# THE LYMPHOMA PROJECT REPORT:

## Current Issues in Research and Treatment of AIDS-Associated Lymphoma

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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 John Stumpf A Proud Mary (19??-199?) *

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FOREWORD by Lawrence D. Kaplan, M.D. Although it is difficult to establish the precise incidence of HIV-associated lymphoma, most estimates place it between 5-10% of HIV-infected individuals, making the occurrence of this aggressive and immediately life-threatening disease a significant clinical problem. Since the occurrence of many of these neoplasms appears to be more strongly related to the duration of HIV infection rather than to the level of immune function, there is good reason to believe that as persons with HIV infection survive longer, as a result of our successes in treating and prophylaxing against opportunistic infection, lymphoma will become an even more common clinical problem, demanding more effective therapeutic interventions.

The etiology of non-Hodgkin's lymphoma in the setting of HIV infection is not known and, indeed, multiple pathways may exist that are capable of giving rise to this group of neoplasms, explaining the high level of molecular heterogeneity that has been observed in these tumors. Although there is evidence to suggest that EBV may play an etiologic role in some HIV-associated lymphomas, particularly those involving the CNS, many lymphomas do not appear to contain EBV DNA sequences. Some laboratory data has suggested a possible direct role of HIV in the occurrence of some lymphomas and this potential mechanism of pathogenesis will require extensive further study. Yet other data indicate a potentially important role for the cytokines interleukin 6 and 10 in the development of lymphoma in HIV infected individuals. Other studies have demonstrated differences in clonality of the tumors and have suggested that molecular features might influence clinical outcome of the disease.

Treatment of the HIV lymphomas has been typically complicated by the occurrence of opportunistic infection as cytotoxic agents cause further immunocomprimise and by neutropenia associated with chemotherapy and the poor myeloid reserve associated with chronic HIV disease. Up until the present time therapeutic approaches have focused on variations of standard combination cytotoxic chemotherapeutic agents. The primary focus of these studies has been to find ways of alleviating the problem of poor bone marrow reserve and associated neutropenia and to determine the importance of maintaining chemotherapy dose intensity. Significant progress has been made in these and clinical trials have clearly demonstrated reduction in chemotherapy-associated morbidity associated either with dose-reduction or with the use of a myeloid colony stimulating factor (G- or GM-CSF). Most recently, in the largest clinical trial conducted to date in this disease, AIDS Clinical Trials investigators demonstrated that a 50% reduction in chemotherapy dosage was just as effective as standard-dose therapy and, for many patients, eliminated the need for a costly and inconvenient myeloid colony stimulating factor. The 8 month median survival time observed in both arms of the study are somewhat longer than those reported in historic series which further suggests that some progress has been made in the management of this disease, perhaps, in part, due to PCP prophylaxis which has substantially reduced the occurrence of PCP during the course of chemotherapy. Although progress has been made in the management of HIV-NHL, median survival of 8 months are suboptimal, and with significant proportions of patients dying of either refractory lymphoma or HIV disease progression, there is a clear need to develop more effective treatment approaches to both illnesses.

The concept of giving immuno- and myelosuppressive therapy to immunocomprimised patients has obvious flaws and significant advances in the treatment of HIV-NHL are unlikely using this approach regardless of dosage schedule or the use of colony stimulating factors. There is a need to look for agents that are less immuno- and myelosuppressive that target some of the unique molecular characteristics of the lymphomas. Already, clinical trials using monoclonal antibody-toxin or radioisotopes conjugates which target unique cell surface antigen are underway and have demonstrated some promising early results. Clinical trials with cytotoxin T-cells are in development as are studies of newer, potentially less toxic chemotherapy agents such as MGBG and the camptothecins are either in progress or planned. MGBG in particular, is a non-myelosuppressive agent which appears to have activity in HIV-NHL.

Although it is unlikely that any of these previously discussed biologic agents will have single-agent activity in patients with advanced lymphoma, the use of these agents in combination with cytotoxic chemotherapy may reduce the amount of chemotherapy required to effect a durable response. Until this will be possible, however, our short term objective must be to move forward in identifying novel therapies based upon a "pathogenesis"-related approach. Since we have only just begun to identify pathogenetic mechanisms in HIV-associated lymphoma, more support within the oncology and AIDS research communities for both laboratory and clinical research should be continued so that we can better understand the pathogenesis of HIV lymphoma and so that we can learn more about these mechanisms of disease and continue to target them as potential therapeutic approaches.

Support from NIAID and NCI for oncology studies in the AIDS Clinical Trials Group (ACTG) will remain essential for continuing access to large numbers of patients for clinical trials. The NCI cooperative oncology groups have just begun to target HIV in their agendas and the first intergroup AIDS oncology study has just begun to accrue patients. These efforts are encouraging and

exciting. But, how well the NCI and the NIAID can work together and combine their resources in this effort will be an important determinant of our success in conducting meaningful clinical trials in the future.

The document you are about to read provides a thorough overview and analyses of the previously discussed issues. It gives as much information as it raises questions that deserved to be answered. Our attempts to answer will hopefully set the stage for productive work that is yet to be done.

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INTRODUCTION Lymphomas are not new. They pre-date AIDS for many many years. We have known for some time that organ transplant patients and others from the general population develop lymphomas -- both non-Hodgkin's lymphoma (NHL) and Hodgkin's disease. Never the less, in 1982 patients with HIV disease were reported to be developing NHL at an alarming rate. This is evident by the Lancet's headline for an article which read, "Outbreak of Burkitt's-like Lymphoma in Homosexual Men" (Ziegler 1982). It wasn't until 1985 that the CDC caught on and added NHL to the list of AIDS-defining illnesses. After those in the know realized that HIV caused severe immunosuppression, it became widely speculated that patients with AIDS would be likely candidates for developing NHL. Recent evidence tells us that AIDS-related malignancies -- namely Kaposi's sarcoma and NHL -- are on the rise due to the fact that we have been fortunate enough to keep many patients alive with the discovery of therapies and prophylaxis for PCP, MAI, CMV, fungal infections, toxoplasmosis, etc. Indeed, in the Concorde study and in ACTG 019, 27% and 26% of the initial AIDS-defining endpoints, respectively, were AIDS-associated cancers. Moreover, 23% of the deaths in ACTG 196 were cancer related. There is no doubt that AIDS-related malignancies will continue to cause severe morbidity and mortality due to the fact that we presently have no prophylactic agents and at best only moderately effective treatments. The initial desire for this research into all aspects of AIDS-NHL was fueled by a need to learn about this ancient neoplasm which David Scadden refers to as a "terrible scourge." Recent review articles detail a myriad of research centered around AIDS-NHL (Karp 1992, Levine 1992 a, Scadden 1994 c). However, these scholarly accounts were not written specifically for those with AIDS-NHL and omitted the history of research on this cancer and the prospects for its cure. Thus, a number of questions needed to be answered, including: * What has taken place over the past 20 years in non-AIDS lymphoma research? * How has this knowledge helped us in treating patients with AIDS who develop NHL? * What work still needs to be confirmed or extended? * What might we be overlooking? * How can our present knowledge base move us quicker into the future? In order to answer these questions, there was a need to: 1) go back 20 years (to McKelvey's fist CHOP study) and review the NHL AIDS and non-AIDS epidemiology, pathogenesis and treatment studies; 2) dialogue with researchers and clinicians about their findings; 3) question them regarding their views about conflicting and ambiguous data and what they feel they really know now. Synthesizing research and querying those who have been working in the field for many years is undertaking suited for an AIDS treatment activist . Their is no professional jealously involved, no financial interests from one or many pharmaceutical companies, and no fear that the most inane or outlandish question could tarnish a sterling reputation. The ability to come at this research -- to actually learn cancer as well as constantly re-learning AIDS -- without years of lab or clinical experience does bring a fresh perspective which might be helpful to patients and those working in the field of AIDS care and treatment. Having a knowledgeable grasp and an understanding of the many aspects of this neoplasm is one step at power for people living with AIDS.

