.: Evidence for a sexually transmitted cofactor for AIDS-related Kaposi's sarcoma in a cohort of homosexual men. *Epidemiology* 3(3):203-209, 1992.

Armenian HK, Hoover DR, Rubb S, et al.: Composite risk score for Kaposi's sarcoma based on a case-control and longitudinal study in th multicenter AIDS cohort study population. *American Journal of Epidemiology* 138(4):256-265, 1993.

Baggish MS, Poiesz BJ, Joert D, et al.: Presence of human immunodeficiency virus DNA in laser smoke. *Laser Surg Med* 11:197-203, 1991.

Barillari G, Buonaguro L, Fiorelli V, et al.: Effect of cytokines from activated immune cells on vascular cell growth and HIV-1 gene expression. *Journal of Immunology* 149:3727-3734, 1992.

Beral V, Peterman TA, Berkelman RL, et al.: Kaposi's sarcoma among persons with AIDS: a sexually transmitted infection? *Lancet* 335:123-128, 1990.

Beral V, Bull D, Jaffe H, et al.: Is risk of Kaposi's sarcoma in AIDS patients in Britain increased if sexual partners came from the United States or Africa? *BMJ* 302:624-625, 1991.

Beral V, Bull D, Darby S, et al.: Risk of Kaposi's sarcoma and sexual practices associated with faecal contact in homosexual or bisexual men with AIDS. *Lancet* 339:632-635, 1992.

Bernson AM, Quincy JM, Harris JW, et al.: Radiation therapy for AIDS-related Kaposi's sarcoma. *Int J Radiat Oncol Bio Phys* 19:569-575, 1990.

Bernstein ZP, Wilson D, Mang TS: Pilot study-photodynamic therapy (PDT) for treatment of AIDS-associated Kaposi's sarcoma (AIDS/KS) [abstract]. *Proc Am Soc Clin Oncol* 13:51, 1994.

Biberfeld P, Kaaya EE, Parravicini, et al.: Heterogeneity, ploidy and proliferation of spindle cells in HIV-associated and endemic Kaposi's sarcoma. Gallo Lab Meeting, September, 1993.

Biggar RJ, Dunsmore N, Kurman RJ, et al.: Failure to detect human papillomavirus in Kaposi's sarcoma. *Lancet* 339:1604-1605, 1992.

Binkin N, Angarano G, Cargnel A, et al.: Epidemic Kaposi's sarcoma in females AIDS patients-a report of 23 Italian cases. *AIDS* 5(4):466-467, 1991.

Bonhomme L, Fredj G, Averous S, et al.: Topical treatment of epidemic Kaposi's sarcoma with all-trans-retinoic acid. *Ann Oncol* 2:234-235, 1991.

Bonhomme L, Fredj G, Maurisson G, et al.: Systemic treatment of AIDS-associated Kaposi's sarcoma (KS) with all-trans retinoic acid (ATRA) [Abstract]. PO-B12-1562, IX Intl Conf AIDS, Berlin, 1993.

Borden EC, Ball LA: Interferon: biochemical, cell growth, inhibitory, and immunologic effects. *Prog Hematol* 12:299-339, 1981.

Borden EC, Hogan TF, Voelkel JG: Comparative antiproliferative activity in vitro of natural interferons alpha and beta for diploid and human cells. *Cancer Res* 42:4948-4953, 1982.

Buchbinder A, Friedman-Kien AE. Clinical aspects of Kaposi's sarcoma. *Current Opinion in Oncology* 4:867-874, 1992.

Carswell EA, Old LJ, Kassel RL, et al.: An endotoxin-induced serum factor that causes necrosis of tumors. *Proc Natl Acad Sci USA* 72:3666-3670, 1975.

Casabona J, Melbye M, Biggar RJ, et al.: Kaposi's sarcoma and non-hodgkins lymphoma in European AIDS cases. No excess risk of Kaposi's sarcoma in Mediterranean countries. *Int J Cancer* 47:49-53, 1991.

Castro A, Pedreira J, Soriano V, et al.: Kaposi's sarcoma and disseminated Tb in HIV-negative individual. *Lancet* 339:868, 1992.

Caumes E, Guernonprez G, Katlama C, et al.: AIDS-associated mucocutaneous Kaposi's sarcoma treated with bleomycin. *AIDS* 6:1483-1487, 1992.

Chew T, Jacobs M, Huckabee M, et al.: Phase II clinical trial of DaunoXome (VS-103, liposomal daunorubicin) in Kaposi's sarcoma of AIDS patients [Abstract]. WS-B15-3 IX Intl Conf AIDS, Berlin, 1993.

Corbeil J, Evans LA, Vasak E, et al.: Culture and properties of cells derived from Kaposi's sarcoma. *J Immunol* 146:2972-2976, 1991.

Cote TR, O'Brien TR, Ward JW, et al.: The completeness of surveillance for people with AIDS and Kaposi's sarcoma: results of registry linkage in the United States. Unpublished, 1993.

Couturier E, Ancelle-Park RA, DeVincenzi I, et al.: Kaposi's sarcoma as asexually transmitted disease. *Lancet* 335:1105, 1992.

Darrow WW, Peterman TA, Jaffe HW, et al.: Kaposi's sarcoma and exposure to faeces. *Lancet* 339:685, 1992.

Delli BP, Donti E, Knowles DM, et al.: Presence of chromosomal abnormalities and lack of AIS-retrovirus DNA sequences in AIDS associated Kaposi's sarcoma. *Cancer Research* 46:6333-6338, 1986.

de Wit R, Schatenkerk JKME, Boucher CAB, et al.: Clinical and virological effects of high-dose recombinant interferon-alpha in disseminated AIDS-related Kaposi's sarcoma. *Lancet* 2:1214-1217, 1988.

de Wit R, Reiss P, Bakker PJM, et al.: Lack of activity of zidovudine in AIDS-associated Kaposi's sarcoma. *AIDS* 3:847-850, 1989.

de Wit R, Smit WGJM, Veenhof KHN, et al.: Palliative radiation therapy for AIDS-associated Kaposi's sarcoma by using a single fraction of 800 cGY. *Radiother Oncol* 19:131-136, 1990.

Dezube BJ, Fridovich-Keil JL, Bouvard I, et al.: Pentoxifylline and wellbeing in patients with cancer [letter]. *Lancet* 335:662, 1990.

Dictor M, Bendsoe N: Transmissible agent of Kaposi's sarcoma. *Lancet* 335:797, 1990.

Dinarello CA: Interleukin-1 and interleukin-1 antagonism. *Blood* 77:1627-1652, 1991.

Dower SK, Wignall JM, Schooley K, et al.: Retention of ligand binding activity by the extracellular domain of the IL-1 receptor. *J Immunol* 142:4314-4320, 1989.

Dower SK, Smith CA, Park LS: Human cytokine receptors. *J Clin Immunol* 10:289-199, 1990.

Elford J, Tindall B, Sharkey T: Kaposi's sarcoma and insertive rimming. *Lancet* 339:938, 1992.

Elford J, McDonald A, Kaldor J, et al.: Kaposi's sarcoma as a sexually transmissible infection: an analysis of Australian AIDS surveillance data. *AIDS* 7:1667-1671, 1993.

Ensoli B, Nakamura S, Salahuddin SZ, et al.: AIDS-Kaposi's sarcoma-derived cells express cytokines with autocrine and paracrine growth effects. *Science* 243:223-226, 1989.

Ensoli B, Bariliari G, Salhuddin SZ, et al.: Tat protein of HIV-stimulated growth of sells derived from Kaposi's sarcoma lesions of AIDS patients. *Nature* 345:84-86, 1990.

Ensoli B, Barillari G, Buonaguro L, et al.: Molecular mechanisms in the pathogenesis of AIDS-associated Kaposi's sarcoma. *Immunology of Proteins and Peptides VI*. 1991.

Ensoli B, Barillari G, Albini A, et al.: Cooperation of HIV-1 tat protein, inflammatory cytokines and basic fibroblast groth factor (bFGF) in the pathogenesis of AIDS-Kaposi's sarcoma [Abstract]. *Laboratory of Tumor Cell Biology, 1993 Annual Meeting, 1993*.

Ensoli B, Markham P, Kao V, et al.: Basic fibroblast growth factor (bFGF) induces lesions in mice resembling Kaposi's sarcoma (KS) and antisense oligonucleotides against this cytokine inhibit the growth and angiogenic activity of KS spindle cells [Abstract]. *Laboratory of Tumor Cell Biology, 1993 Annual Meeting, Bethesda, 1993*.

Ensoli B, Gallo RC: Growth factors in AIDS-associated Kaposi's sarcoma: cytokines and HIV-1 Tat protein. *AIDS Updates* 7(1):1-12, 1994.

Epstein JB, Lozada-Nur F, McLeod WA, et al.: Oral Kaposi's sarcoma in acquired immunodeficiency syndrome. Review of management and report of the effacy of intralesional vinblastin. *Cancer* 64:2424-2430, 1989.

Epstein JB: Treatment of oral Kaposi's sarcoma with intralesional vinblastine. *Cancer* 71:1722-1725, 1993.

Evan LM, Itri LM, Campion M, et al.: Interferon alfa-2a in the treatment of acquired immunodeficiency syndrome-related Kaposi's sarcoma. *J Immunother* 10:39-50, 1991.

Fauci AS (presented by Poli G) . The role of cytokines in the regulation of HIV expression [Abstract E026]. *J Cell Biochem* 17B:58, 1993.

Fazely F, Dezube BJ, Allen-Ryan J, et al.: Pentoxifylline (Trental) decreases the replication of hunam immunodeficiency virus type 1 in human peripheral blood mononuclear cells and in cultured T cells. *Blood* 77:1653-1656, 1991.

Ficarra G, Bernson AM, Silverman S, et al.: Kaposi's sarcoma of the oral cavity: a study of 134 patients with a review of the pathogenesis, epidemiology, clinical aspects, and treatment. *Oral Surg Oral Med Oral Pathol* 66:543-550, 1988.

Fidler IJ, Singh RK, Gutman M, et al.: Interferons alpha and beta downregulate the expression of basic fibroblast growth factor (bFGF) in human carcinomas [Abstract 34]. Proc Amer Assoc Cancer Res 35:57, 1994.

Fiorelli V, Gallo RC, Ensoli B, et al.: The effects of HIV-tat protein on the cell cycle of cytokin-activated endothelial cells resembles that of basic fibroblast growth factor (bFGF) [Abstract]. Laboratory of Tumor Cell Biology, 1993 Annual Meeting, Bethesda, 1993.

Fischl MA, Uttamchandani RB, Resnick L, et al.: A phase I study of recombinant human interferon alfa-2a or human lymphoblastoid interferon alfa-n1 and concomitant zidovudine in patients with AIDS-related Kaposi's sarcoma. J Acquir Immune Defic Syndr 4:1-10, 1991.