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EPIDEMIOLOGY The incidence of NHL appears to have been rising for as long as data have been available. (Biggar 1992)

As the HIV epidemic matures, morbidity of HIV-related Kaposi's sarcoma and non-Hodgkin's lymphoma continues to increase. Control of HIV-related cancers remains an unsolved challenge in the management of HIV infection.

(Rabkin 1994)

There are no completely reliable numbers on the epidemiology of AIDS-related non-Hodgkin's lymphoma (NHL). Published studies have estimated the proportion of AIDS patients with NHL to be as low as 3% (Beral 1991) or as high as 29% (Pluda 1993).

Awareness of AIDS-associated NHL surfaced in 1982 when clinicians started publishing case reports detailing "aggressive B-cell lymphomas in homosexual men with abnormal immune function and persistent, generalized lymphadenopathy" (swelling of the lymph nodes) (Levine 1984; Ziegler 1982, 1984). In 1985, the Centers for Disease Control (CDC) added NHL to the list of AIDS-defining illnesses.

In the pre-AIDS era, data on the incidence of NHL in the United States were available through the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) data base which monitored the incidence of cancer of 25 million people in 10 sentinel states around the country. Using the years 1973 to 1979 as a period to analyze the increased incidence of NHL in the pre-AIDS era, SEER data revealed a steady increase of NHL throughout the decade (Karp 1992). SEER data did not, however, detect an increase in Hodgkin's disease.

For men 20 to 24 years old, the incidence of NHL was 3.4 per 1,000 and for men over 75 years of age, the incidence was 68 per 1,000. During these years, SEER noted that the rates of NHL in women were one-third lower than in men and the incidence for African-Americans was one-third lower than whites of both sexes (Biggar 1992). Most important, however, is the fact that the median age of patients with NHL in the pre-AIDS era was 63 for men and 68 for women.

A dramatic increase in the number of NHLs detected in men ages 20-54 was noticed starting in 1983. A number of studies have been published analyzing this increased incidence in "single young men" and "never- married men"; hence, homosexual men! In one sub-set analysis from the SEER data base of single men in San Francisco, between 1973 and 1987, Rabkin and colleagues (Rabkin 1991) from the NCI revealed a 10-fold increase for men ages 20 to 49. These HIV-positive men were estimated at having a 0.47% risk of developing NHL and the relative risk for NHL was 104.

A follow-up study recently published by Rabkin and Yellin compiled data on 1,390,000 person-years of "never-married-men in San Francisco ages 25-54 (Rabkin 1994). They have divided their analysis by years: 1973-79 (pre-AIDS); 1980-84; 1985-87 and 1988-90. Their data claims;

* Between 1973 and 1988-90, the incidence in 25-54 year old men increased from 9 to 180 per 100,000.

* Extra-nodal primary disease increased much more rapidly than nodal and accounted for half the incidence in the most recent period.

* One-third of these extra-nodal tumors were found in the central nervous system (in the brain).

* Burkitt's/small non-cleaved cell and immunoblastic histologies, which are categorized as "high grade histologies", increased from 2% in the pre-AIDS era of 1973-79 to 36% by 1988-90. The Burkitt's/small non-cleaved cell tumors peaked in incidence between 1985-87, but the immunoblastic lymphomas increased throughout the entire study.

The young age of the men originally presenting with NHL in 1982 was an apparent signal that HIV -- like other immunodeficiencies -- could increase the incidence of lymphomas. Oncologists, pathologists and epidemiologists were also tipped-off to this new opportunistic tumor because these young HIV-positive men were presenting with a rare type of NHL with Burkitt's-like histology. As early as 1982, the Lancet published the article "Outbreak of Burkitt's-like lymphoma in homosexual men" by Ziegler and colleagues (Ziegler 1982) which reported on 4 cases of NHL seen in a 9-month period. It was startling to be suddenly confronted by young homosexual men presenting with a lymphoma that was rare. (Daniel M. Knowles, personal communication). Beral and colleagues (Beral 1991) noted that Burkitt's lymphoma in AIDS patients is 1,000 times more common in AIDS-NHL patients than NHL seen in the general population. In fact, Burkitt's lymphoma occurs in less than 1% of immunosuppressed renal transplant patients who are also at high risk for developing lymphomas.

Moreover, the proportion of NHL in the AIDS population was completely out-of-synch with the proportion of NHL documented in the general population. From a series of 111 AIDS lymphoma patients seen at Lenox Hill Hospital, 11 were Hodgkin's and 100 were NHL. This ratio was noted as "markedly different from that recorded in normal persons of this age, where Hodgkin's lymphomas are by far the most prominent type of lymphomas" (Ioachim 1991, 1992).

This new wave of younger persons presenting with lymphoma due to HIV has been documented outside the United States in the World Health Organization's (WHO) European Region epidemiological data (Serriano 1992). From their data base of 53,042 reported cases of HIV as of the end of June 1991 (from 21 countries), 1,617 (3%) patients had NHL as the presenting clinical manifestation of AIDS. When stratifying the number of cases by age, it is apparent that the vast majority of these patients are between the ages of 20 and 49. AGE: <1 1-9 10-19 20-29 30-39 40-49 50-59 >60

Of Cases: (2) (12) (19) (520) (497) (341) (163) (54)

This rising trend in younger men is also apparent in the in the nation-wide Multicenter AIDS Cohort study (MACS) over the years 1985-1991(Munoz 1993). When trends in the incidence of initial and secondary AIDS-defining illnesses were examined in 2,627 homosexual men, the data revealed an upward trend in the incidence of lymphoma ($p < 0.001$). As expected, a significantly lower incidence of pneumocystis carinii pneumonia (PCP) was seen after 1987 due to the widespread use of chemoprophylaxis.

MACS data also documented a weak association between CD4 cell count and lymphoma as compared with cytomegalovirus/herpes simplex virus infections and neurological disease. There was, however, a "crude upward trend" when analyzing all of the years, and it has been noted that "the incidence of lymphoma will rise as more persons prolong their pre-AIDS state with prophylaxis" (Munoz 1993).

This "disassociation" between CD4 count and lymphoma cited in the MACS data has been confirmed by other studies. In fact, Northfeld and colleagues (Northfeld 1992) analyzed the absolute CD4 count of 80 consecutive patients who presented with systemic/non-central nervous system AIDS-related lymphomas (CNS; lymphoma of the brain) at San Francisco General Hospital between 1989 and 1991. The CD4 counts ranged from as low as 3 to as high as 1,148 with a median of 176. The proportion of patients with CD4 counts greater than 50 was 79% and the proportion of CD4 counts greater than 100 was 58%.

Not being able to associate NHL with a patient's CD4 count is only true with systemic/non-CNS lymphomas. This is documented in a natural history study of 56 patients with CNS NHL (between 1/88 through 12/91) conducted by Lee and colleagues (Lee 1994) at the University of California, San Francisco (UCSF). The median CD4 count for the patients was 20 (n=40; range 1-492). It was also noted that median number of prior OIs in 53 of the patients was 2 and that CNS-NHL was the initial AIDS diagnosis in only 8 of 56 patients. Thus, patients with CNS-NHL have usually had at least one prior OI and develop it much later in the course of their HIV disease.

Do only homosexual men develop AIDS-NHL?

No. Numerous studies have been published documenting that all risk groups for HIV are susceptible to NHL (Rabkin 1992; Biggar 1992; Serraino 1992). Most early cohort studies (MACS, San Francisco City Clinic Cohort study) focused exclusively on homosexual men.

WHO's European data base was able to break down the demographics of their lymphoma cases by country and by HIV transmission category.