Fischl MA, Krown SE, O'Boyle KP, et al.: Weekly doxorubicin in the treatment of patients with AIDS-related Kaposi's sarcoma. AIDS Clinical Trials Group. J Acquir Immune Defic Syndr 6:259-264, 1993.

Friedman-Kien AE, Saltzman BR, Cao Y, et al.: Kaposi's sarcoma in HIV-negative homosexual men. Lancet 339:168-169, 1990.

Fujiwara H, Hashimoto K, Fujiwara K, et al.: Detection of HIV-1 and HPV-16 in AIDS-related and classic Kaposi's sarcoma. Arch Dermatol 129:1620-1622, 1993.

Garay SM, Belenke M, Fazzini E, et al.: Pulmonary manifestations of Kaposi's sarcoma. Chest 91:39-43, 1987.

Gill PS, Bisher A, Colletti P, et al.: Pulmonary Kaposi's sarcoma: clinical findings and results of therapy. Am J Med 87:57-61, 1989.

Gill PS, Rarick MU, Bernstein-Singer M, et al.: Interferon-alpha maintenance therapy after cytotoxic chemotherapy for treatment of acquired immunodeficiency syndrome-related Kaposi's sarcoma. J Biol Response Mod 9:512-516, 1990.

Gill PS: Phase I/II trials of alpha-interferon alone or in combination with zidovudine as maintenance therapy following induction chemotherapy in the treatment of acquired immunodeficiency syndrome-related Kaposi's sarcoma. Semin Oncol 18:53-57, 1991.

Gill PS: Phase I/II trial with liposomal daunorubicin (DaunaXome) in AIDS-related Kaposi's sarcoma [Abstract]. Am Soc Hematol, Denver, 1991.

Gill PS, Rarick MU, McCutchan JA, et al.: Systemic treatment of AIDS-related Kaposi's sarcoma: results of a randomized trial. Am J Med 90:427-433, 1991.

Gill PS, Bernstein-Singer M, Espina BM, et al.: Adriamycin, bleomycin, and vincristine chemotherapy with recombinant granulocyte-macrophage colony-stimulating factor in the treatment of AIDS-related Kaposi's sarcoma. AIDS 6:1477-1481, 1992.

Gill PS, PA-C Kidane S, Tulpule A, et al.: A phase I study of DS-4152, a novel angiogenesis inhibitor in the treatment of AIDS-related Kaposi's sarcoma [Abstract]. NCI-EORTC, Amsterdam, 1994.

Goebel WM, Lucatorto FM: Sodium tetradecyl sulfate treatment of benign vascular abnormalities. J Oral Med 31:9-13, 1976.

Goebel F-D, Bognor JR, Spathling S. et al.: Efficacy and toxicity of liposomal doxorubicin in advanced AIDS-related Kaposi's sarcoma. An open study [Abstract]. WS-B15-6, IX Intl Conf AIDS, Berlin, 1993.

Gompels MM, Hill A, Jenkins P, et al.: Kaposi's sarcoma in HIV infection treated with vincristine and bleomycin. AIDS 6:1175-80, 1992.

Gottlieb GJ, Ackerman AB: Kaposi's sarcoma: an extensively disseminated form in young homosexual men. Human Pathol 13:882-892, 1982.

Granowitz EV, Clark BD, Vannier E, et al.: Effects of interleukin-1 (IL-1) blockade on cytokine synthesis. IL-1 receptor antagonist inhibits IL-1 induced cytokine synthesis and blocks the binding of IL-1 to its type II receptor on human monocytes. Blood 79:2356-2356, 1992.

Hartshorn KL, Vogt MW, Chou T-C, et al.: Synergistic inhibition of human immunodeficiency virus in vitro by azidothymidine and recombinant alpha A interferon. Antimicrob Agents Chemother 31:168-172, 1987.

Haverkos HW, Pinsky PF, Drotman DP, et al.: Disease manifestation among homosexual men with acquired immunodeficiency syndrome: a possible role of nitrites in Kaposi's sarcoma. Sexually Transmitted Diseases 12(4):203-208, 1985.

Haverkos H: Nitrite inhalant abuse and AIDS-related Kaposi's sarcoma. Journal of Acquired Immune Deficiency Syndromes 3(suppl.1) S47-S50, 1990.

Hebeda K, Bakker BJM, Huizing MT, et al.: Photodynamic therapy (PDT) in AIDS related cutaneous Kaposi's sarcoma (KS) [Abstract]. PO-B12- 1599, IX Intl Conf AIDS, Berlin, 1993.

Herrmann F, Andreeff M, Gruss H, et al.: Interlukin-4 inhibits growth of of multiple myelomas by supressing interlukin-6 expression. Blood 78:2070-2074, 1991.

Heslop HE, Bianchi ACM, Cordingley FT, et al.: Effects of interferon-alpha on autocrine growth factor loops in B lymphoproliferative disorders. J Exp Med 172:1729, 1990.

Hoover DR, Black C, Jacobson LP, et al.: Epidemiologic analysis of Kaposi's sarcoma as an early and later AIDS outcome in homosexual men. American Journal of Epidemiology 138(4):266-278, 1993.

Huang YQ, Buchbinder A, Li JJ, et al.: The absence of Tat sequence in tissues of HIV-negative patients with epidemic Kaposi's sarcoma. AIDS 6:1139-1142, 1992.