European AIDS lymphomas by risk category

Number of AIDS cases AIDS cases with non-Hodgkin's lymphoma Percent of AIDS cases with NHL

Transmission category No. No. %

IVDUs 17,695 467 2.6

Homosexual men 23,275 791 3.4

Homosexual men and IVDUs 1,012 22 2.2

Heterosexuals 4,487 116 2.6

Hemophiliac 1,422 55 3.9

Blood transfusion recipients 1,645 52 3.2

Mother to child 885 10 1.1

Thus, while homosexual men and IVDUs made up by far the majority of people who have HIV, these risk groups do not have a statistically greater risk than other HIV-infected individuals for developing AIDS-NHL. Serraino and colleagues attribute this high excess of European IVDUs with NHL (2.6%) -- as compared to Beral and colleagues' (Beral 1991) US data with 1.6% -- to the fact that IVDUs

in North America "are in a substantial proportion black" and have a "lower predisposition toward the development of NHL."

Lymphomas are twice as common in whites as in blacks according to 1989 CDC data (Beral 1991), but it has not been statistically proven that African-Americans don't get lymphoma or have "a lower predisposition." Many epidemiologists admit that many cases of AIDS-lymphoma go under-reported to the CDC (Levine 1992 a; Bernstein 1993) and might well be from city hospitals and emergency clinics that often treat patients from marginalized communities.

Lymphoma has been found to be "common in patients with hemophilia and clotting disorders" compared to homosexual men and IVDUs. Beral and colleagues (Beral 1991) calculated that the relative risk of lymphoma for hemophiliacs is 1.86+ compared to that of homosexual and bisexual men (1.13) or IVDUs (0.6+).

To determine the types and rates of malignancies occurring in HIV-infected hemophiliacs, Rabkin and colleagues (Rabkin 1992) studied a cohort of 1,710 patients with hemophilia of whom 1,065 (63%) were HIV-positive. Collected data on these patients demonstrated that their relative risk compared with general population rates is 38-fold greater in patients 10 to 39 years of age.

The proportion of people with AIDS who develop lymphoma

Trying to calculate the exact percentage of people with HIV who have developed lymphoma is a nearly impossible task. Almost all studies published over the past four years rely heavily on the CDC's 1989 data base of 97,258 reported AIDS cases of whom 2,824 (2.9%) had NHL (Beral 1991). There are number of explanations as to why this percentage is so low.

* NHL is usually not the presenting disease in patients with HIV. Most often the development of lymphoma comes after the occurrence of KS or other OIs (Lowenthal 1988).

* Routine AIDS reporting to the CDC only notes the AIDS-incident diagnosis, and follow-up diagnoses are not recorded. [However, certain cohort studies may indicate lifetime risk of lymphoma - check out the CDC's Adult Spectrum of Disease Study, the MACS and the CPCRA Observational Database.]

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ETIOLOGY & PATHOGENE SIS

With regard to the pathogenesis of AIDS lymphoma, there are very few established facts.

(JE Karp & S Broder 1992)

NHL develops in HIV-positive individuals as an opportunistic neoplasm just as OIs occur after years of progressive immunodeficiency. HIV infection in and of itself is not the sole reason for the development of NHL. It can, however, induce polyclonal B-cell hyperactivation (Lane 1983). Numerous pathogenesis based studies have detailed that there are at least three basic reasons why NHL might develop: 1) transforming infectious agents (e.g., EBV); 2) inadequate tumor surveillance (i.e., c-myc translocation and alteration of the p53 suppressor gene); and 3) the up regulation of proliferating B-cells responding cytokine dysregulation or overexpression (i.e., IL-6, IL-10, IL-12).

EBV: What we know and what we don't

EBV, a member of the herpes family of viruses, infects about 90% of the human population worldwide (Sample 1991). EBV has been linked to a number of clinical disorders in people with suppressed immune systems.

Studies as far back as 1983 documented EBV's deleterious effects in the pathogenesis of AIDS (Lipscomb 1983-84). With HIV infection, EBV becomes more pathogenic for one simple reason: "EBV antigens are commonly targeted by cytotoxic T-cells" (Ambinder 1994). When individuals are immumocompromised -- those with HIV and organ transplant recipients -- with little or no T-cells, EBV goes undetected and is free to roam wild. In fact:

The frequency of precursors for HLA-restricted cytotoxic T cells has been estimated to be as high as 1/550 peripheral blood mononuclear cells in normal EBV-seropositive individuals and may not substantially differ in patients with AIDS. (Ambinder 1994)

EBV's ability to infect B cells, proliferate, immortalize and transform cytokines is well documented. A number of studies have documented that EBV infection often precedes the clonal B-cell expansion that leads to the development of NHL and might be a central risk factor for the progression of lymphadenopathy to lymphoma (Knowles 1989; Shibata 1991, Neri 1991).

EBV enters the body through the oropharyngeal epithelial cells (the mouth) where it replicates and sometimes causes an acute, self limiting infection like that of many other viruses (including CMV and HIV itself in its acute primary stage). Most often, EBV will subside into latency for life and not cause problems. If, however, EBV is allowed liberation, it then goes on to infect B lymphocytes, the antibody producing cells of the immune system. EBV enters B cells by binding to the CD21 receptor displayed on the surface of some (but not all) B cells.

The state of EBV activation is reflected by the viral proteins which can be detected in the host cells at various times, and by the levels of circulating antibodies to those proteins. The use of EBV-immortalized lymphoblastoid (baby B cells) cells lines has demonstrated many of the viral products involved in the maintenance of EBV's latency, viral replication, cell transformation and cell destruction.

In those cell lines, at least six viral nuclear proteins, referred to Epstein-Barr nuclear antigens(EBNAs), three membrane proteins, designated latent membrane proteins (LMPs) and two small nuclear Epstein-Barr encoded RNAs (EBERs) are expressed (Sample 1991).

EBNA1 is needed in order to maintain the viral genome that exists within the cell nucleus and EBNA2 is required for immortalization of B cells by EBV. The cellular genes that are activated by EBNA2 include: CD23 (a marker of B cell activation and growth factor), c-frg (a tyrosine kinase proto-oncogene, and CD21 (the EBV receptor). EBNA3C is also able to upregulate the expression of CD21 (Sample 1991). EBV is thus able to upregulate its own receptors and stimulates the replication of its host cell type.

LMPs are well know for having transforming and oncogenic properties. In fact, in vitro studies have documented that EBV LMP-1 has the capacity to transform B lymphocytes, and LMP-2 has been found to interact with growth regulatory intracellular tyrosine kinase (Klein 1989).

EBV was initially isolated from a laboratory B-cell line derived from an African patient with Burkitt's lymphoma (Epstein 1960). Later EBV infection was found to be associated with nasopharyngeal carcinoma (NPC) in China. The Burkitt's like histology of many AIDS-associated lymphomas suggested that EBV might act as a triggering agent, an inducer or a promoter of these diverse cancers, but not the sole causal agent. Numerous studies over the past 12 years have demonstrated that EBV is only one of many factors which induce or promote AIDS-NHL. EBV is present in roughly 100% of AIDS-CNS NHLs. In a study of 21 AIDS patients with primary central nervous system (PCNS) NHL at Johns Hopkins School of Medicine, MacMahon and colleagues (MacMahon 1991) revealed that there was an "abundant expression" of the EBV-EBER-1 in 100% of the patients, and 45% of them also expressed EBV-LMP.

While EBV is expressed in roughly all PCNS NHLs, the percentages of EBV documented in different groups' studies on systemic NHLs varies considerably.

Shibata and colleagues (Shibata 1993) from USC recently studied 59 patients with systemic NHL and found that 39 (66%) were associated with EBV. Subar and colleagues (Subar 1988), using Southern blot hybridization or EBV proteins by indirect immunofluorescence, detected EBV sequences in only 6 out of 16 (38%) tissues sampled.

Recent studies have also documented that the prevalence of EBV expression often depends on the histology of the tumors studied, thus making generalized case study comparisons unreliable. Hence, Hamilton-Dutoit and colleagues (Hamilton-Dutoit 1991) demonstrated this in 1991 when they found EBV DNA in 11 of 17 (65%) cases of systemic large-cell immunoblastic lymphoma by in situ hybridization versus 1 of 5 (21%) cases of Burrkitt's-like SNCC lymphoma.