Huang YQ, Li JJ, Rush MG, et al.: HPV-16-related sequences in Kaposi's sarcoma. Lancet 339:515-518, 1992.

Huang YQ, Friedman-Kien AE, LI JJ, et al.: Cultured Kaposi's sarcoma cell lines express factor XIIIa, CD14, and VCAM-1, but not factor VIII or ELAM-1. Arch Dermatol 129:1291-1296, 1993.

Huang YQ, Li JJ, Moscacelli D, et al.: Expression of int-2 oncogene in Kaposi's sarcoma lesions. Journal of Clinical Investigation 91:1191-1197, 1993.

Ingber D, Fugita T, Shoi K, et al.: Synthetic analogues of fumagillin thet inhibit angiogenesis and suppress tumor growth. Nature 348:555-557, 1990.

Ireland-Gill A, Espina BM, Akil B, et al.: Treatment of acquired immunodeficiency syndrome-related Kaposi's sarcoma using bleomycin-containing combination chemotherapy regimens. *Semin Oncol* 19:32-37, 1992.

Jablonowski H, Szelenyi H, Armbrecht C, et al.: Liposomal doxorubicin - a new formulation for the treatment of Kaposi's sarcoma: A study on safety and efficacy in AIDS patients [Abstract]. PO-B12-1573 IX Intl Conf AIDS, Berlin, 1993.

Jacobson LP, Munoz A, Fox R, et al.: Incidence of Kaposi's sarcoma in a cohort of homosexual men infected with HIV-1. *Journal of Acquired Immune Deficiency Syndromes* 3(suppl. 1):S24-S31, 1990.

Kahn JO, Kaplan LD, Volberding PA, et al.: Intralesional recombinant tumor necrosis factor alpha for AIDS-associated Kaposi's sarcoma: A randomized double-blind trial. *J AIDS* 2:217-223, 1989.

Kahn JO, Ruiz R, Kerschman R, et al.: A phase I/II study of recombinant platelet factor 4 (rPF4) in patients with AIDS-related Kaposi's sarcoma (KS) [Abstract]. *Proc Am Soc Clin Oncol* 12:50, 1993.

Kaplan L, Abrams D, Volberding P: Treatment of Kaposi's sarcoma in acquired immunodeficiency syndrome with alternating vincristine-vinblastine regimen. *Cancer Treat Rep* 70:1121-1122, 1986.

Kitchen VS, French MA, Dawkins RL: *Letter Lancet* 335:797-798, 1990.

Klimas NC, Fletcher M, Walling J, et al.: Phase I trial of adoptive therapy with purified CD8 cells in HIV infection [Abstract]. PO-B-3446, VIII Intl Conf AIDS, Amsterdam, 1992.

Klimas NC, Fletcher M, Walling J, et al.: Response of Kaposi's sarcoma (KS) to autologous CD8 cells expanded and activated ex vivo and reinfused with rIL-2 [Abstract]. WS-B15-2, IX Intl Conf AIDS, Berlin, 1993.

Kovacs JA, Deyton L, Davey R, et al.: Combined zidovudine and interferon-alpha therapy in patients with Kaposi's sarcoma and the acquired immunodeficiency syndrome (AIDS). *Ann Intern Med* 111:280-287, 1989.

Kovacs JA, Vogel S, Falloon M, et al.: Intermittent interleukin-2 therapy leads to sustained increases in CD4 counts in some HIV-infected patients [Abstract]. PO-B28-2155 IX Intl Conf AIDS, Berlin, 1993.

Krown SE, Real FX, Cunningham-Rundles S, et al.: Preliminary observations on the effect of recombinant leukocyte A interferon in homosexual men with Kaposi's sarcoma. *N Engl J Med* 308:1071-1076, 1983.

Krown SE, Gold JWM, Niedzwiecki D, et al.: Interferon-alpha with zidovudine: Safety, tolerance, and clinical and virologic effects in patients Kaposi's sarcoma associated with the acquired immunodeficiency syndrome (AIDS). *Ann Intern Med* 112:812-821, 1990.

Krown SE, Myskowski PL, Paredes J: Kaposi's sarcoma: medical management of AIDS patients. *Med Clin North Am* 76:235-257, 1992.

Krown SE, Paredes J, Bundow D, et al.: Interferon-alpha, zidovudine, and granulocyte-macrophage colony stimulating factor: a phase I AIDS clinical trials group study in patients with Kaposi's sarcoma associated with AIDS. *J Clin Oncol* 10:1344-1351, 1992.

Krown SE: The "changing face" of Kaposi's sarcoma. *Oncology* 7(12):33, 37, 1993.

Lahdevirta J, Maury DPT, Teppo A-M, et al.: Elevated levels of circulating cachectin/tumor necrosis factor in patients with acquired immunodeficiency syndrome. *Amer J Med* 85:289-291, 1988.

Lane HC, Kovacs JA, Feinberg J, et al.: Anti-retroviral effects of interferon-alpha in AIDS-associated Kaposi's sarcoma. *Lancet* 2:1218-1222, 1988.

Lane HC, Falloon J, Walker RE, et al.: Zidovudine in patients with human immunodeficiency virus (HIV) infection and Kaposi's sarcoma. *Ann Intern Med* 111:41-50, 1989.

Lane HC, Davey V, Kovacs JA, et al.: Interferon-alpha in patients with asymptomatic human immunodeficiency virus (HIV) infection. A randomized, placebo-controlled trial. *Ann Intern Med* 112:805-811, 1990.

Lassoued K, Clauvel JP, Katlama C, et al.: Treatment of acquired immunodeficiency syndrome-related Kaposi's sarcoma with bleomycin as a single agent. *Cancer* 66:1869-1872, 1990.

Lassoued K, Clauvel JP, Fegueux S, et al.: AIDS-associated Kaposi's sarcoma in female patients. *AIDS* 5:877-880, 1991.

Laubenstein LJ, Krigel RL, Odajnyk CM, et al.: Treatment of epidemic Kaposi's sarcoma with etoposide or a combination of doxorubicin, bleomycin and vinblastine. *J Clin Oncol* 2:1115-1120, 1984.

Levine AM: AIDS-related malignancies: the emerging epidemic. *J Natl Cancer* 85:1382-1397, 1993.

Li JJ, Huang HQ, Mostacelli D, et al.: Expression of fibroblast growth factors and their receptors in acquired immunodeficiency syndrome-associated Kaposi's sarcoma tissue and derived cells. *Cancer* 72(7):2253-2259, 1993.

Lifson AR, Darrow WW, Hessol NA, et al.: Kaposi's sarcoma in a cohort of homosexual and bisexual men. *American Journal of Epidemiology* 131(2):221-231, 1990.

Lowdell CP, Glaser MG: Long-term survival of male homosexual patients with Kaposi's sarcoma. *Journal of the Royal Society of Medicine* 82:226-227, 1989.

Lucatorto FM, Sapp JP: Treatment of oral Kaposi's sarcoma with a sclerosing agent in AIDS patients. A preliminary study. *Oral Surg Oral Med Oral Pathol* 75:192-198, 1993.

Lunardi-Iskandar Y, Lam V, Gill PS, et al.: The first Kaposi's sarcoma derived cell line (KS Y-1): related to and differences from KS cell strains [Poster]. M-48, Laboratory of Tumor Cell Biology 1993 Annual Meeting, Bethesda, 1993.

Maione TE, Gray J, Petro AJ, et al.: Inhibition of angiogenesis by recombinant human platelet factor-4 and related peptides. *Science* 247:77-79, 1990.

Mansukhani A, Mostacelli D, Talarico D, et al.: A murine fibroblast growth factor (FGF) receptor expressed in CHO cells is activated by basic FGF and Kaposi's FGF. *Proc Natl Acad Sci* 87:4378-4382, 1990.

Marmor M, Friedman-Kien AE, Zolla-Pazner S, et al.: Kaposi's sarcoma in homosexual men: a seroepidemiologic case-control study. *Annals of Internal Med* 100:809-815, 1984.

Meduri GU, Stover DE, Lee M, et al.: Pulmonary Kaposi's sarcoma in the acquired immunodeficiency syndrome: clinical, radiographic, and pathologic manifestations. *Am J Med* 81:11-18, 1986.

Miles SA, Rezai AR, Salazar-Gonzalez JF, et al.: AIDS Kaposi's sarcoma-derived cells produce and respond to interleukin-6. *Proc Natl Acad Sci* 87:4068-4072, 1990.

Miles SA, Rezai A, Martines-Maza O, et al.: Recombinant platelet factor 4 (rPF4) and a non-heparin binding derivative inhibit AIDS-Kaposi's sarcoma derived cell lines [Abstract]. W.A.1066, VII Intl Confr AIDS, Florence, 1991.

Miles SA, Martinez-Maza O, Rezai A, et al.: Oncostatin-M as a potent mitogen for AIDS-Kaposi's sarcoma derived cells. *Science* 255:1432-1434, 1992.

Miles SA, Mitsuyasu RT: Kaposi's sarcoma. (In press, 1994).

Miles SA, Wangt H, Elashoff R, et al.: Improved survival for patients with AIDS-related Kaposi's sarcoma. Unpublished, 1994.

Mintzer DM, Real FX, Jovino L, et al.: Treatment of Kaposi's sarcoma and thrombocytopenia with vincristine in patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 102:200-202, 1985.

Mitsuyasu RT: Clinical aspects of AIDS-related Kaposi's sarcoma. *Curr Opin Oncol* 5:835-844, 1993.

Mitsuyasu RT, Gill PS, Paredes J, et al.: Preliminary results of a phase I/II trial of combination chemotherapy with ddI or ddC in AIDS-related Kaposi's sarcoma (ACTG 163) [abstract]. PO-B12-1565, IX Intl Conf AIDS, Berlin, 1993.

Munoz A, Schragger LK, Bacellar H, et al.: Trends in the incidence of outcomes defining AIDS in the multicenter AIDS cohort study: 1985-1991. *American Journal of Epidemiology* 137(4):423-438, 1993.

Murphy WK, Fossella FV, Winn RJ, et al.: Phase II study of taxol in patients with untreated advanced non-small-cell lung cancer. *J Natl Cancer Inst* 85(5):384-388, 1993.

Myskowski PL, Niedzwieck D, Shurgot BA, et al.: AIDS-associated Kaposi's sarcoma: variables associated with survival. *J Am Acad Dermatol* 18:1299-1306, 1988.

Nakamura S, Salahuddin SZ, Bidderfeld P, et al.: Kaposi's sarcoma cells: Long-term culture with growth factors from retrovirus-infected CD4+ T cells. *Science* 242:426-430, 1988.