If histology rather than anatomical site is more predictive of the presence of EBV, then CNS NHL might uniformly be EBV positive because it displays an immunoblastic or large cell morphology. Thus, "whether the presence of EBV in primary CNS AIDS-associated lymphoma is actually related to the anatomic site of origin or the histopathologic category, or both, is unclear" (Knowles 1993).

There are also pathologists who do not believe that EBV plays a pivotal role in lymphomagenesis. In fact, Ganser and colleagues (Ganser 1988) from the University of Frankfurt suggest that EBV-negative AIDS NHLs develop through a similar, yet more complicated, process. They contend that a whole host of agents -- bacterial, fungal, or viral -- cause chronic antigenic stimulation which then causes nonspecific B cell activation. This over-activation in turn may lead to the eventual development of monoclonal B-cell expansions with an increased risk of chromosomal translocation and the rearrangement of c-myc and immunoglobulin loci at the time of immunoglobulin gene rearrangement.

The Role of c-myc, ras and bcl [onco]gene Dysregulation

Although the molecular events leading towards a malignant transformation are incompletely understood, many researchers believe that abnormalities involving the c-myc proto-oncogene are involved in the pathogenesis of AIDS-NHL. Before AIDS, there are well-documented cases of endemic (African) Burkitt's lymphoma -- as well as some sporadic (Western) Burkitt's lymphoma -- that reciprocal chromosomal translocation develop between c-myc on chromosomal 8 and the immunoglobulin heavy chain chromosomes 14, 2 and 22 (i.e., t(8;14), t(2:8), and t(8;22) (Pelicci 1986).

With regards to AIDS-NHL, rearrangement of the c-myc gene occurs in approximately 75% of all systemic cases. Subar and colleagues (Subar 1988) detected c-myc rearrangement in 12 of 16 (75%) cases and Ballerini and colleagues (Ballerini 1993) detected c-myc rearrangement in 19 of the 24 AIDS-NHL samples tested. c-myc rearrangement, however, is not distributed evenly among all histologic subtypes and tends to occur more frequently in Burkitt's and non-Burkitt's SNCC. In fact, Ballerini and colleagues documented alterations of the c-myc gene in all 16 (100%) of AIDS-NHLs of SNCC histology (Burkitt's and non-Burkitt's), while only one third (or fewer) of immunoblastic or diffuse large-cell confer with c-myc rearrangement (Ballerini 1993). While these numbers can be debated, there is no evidence of c-myc rearrangement in CNS lymphomas (Shiramizu 1992).

The belief that a c-myc translocation is a necessary precursor to or prognostic factor of NHL has recently been called into question by data from Charles Rabkin and J□rgen M□ller of the NCI (Rabkin 1994). From a cohort of 245 homosexual men enrolled in mid-1982, 131(53%) were HIV-positive as of January 1993 and 13 of them developed NHL. Only 1 of these 13 NHL patients had a c-myc t(8;14) translocation as detected by PCR in their peripheral blood lymphocytes. Interestingly, there were 11 HIV-positive men who were found to have a detectable c-myc recombination during their HIV infection but did not go onto develop NHL after approximately 10 years of follow up. Some of these men who were found to have a c-myc recombination in their peripheral blood at one point over the 12 years never again had a detectable c-myc rearrangement on subsequent tests.

The fact that these men with a c-myc t(8;14) translocation did not develop NHL is important because it calls into question the theory that a chromosomal abnormality is necessary and sufficient for the development of lymphoma. Nevertheless, c-myc is an early event in lymphomagenesis and a minority of these translocation-containing cells might eventually become tumor cells. The fact some of these men had cells with translocations that were later removed or undetectable reiterates that mechanisms exist even in the immunocompromised HIV patient to block tumor development (J□rgen M□ller, personal communication).

Point mutations in the ras gene family are mostly associated with precursor B-cell acute lymphoblastoid leukemia and multiple myeloma and are extremely rare in non-AIDS lymphomas (Knowles 1993). However, Ballerini and colleagues detected a ras gene mutation in 4 of the 27 (14.8%) AIDS-NHL samples tested (Ballerini 1993).

bcl-1 and bcl-2 gene rearrangements -- considered one of the hallmarks in the pathogenesis of non-AIDS lymphomas -- are not found in AIDS-NHLs (Subar 1988). Recent data from a study conducted by Gaidano and colleagues in Ricardo Dalla-Favera's lab at Columbia (Gaidano 1994) have demonstrated that rearrangements of the putative proto-oncogene bcl-6 were found in 5 of the 24 (20%) AIDS-NHL specimens of diffuse large-cell histology. The bcl-6 gene rearrangements were detected in some of the tissue samples that were EBV-positive, but were in no way associated with activation of c-myc or mutation of the p53 suppressor gene.

TUMOR-SUPPRESSOR GENES

The apparent loss of normal tumor suppressor genes and proper gene product function plays an integral role in the progression of a myriad of cancers (Stanbridge 1990). p53 (twice selected as Science Magazine's molecule of the year) is classified as a suppressor gene. However, various mutations can provide a transdominant status on p53 and make it paradoxically resemble an oncogene

(Karp 1992). The loss of p53 on chromosome 17p13 in conjunction with the retinoblastoma (RB) gene on chromosome 13q14 was detected in lymphoid leukemia and lymphomas by researchers Stanbridge and Nowell (Stanbridge 1990).

Ballerini and colleagues (Ballerini 1993) found the loss or mutation of p53 occurred in 10 of 27 (37%) of the AIDS-NHL tissue samples (SNCC, immunoblastic and diffuse). As with c-myc, the distribution of p53 is not uniform and tends to cluster with a specific histologic type of AIDS-NHL; all 10 of the NHLs were of a SNCC histology. The fact that p53 gene mutation tends to cluster in AIDS-SNCC NHL at twice the rate of non-AIDS-SNCC NHL does "underscore the pathogenic relevance of p53 gene inactivation in AIDS-associated lymphomagenesis (Knowles 1993). MOLECULAR GENOTYPES OF AIDS-ASSOCIATED LYMPHOMAS

HISTOLOGY No. EBV c-myc p53 Study

SNCC Large non-cleaved cell Immunoblastic plasmacytoid 16 MC 6 MC 5 MC 5/16 1/4 4/4 16/16 2/4 1/4 10/6 0/6 0/5 Ballerini 1993

SNCC

Large-cell lymphoma

CNS 7 MC 1 PC 9 MC 16 PC 7 MC 2/7 0/1 4/9 3/16 6/7

4/7 0/1 2/9 0/16 0/7

Shiramizu 1992

SNCC Immunoblastic 8 MC 7 MC 6/8 5/7 4/8 2/7

Shibata 1993

SNCC Immunoblastic

7 MC 4 MC 3 PC 4/7 4/4 3/3 6/7 2/4 0/3

Delecluse 1993

(Herndier 1994) INTERLEUKINS

Interleukin-6 (IL-6)

Interleukin-6 (IL-6) is thought to be "especially relevant to both "pre-malignant" polyclonal B-cell expansion and to eventual malignant transformation in AIDS-NHL" (Karp 1992). McGrath and colleagues (McGrath 1993) demonstrated that production of IL-6 has been localized to the tumor-associated macrophages, which some have shown to be infected by HIV. Likewise, Emile and colleagues have data that reveals deregulation of IL-6 gene expression is confined to NHL (both AIDS and non-AIDS) of immunoblastic and diffuse large-cell histology (Emile 1992).

Increases in serum IL-6 levels -- along with HIV-infection -- are associated with the clonal defects of B-cell maturation. IL-6 gene expression is also up-regulated by a number of other growth factors and cytokines, including, Il-I, tumor necrosis factor (TNF), platelet derived growth factor (PDGF) and beta-

interferon (Birx 1990). Thus, stimulation of these other cytokines and HIV allows IL-6 to create a continuous autocrine loop.

Some researchers have also postulated that high levels of circulating Il-6 might account for many of the systemic manifestations often associated with NHL which include, fever, night sweats, and cachexia (Emile 1994).