Nakamura S, Sakurada S, Salahuddin SZ, et al.: Inhibition of development of Kaposi's sarcoma-related lesions by a bacterial cell wall complex. *Science* 255:1437-1440, 1992.

Ndimbie OK, Hutchins GM, Variakojis D et al.: Skin, visceral, and skin and visceral Kaposi's sarcoma in autopsies of homosexual men in the multicenter AIDS cohort center study (MACS) [Abstract 501]. 1st Nat Conf on Hum Retroviruses, 1993.

Newman S: Treatment of epidemic Kaposi's sarcoma with intralesional vinblastine injection [abstract]. *Proc Am Soc Clin Oncol* 7:5, 1988.

Nisce LZ, Safai B, Poussin-Rosillo H: Once weekly total and subtotal skin electron beam therapy for Kaposi's sarcoma. *Cancer* 47:640-644, 1981.

Nisce LZ, Kaufman T: Radiation therapy for Kaposi's sarcoma. *Infect Med* 10(3):54-58, 1993.

Northfelt DW, Martin FJ, Kaplan LD, et al.: Pharmacokinetics (PK), tumor localization (TL), and safety of Doxil (liposomal doxorubicin) in AIDS patients with Kaposi's sarcoma (AIDS-KS) [Abstract]. *Proc Am Soc Clin Oncol* 12:51 (8A), 1993.

Northfelt DW: StealthR liposome doxorubicin (SLD) delivers more doxorubicin (DOX) to AIDS-Kaposi's sarcoma (AIDS-KS) lesions than to normal skin [Abstract]. *Proc Am Soc Clin Oncol* 13:51 (5), 1994.

Oikawa T, Hirotsu K, Nakamura O, et al.: A highly potent antiangiogenic activity of retinoids. *Cancer Letters* 48:157-162, 1989.

Payne SF, Lemp GF, Rutherford GW: Survival following diagnosis of Kaposi's sarcoma for AIDS patients in San Francisco. *Journal of Acquired Immune Deficiency Syndromes* 3(suppl.1):S14-S17, 1990.

Peterman TA, Friedman-Kien AE, Jaffe HW, et al.: (Letter) *Lancet* 339:685-686, 1992.

Peterman TA, Jaffe HW, Beral V. Epidemiologic clues to the etiology of Kaposi's sarcoma. *AIDS* 7:605-611, 1993.

Peters BS, Beck EJ, Wadsworth MJH, et al.: Changing disease pattern in patients with AIDS in a referral center in the United Kingdom: the changing face of AIDS. *BMJ* 302:203-206, 1991.

Pluda JM, Parkinson DR, Feigal E, et al.: Noncytotoxic approaches to the treatment of HIV-associated Kaposi's sarcoma. *Oncology* 7(12):25-33, 1993.

Pluda JM, Shay LE, Foli A, et al.: Administration of pentosan polysulfate to patients with human immunodeficiency virus-associated Kaposi's sarcoma. *J Natl Cancer Inst* 85:1585-1592, 1993.

Pluda JM, Wyvil K, Figg D, et al.: A phase I trial of TNP-470 (AGM-1470) administered to patients with HIV-associated Kaposi's sarcoma (KS) [Abstract 31]. The First National Conference on Human Retroviruses and Related Infections, Washington, D.C. 1993.

Poli G, Oronstein JM, Kinter A, et al.: Interferon-alpha but not AZT suppress HIV expression in chronically infected cell lines. *Science* 244:575-577, 1989.

Presant CA, Scolaro M, Kennedy P, et al.: Liposomal daunorubicin treatment of HIV-associated Kaposi's sarcoma. *Lancet* 341:1242-1243, 1993.

Rabkin CS, Goedert JJ, Biggar RJ, et al.: Kaposi's sarcoma in three HIV-infected cohorts. *Journal of Acquired Immune Deficiency Syndromes* 3(suppl.1):S38-S43, 1990.

Rabkin CS, Hilgartner MW, Hedberg KW, et al.: Incidence of lymphomas and other cancers in HIV-infected and HIV-uninfected patient with hemophilia. *JAMA* 267(8):1090-1094, 1992.

Rarick MU, Gill PS, Montgomery T, et al.: Treatment of epidemic Kaposi's sarcoma with combination chemotherapy (vincristine and bleomycin) and zidovudine. *Ann Oncol* 1:147-149, 1990.

Real FX, Krown SE, Oettgen HF: Kaposi's sarcoma and the acquired immunodeficiency syndrome: Treatment with high and low doses of recombinant leukocyte A interferon. *J Clin Oncol* 4:544-551, 1986.

Regezi SA, MacPhail LA, Daniels TE, et al.: Human immunodeficiency virus-associated oral Kaposi's sarcoma: a heterogeneous cell population dominated by spindle-shaped endothelial cells. *Am J Pathol* 43:240-249, 1993.

Reynolds P, Layefsky ME, Saunders LD, et al.: Kaposi's sarcoma reporting in San Francisco: A comparison of AIDS and cancer surveillance systems. *Journal of Acquired Immune Deficiency Syndromes* 3(suppl. 1):S8-S13, 1990.

Reynolds P, Saunders LD, Layefsky ME, et al.: The spectrum of acquired immunodeficiency syndrome (AIDS)-associated malignancies in San Francisco, 1980-1987. *American Journal of Epidemiology* 137(1):19-30, 1993.

Roth WK, Werner S, Schirren CG, et al.: Depletion of PDGF from serum inhibits growth of AIDS-related and sporadic Kaposi's sarcoma cells in culture. *Oncogene* 4:483-487, 1989.