Interleukin-10 (IL-10)

IL-10, originally called cytokine synthesis inhibitory factor (CSIF), has been well studied for its lymphomatous properties and its close bonding relationship with EBV. Studies have confirmed that NHLs of diffuse large-cell and immunoblastic histology express high levels of IL-10 which are produced directly in the tumor cells (McGrath 1993).

Most interestingly, is the proof that EBV encodes IL-10 (by sharing a significant homology with the EBV protein BCRF-1) which then shuts off the T cell surveillance mechanism for eliminating EBV (Moore 1990). IL-10 also inhibits IL-2 (a T cell growth factor), gamma-interferon, and encourages the development of B cells by up-regulating the B-cell growth factor IL-4, IL-5 and IL-6 (Rousset 1992). Moreover, Gill and colleagues (Masood 1995) recently confirmed IL-10's role and autocrine growth mechanism in the pathogenesis of AIDS lymphoma. Using antisense oligonucleotide, they noted inhibition of IL-10 mRNA expression, IL-10 protein production and all B-cell lines.

Does AZT cause NHL?

The speculations that AZT causes AIDS-NHL started because of the high incidence of lymphomas seen in long-term follow-up from the early AZT trials conducted by Yarchoan, Pluda and colleagues at the NCI in the late 1980s (Pluda 1990). In total, 8 of the 55 patients receiving AZT for primary HIV infection developed NHL as of 1993 (Pluda 1993). Investigators noted that the estimated probability of developing NHL after AZT therapy was 12% after 24 months and 29.2% after 36 months. While this does seem high, it must be noted that these were patients with low CD4 counts and many had been on antiretroviral therapy for more that 2 years. In addition, patients with less that 50 CD4 cells developed NHL at a statistically significant higher rate (p=.0085).

To investigate this theory that AZT might be involved in the pathogenesis of NHL, Widney and colleagues (Widney 1994) at UCLA recently conducted a study to ascertain the effects of AZT on B lymphocyte activation. In their many exhaustive in vitro and in vivo experiments, they found that exposure to AZT does not induce B cell activation in vivo or in vitro. It did not enhance spontaneous immunoglobulin or IL-6 secretion and did not induce EBV nor affected the ability of T cells to regulate EBV.

All in all, there does not seem to be a single, simple explanation of why and how B cell dysfunction associated with HIV disease causes polyclonal B cell activation leading to NHL. There are many possibilities, yet many theories need to be confirmed, rejected or modified. We do see, in many instances, features of the pathogenesis of AIDS-NHLs that differ from non-AIDS-NHL. This just might open the door for possible therapeutic options. Pathogenesis debates about etiology, the role of EBV, gene rearrangement, clonality and location have yet to make a major impact on treatment research.

KSHV and Body-Cavity-Associated Lymphoma in AIDS Patients

The most obviously exciting recent development in AIDS-related cancer research is the discovery by Yuan Chang and Patrick S. Moore, later confirmed by virologists Robin Weiss and Jay Levy, of herpesvirus-like sequences in tissue samples taken from patients with AIDS and non-AIDS-related, epidemic, classic and endemic Kaposi's sarcoma. Chang and Moore hypothesize that a new herpesvirus, tentatively named Kaposi's sarcoma associated herpes virus (KSHV) may be an etiologic agent in the development of both kinds of Kaposi's sarcoma. This discovery could well lead to the rapid identification of screening assays, a clearer understanding of the pathogenesis, epidemiology and transmission of KS, and the potential use of anti-herpesvirus treatments as prophylactic or therapeutic agents in conjuction with standard chemotherapy or novel immunotherapeutic approaches. The identification of identical sequences in a relatively rare subset of HIV-associated lymphomas (body cavity-based lymphomas found in pleural, peritoneal or pericardial areas) may provide additional clues about the role of this potential new herpesvirus in oncogenesis. These lymphomas are EBV-positive and c-myc gene rearrangement negative, and are characterized clinically by a poor prognosis. 2/8 people with these lymphomas presented with both KS and body cavity-based lymphomas. KSHV appears most closely related, among herpesviruses, to EBV and the saimiri virus which infects the squirrel monkey.

*
DIAGNOSIS

In the setting of HIV disease, NHL can be difficult to diagnose because its presentation is so variable. This is true for three reasons: 1) simple swelling of the lymph nodes (lymphadenopathy) is a common manifestation of the HIV disease process itself (Lane 1983); 2) constitutional/"B" symptoms (night sweats, fever and weight loss) are also common symptoms of advanced HIV infection or OIs; and 3) those with HIV can present with extranodal tumors, without lymph node enlargement. These extranodal tumors will most often be found because of symptoms pertaining to a specific involved area of the body. For example, PCNS NHL patients may present with a wide variety of symptoms including, headaches, nausea, unsteadiness, weakness, speech, vision and personality changes (Levine 1992 a).

Swollen lymph nodes, however, should not be taken lightly, especially when they are asymmetrically enlarged or in the presence of otherwise unexplained "B" symptoms. Such manifestations might warrant a biopsy, which is generally required for the diagnosis of lymphoma. According to the ACTG Oncology Committee's guidelines (ACTG Oncology Committee, unpublished, 1994) for the definitive diagnosis of systemic NHL in patients in ACTG trials:

Pathological/biopsy confirmation of NHL is mandatory in all cases. [A confirmed diagnosis is made by] positive histopathology/cytology/fine-needle aspiration or tissue biopsy sampling from any site/organ. (Note: bone marrow sampling may confirm diagnosis despite non-diagnostic biopsies from other sites.)

Hence, a biopsy is imperative because this definition only allows for a "confirmed" and not a "probable" diagnosis. With PCNS NHL, the ACTG is more flexible in their requirements which state:

Pathological/biopsy confirmation of Primary CNS Lymphoma is strongly recommended and is to be encouraged in all cases. 1) Confirmed diagnosis: * Positive histopathology/cytology on tissue biopsy of brain or cerebrospinal fluid analysis.

2) Probable diagnosis: * neurologic signs and a compatible clinical syndrome with CD4 lymphocyte < 100/mm3 and * contrast enhancing mass lesion(s) on head CT/MRI scan * failure of clinical response to antitoxoplasmosis chemotherapy or other anti-infective chemotherapy (e.g. tuberculosis, cryptococcosis) or * lesion(s) become markedly reduced or disappear following high-dose glucocorticoid and/or radiation therapy. This flexibility reflects the fact that patients with advanced HIV infection and mass lesions in the brain may be too ill to undergo an invasive procedure. Some brain biopsies -- especially if the craniotomy is not involved -- may be simple procedures with little morbidity and with patients recovering rapidly (Lawrence Kaplan, personal communication). In addition, neurosurgeons unfamiliar with AIDS patients have been reticent to perform biopsies (Levine 1992).

HOW IS THE BIOPSY PERFORMED AND WHAT ELSE IS NEEDED?

A biopsy always requires some kind of an invasive procedure, either by a needle, the endoscopist's forceps or the surgeon's scalpel. Fine needle biopsies (also referred to as fine needle aspirates or FNAs) are a newer technique and a lesser invasive procedures. After comparing the accuracy of FNA vs. tissue biopsies performed on 19 patients suspected of having AIDS-NHL, Strigle and colleagues (Strigle 1993) commented that FNAs are highly sensitive and:

In patients with HIV suspected of having an atypical lymphoproliferative process, FNA is a useful tool in patient management and is accurate in subclassifying and grading lymphomas. [And] FNA sampling may prove to be the to be the initial diagnostic tool. A conclusive FNA can spare the patient a more invasive and risky surgical procedure. Some oncologists are skeptical of the accuracy of FNA diagnosis for NHL and recommend a tissue biopsy whenever possible. A FNA does not give a clear picture of the architecture of the tumor (i.e., nodule vs. diffuse) and an inexperienced pathologist may have difficulty in the diagnosis unless the cells are completely a-typical (Jamie von Roenn, personal communication). Thus, a FNA might be appropriate if the biopsy site is not readily accessible and will spare the patient an invasive procedure such as a laparotomy (surgery of the abdomen), but a peripheral lymph node should be biopsied whenever possible. The overall condition of the patient is also critical in evaluating the potential risks of the more invasive biopsy.