Roth WK, Brandsetter H, Sturzl M: Cellular and molecular features of HIV-associated Kaposi's sarcoma. *AIDS* 6:895-913, 1992.

Rozenbaum W, Gharakhanian S, Navarette MS, et al.: Long-term follow-up of 120 patients with AIDS-related Kaposi's sarcoma treated with interferon alpha-2A. *Invest Dermatol* 95:161S-165S, 1990.

Ruprecht RM, O'Brien L, Rosas D, et al.: Recombinant human interferon alphaA/D (rHuIFN-alphaA/D) enhances the anti-retroviral effect of 3'-azido-3'-deoxythymidine (AZT) in mice. *Proc Am Assoc Cancer Res* 28:456, 1987.

Ruprecht RM, Chou T-C, Chipty F, et al.: Interferon-alpha and 3'-azido-3'-deoxythymidine are highly synergistic in mice and prevent viremia after acute retrovirus exposure. *J AIDS* 3:591-600, 1990.

Rutgers JL, Wieczorek R, Bonetti F, et al.: The expression of endothelial cell surface antigens by AIDS-associated Kaposi's sarcoma: Evidence for a vascular endothelial cell origin. *Am J Pathol* 122:493-499, 1986.

Rutherford GW, Payne SF, Lemp GF: The epidemiology of AIDS-related Kaposi's sarcoma in San Francisco. *Journal of Acquired Immune Deficiency Syndromes* 3(suppl.1):S4-S7, 1990.

Salahuddin SZ, Nakamura, Biberfeld P, et al.: Angiogenic properties of Kaposi's sarcoma-derived cells after long-term culture in vitro. *Science* 242:430-433, 1988.

Samaniego F, Kao V, Zon G, et al.: Inflammatory cytokines increased in HIV-1-infected individuals stimulate AIDS-Kaposi's sarcoma (AIDS-KS) cell growth and this effect is blocked by antisense oligonucleotides against basic fibroblast growth factor (bFGF) [Poster]. M-50, Laboratory of Tumor Cell Biology 1993 Annual Meeting, Bethesda, 1993.

Sandor P, Bogner JR, Held M, et al.: Use of G-CSF in the management of chemotherapy-induced neutropenia in patients with advanced-stage Kaposi's sarcoma [abstract]. PO-B21-1890, IX Intl Conf AIDS, Berlin 1993.

Sat N, Goto T, Haranaka K, et al.: Action of tumor necrosis factor in cultured vascular endothelial cells: morphologic modulation, growth inhibitions and cytotoxicity. *J Natl Cancer Inst* 76:1113-1121, 1986.

Scadden DT, Bering HA, Levine JD, et al.: Granulocyte macrophage colony-stimulating factor mitigates the neutropenia of combined interferon alfa and zidovudine treatment of acquired immunodeficiency syndrome-associated with Kaposi's sarcoma. *J Clin Oncol* 9:802-808, 1991.

Schechter MT, Marion SA, Elmslie KD, et al.: Geographic and birth cohort associations of Kaposi's sarcoma among homosexual men in Canada. *American Journal of Epidemiology* 134(5):485-488, 1991.

Schwartz JJ, Myskowski PL: New treatments for Kaposi's sarcoma. *The AIDS Reader* July/August:129-132, 1992.

Schweitzer VG, Visscher D: Photodynamic therapy for treatment of AIDS-related Kaposi's sarcoma. *Otolaryngol Head Neck Surg* 102:639-649, 1990.

Selik RM, Starcher T, Curran JW: Opportunistic diseases reported in AIDS patients: frequencies, associations, and trends. *AIDS* 1:175-182, 1987.

Serraino D, Zaccarelli M, Franceschi S, et al.: The epidemiology of AIDS-associated Kaposi's sarcoma in Italy. *AIDS* 6:1015-1019, 1992.

Shepherd FA, Burkes RL, Paul KE, et al.: A phase II study of 4'-epirubicin in the treatment of poor-risk Kaposi's sarcoma and AIDS. *AIDS* 5:305-309, 1991.

Sidell N, Taga T, Hirano T, et al.: Retinoic-acid induces growth inhibition of a human myeloma cell line via down-regulation of IL-6 receptors. *J Immunol* 146:3809-3814, 1991.

Sidky YA, Borden EC: Inhibition of angiogenesis by interferons: Effects on tumor- and lymphocyte-induced vascular response. *Cancer Res* 47:5155-5156, 1987.

Sinovics JG, Szakacs JE, Gyorkey F. Multiple pathogens may induce growth factor cascade resulting in KS. *Drugs of Abuse, Immunity, and AIDS*. 1993.

Smith KJ, Skelton HG, Yeager J, et al.: Cutaneous neoplasms in a military population of HIV-1-positive patients. *Journal of the American Academy of Dermatology* 29(3):400-406, 1993.

Staddon A, Henry D, Bonnem E, et al.: A randomized dose finding study of recombinant platelet factor 4 (rPF4) in cutaneous AIDS-related Kaposi's sarcoma (KS) [Abstract]. *Proc Am Soc Clin Onco* 13:50, 1994.

Sturzl M, Roth WK, Brockmeyer NH, et al.: Expression of platelet-derived growth factor and its receptor in AIDS-related Kaposi's sarcoma in vivo suggests paracrine and autocrine mechanisms of tumor maintenance. *Proc Natl Acad Sci* 89:7046-7050, 1992.