Various types of X-ray studies are needed to ascertain what areas are involved with the tumor and help in determining the patient's treatment options. These studies generally include evaluation of the brain, chest, and abdomen with CT (computed tomography) or MRI (magnetic resonance imaging) scans. A patient might also have to undergo a gallium scan. This procedure involves injection of a radioactive isotope (dye) into the body and lying under a sensor for approximately an hour, two to three days after the injection. The dye localizes to sites of inflammation, such as infections or tumors. A further visit is sometime required for additional scanning. A bone marrow biopsy and a spinal tap are usually also done to ascertain if there are cancer cells in these areas. While these procedures are uncomfortable, they are extremely useful in determining both prognosis and the most appropriate treatment. Also, depending on the those treatment decisions and the extent of the tumor, many of these tests need to be repeated on a periodic basis.

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CLINICOPATHOLOGIC CHARACTERISTIC & MANIFESTATIONS

Unlike AIDS-related Kaposi's sarcoma, AIDS NHLs have not changed in their clinical manifestations since 1984 when the first major multi-institutional clinical assessment study was published (Ziegler 1984).

There are generally three "types" of AIDS-lymphomas: large-cell immunoblastic, small noncleaved-cell (Burkitt or Burkitt's-like), and diffuse large-cell. Large-cell immunoblastic (often referred to as immunoblastic) and small noncleaved-cell (SNCC) are considered high-grade B-cell tumors which make up approximately 60%+ of all AIDS-lymphomas (Scadden 1994 c). Large-cell diffuse AIDS-lymphoma (also referred to as large noncleaved-cell lymphoma) is also considered clinically aggressive and is categorized as "intermediate grade." Large-cell immunoblastic and diffuse large-cell are often lumped together in data analyses and referred to as large-cell.

Data from Ziegler and colleague's 1984 multi-center clinical analysis report of 90 homosexual men documented the histological grade of the patient's lymphomas as: 24 (26%) immunoblastic; 32 (36%) SNCC; and 17 (19%) diffuse large-cell. Ten years later, unpublished data on 183 patients from the recently completed ACTG 142 (the largest of all AIDS-NHL studies) documented: 84 (46%) immunoblastic; 37 (20%) SNCC; and 62 (34%) diffuse large-cell (Lawrence Kaplan, personal communication).

Conversely, "high-grade" lymphomas -- the most severe and fast-growing -- are less common and characterize only 30% to 40% of the non-AIDS-NHL. This was demonstrated in a case-controlled study of 294 patients in Los Angeles county conducted by Levine and colleagues at USC (Levine 1992 c). High-grade lymphomas were documented in 82% of the 55 HIV-positive lymphomas whereas only 40% of the HIV-negative lymphoma patients were diagnosed with high-grade histology ($P < 0.001$).

Low-grade B-cell lymphoma, T-cell lymphomas and Hodgkin's disease sometimes develop in HIV positive individuals as well; however, they are relatively rare and are not believed to be increasing in frequency (Scadden 1994 c). They are also not considered AIDS-defining conditions by the CDC.

Another significant hallmark of AIDS-NHLs is the widespread extent of the tumor and their extra-nodal involvement . NHL can appear at almost any site in the body with a noted tendency for the gastrointestinal tract, liver, bone marrow and the CNS. This was first documented in Ziegler's study (Ziegler 1984) where 88 of their 90 patients had extra-nodal involvement. Other more recent studies including, Gisselbrecht and colleagues' 150 patient combination chemotherapy trial documented that 114 (76%) of the patients presented with extra-nodal involvement (Gisselbrecht 1992). It is also quite common that AIDS-NHL is exclusively extra-nodal with no involvement of the lymph nodes. Raphael and colleagues documented that 56% of their high-grade NHL patients presented exclusively with extra-nodal involvement (Raphael 1991).

While CNS NHLs comprise of approximately 15%-20% of all extra-nodal tumors (Scadden 1994 c), NHL in AIDS patients has been noted to appear in rather unusual sites in the body including anus and rectum, heart, adrenal, gingiva and mouth, muscle and soft tissue (Levine 1992 a). Some clinicians who speculate that the lymphomas presenting in the oral cavity and in the anus (rectal masses) of homosexual men -- even though they are rare -- might be confined to their risk group (sexual practice) in the same way as Kaposi's sarcoma (Ioachim 1992).

Sites of extra-nodal involvement for AIDS high-grade B-cell lymphomas

No. patients % Extra nodal % CNS % GI % Marrow % Liver Study

90 98 42 17 33 9 Ziegler 1984

84 76 17 4 31 26 Kaplan 1989

89 74 21 28 21 16 Knowles 1988

Lymphomas are staged to describe the extent of involvement (disease/tumor spread) at the time of diagnosis and to provide prognostic information. Patients are staged according to the Ann Arbor classification developed originally for Hodgkin's disease. Most AIDS-lymphomas are diagnosed as stage II or greater, most often presenting at stage IV. Only 15%-30% of AIDS-lymphoma patients are diagnosed at stage I and II; some will have evidence of extra-nodal disease or relapse in remote sites (Scadden 1994 c). Stage of disease for AIDS lymphomas No. Patients Stage I,II %Stage III,IV Study 90 38 (42%) 52 (58%) Ziegler 1984 84 14 (17%) 69 (82%) Kaplan 1989 89 27 (30%) 57 (64%) Knowles 1988

Many clinicians (AIDS and non-AIDS) feel that the Ann Arbor staging classification for AIDS-NHL is not as useful for NHL as it is for Hodgkin's disease because (1) the Ann Arbor classification was developed in 1971 before the first reported case of AIDS and (2) it was originally developed for Hodgkin's disease (Shipp 1993). According to Shipp and a host of American, Canadian and European clinicians who make up The International Non-Hodgkin's Lymphoma Prognostic Factors Project:

this classification emphasizes the distribution of nodal disease sites because Hodgkin's disease commonly spreads through the contiguous lymph nodes. Since the pattern of disease spread in Hodgkin's disease and non-Hodgkin's lymphoma are different, it is not surprising that the Ann Arbor classification system is less accurate in identifying prognostic subgroups of patients with aggressive non-Hodgkin's lymphoma (Shipp 1993).

Moreover, data from several large series of patients clearly demonstrates that AIDS-NHL are very often extra-nodal and are much more aggressive than non-AIDS-NHL. Thus, Ann Arbor does not have the ability to detail the myriad of prognostic factors seen with AIDS-NHL.

"B" symptoms -- fever, night sweats, and/or weight loss in excess of 10% of normal body weight -- are another hallmark of AIDS-NHL. It is estimated that 82% of the patients with systemic NHL and 91% with primary CNS involvement present with "B" symptoms (Levine 1991). In non-HIV lymphoma, "B" symptoms are seen in approximately 33% of patients (Sertoli 1994).

"B" symptoms are most often the quintessential outward manifestation of a patient's NHL. "B" symptoms -- often considered ARC -- can mimic other OIs and/or reactions to medication. Never the less, it is advisable that after other OIs are ruled out, patients be aware that persistent "B" symptoms lasting for more than a week might be a warning sign of lymphoma (David Scadden, personal communication).

*
Clonality & Molecular Characteristics

There is little debate among clinicians and pathologists concerning the grade or stage of patients with AIDS-NHL. The proportions of reported cases from various institutions might differ on the diagnosis of immunoblastic vs. SNCC histologies, but it has yet to become a serious issue. The biggest debate, however, is taking place around the "clonality" of AIDS-NHL.

Most "malignant B-cell lymphomas apparently arise as monoclonal outgrowths from a pool of proliferating polyclonal B lymphocytes" (Ziegler 1984). Most pathologists won't diagnose a tumor as "lymphoma" unless it is monoclonal. There are those that will just use the term "B-cell lymphoproliferative disease" if the tumor is not monoclonal.