Sulis E, Floris C, Sulis ML, et al.: Interferon administered intralesionally in skin and oral cavity in heterosexual drug-addicted patients with AIDS-related Kaposi's sarcoma. *Eur J Cancer Clin Oncol* 25:759-761, 1989.

Supapannachart N, Breneman DL, Linneman CC Jr.: Isolation of human immunodeficiency virus type 1 in cutaneous blister fluid. *Arch Dermatol* 127:1198-2000, 1991.

Tappero JW, Berger TG, Kaplan LD, et al.: Cryotherapy for cutaneous Kaposi's sarcoma (KS) associated with acquired immunodeficiency syndrome (AIDS): a phase II trial. *J Acquir Immune Defic Syndr* 4:839-46, 1991.

Tappero JW, Grekin RC, Zanelli GA, et al.: Pulsed-dye laser therapy for cutaneous Kaposi's sarcoma associated with acquired immunodeficiency syndrome. *J Am Acad Dermatol* 18:297-300, 1992.

Tappero JW, Berger TG: Caution in the use of local therapies for Kaposi's sarcoma [letter]. *Arch Dermatol* 129:42, 1993.

Tappero JW, Conant MA, Wolfe SF, et al.: Kaposi's sarcoma: Epidemiology, pathogenesis, histology, clinical spectrum, staging criteria and therapy. *J Am Acad Dermatol* 28:371-95, 1993.

Tepper RI, Pattengale PK, Leder P, et al.: Murine interleukin-4 displays potent anti-tumor activity in vivo. *Cell* 57:503-512, 1989.

te Velde AA, Hiijbens RFJ, Heije K, et al.: Interleukin-4 (IL-4) inhibits secretion of IL-1B, tumor necrosis factor α , and IL-6 by human monocytes. *Blood* 76:1392-1397, 1990.

Thommes J, Northfelt D, Rios A, et al.: Open-label trial of StealthR liposome doxorubicin (D-SL) in the treatment of moderate to severe AIDS-related Kaposi's sarcoma (AIDS-KS) [Abstract]. *Proc Am Soc Clin Oncol* 13:55 (24), 1994.

Thompson EW, Nakamura S, Shima TB, et al.: Supernatants of acquired immune deficiency syndrome-related Kaposi's sarcoma cells induce endothelial cell chemotaxis and invasiveness. *Cancer Research* 51:2670-2676, 1991.

Tilg H, Mier JM, Vogel W, et al.: Induction of circulating IL-1 receptor antagonist by IFN treatment. *J Immunol* 150:4687, 1993.

Tirelli U, Vaccher A, Lazzarin A, et al.: Epidemic Kaposi's sarcoma in Italy, a country with intravenous drug users as the main group affected by HIV infection. *Annals of Oncology* 2:373-376, 1991.

Volberding PA, Abrams DI, Conant MA, et al.: Vinblastine therapy for Kaposi's sarcoma in the acquired immunodeficiency syndrome. *Ann Intern Med* 103:335-338, 1985.

Vogel J, Hinrichs SH, Reynolds RK, et al.: The HIV tat gene induces dermal lesions resembling Kaposi's sarcoma in transgenic mice. *Nature* 335:606-611, 1988.

Von Roenn J, et al.: All-trans retinoic acid (TRA) in the treatment of AIDS-associated Kaposi's sarcoma [Abstract]. PO-B12-1571, IX Intl Conf AIDS, Berlin, 1993.

Warrell RP, Frankel SR, Miller WH, et al.: Differentiation therapy of acute promyelocytic leukemia with tretinoin (all-trans-retinoic acid). *N Engl J Med* 324:1385-1393, 1991.

Way DL, Witte MH, Fiala M, et al.: Endothelial transdifferentiated phenotype and cell cycle kinetics of AIDS-associated Kaposi's sarcoma cells. *Lymphology* 26:79-89, 1993.

Weich HA, Salahuddin SZ, Gill PS et al.: AIDS-associated Kaposi's sarcoma cells in long-term culture express and synthesize smooth muscle alpha-actin. *Am J Pathol* 139:1251-1258, 1991.

Weindel HA, Marme D, Weich HA: AIDS-associated Kaposi's sarcoma cells in culture express vascular endothelial growth factor. *Biochem Biophys Res Commun* 183:1167-1174, 1992.

Wellstein A, Lupu R, Zugmaier G, et al.: Autocrine growth stimulation by secreted Kaposi fibroblast growth factor but not by endogenous basic fibroblast growth factor. *Cell Growth Differ* 1:63-71, 1990.

Wellstein A, Zugmaier G, Califano JA, et al.: Tumor growth dependent on Kaposi's sarcoma-derived fibroblast growth factor inhibited by pentosan polysulfate. *J Natl Cancer Inst* 83:716-720, 1991.

Wheeland RG, Balin PL, Norris MJ: Argon laser photocoagulative therapy for Kaposi's sarcoma: A clinical and histologic evaluation. *J Dermatol Surg Oncol* 11:1180-1185, 1985.

Wright SC, Jewett A, Mitsuyasu RT, et al.: Spontaneous cytotoxicity and tumor necrosis factor production by peripheral blood monocytes from AIDS patients. *J Immunol* 141:99-104, 1988.

Zucker-Franklin D, Huang YQ, Grusky GE, et al.: Kaposi's sarcoma in HIV-negative patient with asymptomatic HTLV-I infection. *JID* 167:987-989, 1993.