"Lymphoproliferative disease" and "B-cell proliferative lymphadenopathy" were shown early on to be manifestations of HIV disease (Lane 1983), but it is also considered to a "pre-lymphomatous state for B-cell lymphoma" (Meyer 1984). This aggressive B-cell lymphoproliferation has been historically observed in immunosuppressed renal-transplant patients and those with congenital abnormalities -- who are also at high risk of lymphoma (Hoover 1992).

The issue at hand is whether or not HIV-positive patients with B-cell lymphoproliferative disease, who are often being diagnosed with "a polyclonal lymphoma" by pathologists at UCSF really exist and should carry the diagnosis of "lymphoma." The data on the polyclonal lymphomas from McGrath and colleagues has been documented in pathogenesis studies (McGrath 1991; Shiramizu 1992) on at least 20 patients.

The occurrence of polyclonal lymphomas in the setting of HIV disease was first described in 1991 by McGrath and colleagues (McGrath 1991) after conducting an autopsy study of three patients who died with widespread AIDS-associated diffuse large-cell lymphoma. A minority of sites studied were monoclonal as measured by immunoglobulin gene rearrangement, while other histologically identical sites demonstrated no evidence of monoclonal proliferation. McGrath comments that this polyclonal disease is "an extremely aggressive B-cell proliferation that, unlike lymphadenopathy syndrome, is associated with widespread metastatic activity."

In a molecular analysis of 40 patients biopsied at UCSF/SFGH (Shiramizu 1992) between 1986 and 1991, classifications of AIDS-NHL were defined for clonality, infection with EBV and the presence of a c-myc gene rearrangement by Southern blot analysis. 20 (50%) of the 40 patient's biopsies were determined to be polyclonal. 17 of the 20 were EBV-negative without c-myc rearrangements and only 3 of the 20 were determined to be EBV-positive. 19 of the 20 polyclonal lymphoma specimens were large cell and the other one was of SNCC histology (Shiramizu 1992).

A recently published follow-up study conducted at the same institution documented the molecular analysis of 45 patients (Kaplan 1995). In this group, 20 were identified as monoclonal and 25 as polyclonal. Southern blot and reverse transcriptase-polymerase chain reaction (RT-PCR) of extracted RNA was done to confirm these tumors as polyclonal B-cell lymphomas. The most striking difference between the two groups was their median CD4 count. Below are the characteristics of the 45 patients:

| | Total (range) | Polyclonal | Monoclonal | p. value |
|---|---|---|---|---|
| Age(median years) | 43 (30-72) | 42 (33-54) | 44 (30-72) | NS |

CD4 (median) 162 (12-1,148) 227 (12-1, 148) 123 (23-360) .04

Karnofsky (median) 90 (40-100) 90 (50-100) 80 (40-100) NS

LDH (median) 311 (93-5, 100) 395 (93-888) 294(152-5,100) NS

Investigators from three other laboratories have recently published findings of polyclonality based upon immunohistochemical staining or immunoglobulin (Ig) gene rearrangement. In a molecular analysis of 14 lymphomas studied by Delecluse and colleagues (Delecluse 1993) of the French Study group of Pathology for Human Immunodeficiency, 3 HIV-polyclonal lymphomas were identified. The three that were identified were immunoblastic, EBV+ and without c-myc gene rearrangement .

The absence of EBV in the polyclonal lymphomas documented thus far makes them different from transplant-associated lymphomas. Most of the latter lymphomas -- especially those occurring in renal transplant patients -- are EBV driven (Hanto 1983). Many speculate that this specific difference between AIDS-associated lymphomas and other immunodeficiency-related lymphomas "suggests fundamental differences in pathophysiology" (Scadden 1994 c).

Strigle and colleagues (Strigle 1993) have also come to regard the notion of "polyclonal lymphomas" as possible even though monoclonality is usually "a criterion important in the diagnosis of B-cell NHL." In a prospective study of 21 patients with palpable lymphadenopathy, fine needle aspirations (FNA) were conducted to determine their utility. In more than half of the FNA specimens analyzed, Strigle was unable to show antibody light-chain exclusion. Strigle noted that some of the samples were "immunohistochemically also polyclonal" (Strigle 1993).

*
Prognostic Factors

Patients with HIV-associated lymphoma typically present with advanced extra nodal disease and most die less than one year from the time of diagnosis. (Kaplan 1995 a)

Response rates for therapy are just a bookkeeping thing. What really matters is how the patient does off treatment and remains disease free. (David Straus, 1.27.95)

A few often-cited studies detail the factors predictive of survival for patients diagnosed with AIDS-NHL (Kaplan 1989; Levine 1991 a; Ziegler 1984; Ioachim 1992 ). These studies combined don't have data on more than a few hundred patients. This small AIDS data base -- compiled by a handful of clinicians -- is dwarfed in effort, substance, and size when compared to the 25 American, Canadian and European clinicians who make up the International Non-Hodgkin's Lymphoma Prognostic Factors Project (Shipp 1993). Together, they were able to compile analyze data on 2,031 patients with non-AIDS-NHL and come up with 4 risk groups with predicted five-year survival rates of 73%, 51%, 43% and 26%.

For AIDS patients with NHL, however, it is impossible to think of using the term "five-year survival rate." when talking about PWAs with lymphoma. This is evident for 3 simple reasons:

* Even if a patient was "cured" of his lymphoma and no longer has "cancer," he would still have HIV running through his peripheral blood and lymph nodes. This HIV will eventually destroy the patient's immune system opening him up to a host of OIs that might no longer be treatable.

* Very few AIDS-NHL patients are alive five years after treatment. Most die within one year after diagnosis. The median survival of the 188 patients from ACTG 142 was approximately 8 months (Kaplan 1995 b).

* Even before the AIDS-NHL patient can have a complete response to therapy and go on to be cured of his/her cancer, death can result from the toxicity of chemotherapy.

With such grim facts understood, there are still a number of prognostic features that permit an estimate of how a patient with AIDS-NHL might respond to therapy and how long he/she might survive.

To facilitate this discussion, AIDS-NHL must first be separated into two types: primary CNS (PCNS) and systemic lymphoma. It is undeniable that having P-CNS involvement is the worst of all prognostic factors for NHL. In Levine and colleague's (Levine 1991 a) retrospective study of 60 AIDS patients (11 with PCNS and 49 with systemic NHL), the median survival of patients with PCNS NHL was 2.5 months vs. 6.0 months for those with systemic disease (P = 0.04). Numerous articles and abstracts mention the poor prognosis of AIDS patients with PCNS NHL, many of whom died before a definitive diagnosis was made (Gill 1985; So 1986; Lee 1994). The underlying immune deficiency of these patients is staggering. In Lee and colleagues' (Lee 1994) natural history study of 56 HIV-infected patients with PCNS, the median CD4 count was only 20 and median number of prior OIs was 2. Some had as many as 5 previous OIS before their diagnosis of P-CNS NHL.

Kaplan and colleagues' natural history studies of 1989 and 1995 documented that the most important predictor of survival for patients with systemic NHL was CD4 count at the time of diagnosis (Kaplan 1995 a, 1989). In their recent study, which includes an analysis of patients with both monoclonal and polyclonal tumors, the CD4 count stratified by clonality was highly predictive of survival:

Survival Based on Patients' CD4 Count: Stratified for Clonality

CD4 Count Monoclonal Polyclonal < 200 3.5 months (n=15) 5.5 months (n=7) > 200 4.9 months (n=4) not reached

(Kaplan 1995 a)

Many other investigators also rank the CD4 count as one of the best survival predictors, and generally use a cut off of more or less than 100 CD4 cells (Scadden 1994 c; Pluda 1992).

The prognostic value of the CD4 count was documented in two separate AIDS-NHL trials conducted by the French-Italian Cooperative Study Group (Tirelli 1992; Oksenhendler 1994). In the Tirelli study, 37 patients with a "poor prognosis" (median CD4 count of 35 (range 2 - 556) poor performance status, and/or prior OIs) were given a modified (less myelosuppressive) combination chemotherapy regimen with AZT. Only 14% of the 29 evaluable patients achieved a CR. (Of the 8 non-evaluable patients who received only one dose of chemotherapy, 2 died of toxicity, 4 died of OI, and 2 were lost to follow-up.) The median survival of the treated patients was only 3.5 months. There was no significant difference in

survival between those who achieved a CR versus the non-responders (P = 0.25). Investigators concluded that a CD4 count of less than 100 was significantly related to shorter survival (P = 0.05).

Oksenhendler and colleagues tested an aggressive combination chemotherapy regimen (LNHIV-91) + G-CSF on 31 "good prognosis" patients with NHL who had a CD4 count above 100 (mean 344; range 100 - 910), and no prior OIs. A 70% CR was achieved with a median survival of 13 « months. The 2 year probability of survival for responders was 50%.

Levine and Kaplan's group both agree that in addition to the CD4 count there are three other major predictors of shorter survival: a prior AIDS diagnosis (OIs and KS), Karnofsky performance score (KPS) of less than 70%, and the presence of extra nodal disease. (Levine singles out bone marrow involvement as the worst site of extra nodal disease.)

23 of the patients in Levine's study who presented with all three poor-risk indicators were deemed as having a "poor prognosis" whereas 17 patients with none of the three poor-risk factors were deemed to have a "good prognosis." A post-hoc subset analysis documented a median survival of 4.0 months for the poor prognosis group and a median survival of 11.0 months for the good prognosis group (P = 0.0002).

Whether the NHL responds to therapy is also an important factor in survival; those who achieved a complete response (CR) to therapy fared significantly better than those who attained only a partial response (PR) or no response (NR). In Levine's study, 36 patients received a variety of combination chemotherapy regimens: patients in the good prognosis group who attained a CR survived longer than those who attained only a PR or NR (17.8 months vs. 5.0 months), and patients in the poor prognosis group also survived longer if they achieved a CR (6.3 months) vs. no response (3.4 months).

This study also concluded that three other prognostic factors, the presence of "B" symptoms, elevated LDH, and the presence of bulky tumors (greater than 10 centimeters or advance stage disease) had no significant impact on survival. This is a direct contradiction to Shipp and colleague's non-AIDS NHL analysis, which singled out these three factors as predictors of survival. An obvious reason for one of these differences is the fact that the vast majority of AIDS-NHL patients have advanced (stage III/IV) disease and extra nodal involvement at diagnosis.

In light of what we know about the major prognostic factors for survival in patients with AIDS-NHL, three questions must be addressed in developing a standard of care:

* Does it matter what type of treatment regimen is used if the patient has a low CD4 count and a depleted immune system?

* Is there any hope that patients with fewer than 50 CD4s will be able to successfully tolerate chemotherapy regimens, let alone respond? Should they even seek treatment?

* In an attempt to clarify the results of therapy, should patients be stratified up front based on their prognostic factors?

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TREATMENTS & THE STANDARD OF CARE It has been over 20 years since the original CHOP regimen was first tested in patients with advanced non-Hodgkin's lymphoma. After multiple attempts to improve on these first results by the addition of other chemotherapeutic agents, or alternative dose modalities, we are still left with the question of what is the best therapy for advanced non-Hodgkin's's lymphoma.

(Vose 1993)

...early trials evaluating standard and intensive dose chemotherapy regimens [for AIDS-non-Hodgkin's lymphoma] were complicated by high rates of treatment-related morbidity and death. These trials set in motion efforts in the United States to find less toxic chemotherapy regimens.

(Scadden 1994 c)

CHOOSING A TREATMENT

Once lymphoma is diagnosed, the pathologist's report, the radiographic and staging studies, and the patient's overall state of health are all considered by the physician in making treatment recommendations. Except when the brain is involved, local therapies are not very beneficial and combination chemotherapy -- a modified or aggressive cocktail of at least four agents -- is generally recommended. When the brain is involved, radiation therapy is almost always recommended.

Chemotherapy involves frequent visits to an outpatient clinic; in-hospital treatment is not usually necessary unless complications arise. Most chemotherapy regimens are given in "cycles" every 2, 3, or 4 weeks. There is a predictable sequence of events that follow. On the day of administration, patients generally feel tired or washed out and also can have problems with nausea and vomiting. Various medication classified as anti-emetics (i.e., Zofran) can significantly help control nausea and vomiting.

About a week to ten days later, the patient's white blood cell count will start dropping -- sometimes dramatically -- because of the chemotherapy. Patients can take G-CSF or GM-CSF to lessen dramatic decrease, or wait until the white blood cell count falls and then take either drug to boost up their counts. If a fever does develop during this time (referred to as a neutropenic fever or febrile neutropenia), hospitalization with intravenous antibiotics is most often required to help fight off possible bacterial infections. Also during this time the platelet count may fall (increasing the risk of bleeding) and mouth sores (stomatitis) or diarrhea might occur. Hair usually begins to thin during this time and will continue to fall out during the course of chemotherapy, usually regrowing only several months after all chemotherapy has been discontinued. Numbness and tingling (peripheral neuropathy) in the fingers and toes, constipation and jaw pain are not uncommon. Rare toxicities, including kidney failure (from rapid destruction of the tumor) and heart or spinal cord damage can occur as side effects of some of the drugs used to treat NHL.

The length of therapy can be quite variable. The shortest duration of therapy -- if all goes well -- is usually four to six months. It is often necessary to make changes in the therapeutic regimen along the way depending on the patient's tolerance to the various medications and whether or not the tumor is responding. During treatment, it is extremely important that all patients -- regardless of their CD4 count -- be prophylaxed for PCP. Prophylaxing for MAI, CMV and fungal infections might be necessary if the patient's CD4 count warrants such therapy.

If a patient fails to respond completely to the initial therapy (about 50% chance) or if they initially respond but then relapse (again, a 50% chance) there are other possible treatments using approved antineoplastic agents. Some patients may also be good candidates for experimental medications being studied in clinical trials.

Standard Chemotherapy for AIDS-NHL Chemotherapy -- almost always in combination -- is the only thing that destroys cancer cells and cures some patients of their systemic AIDS-NHL. It is possible to beat NHL.

Chemotherapy can also kill the patient. It is a double-edged sword. Patients can opt not to have chemotherapy. That decision may be understandable in view of the many toxicities seen with the powerful regimens used over the years.

Patients with AIDS are immunodeficient and also have poor bone marrow reserve. Most chemotherapeutic agents used for cancers as well as a number of therapies for primary HIV infection (AZT) and OIs (Ganciclovir for CMV) deplete a patient's neutrophils. Neutrophils -- a kind of white blood cells -- are essential for fighting off a host of bacterial infections.

Neutropenia developing 7 to 10 days after the administration of combination chemotherapy is almost inevitable. Before 1987, deaths due to PCP because of chemotherapy's effect on T cell depletion and function were common in AIDS-NHL and sometimes seen in non-AIDS NHL patients. AIDS-NHL patients are usually more immune suppressed than normal cancer patients. It is often possible to halt the immune suppression in organ transplant patients by stopping the administration of immune suppressive drugs like Cyclosporin-A. It would be nice to stop the immune suppression in AIDS patients that easily; but 13 years into the epidemic, we still don't have a clue.

To avoid repetitive and prolonged episodes of neutropenia -- which may cause delays in the administration of chemotherapy, dose-reductions, febrile neutropenia and infections -- studies have been conducted to find combinations that would be less myelosuppressive. In the early 90s, these new regimens were combined with colony stimulating factors (GM-CSF and G-CSF).

Below is a detailed history of the many AIDS-NHL (and non-AIDS-NHL) chemotheraputic studies conducted over the past 10 years that have brought us to a basic -- albeit still moderately effective -- standard of care.

THE MORE THE MERRIER?

The belief that using many chemotherapeutic agents in combination with dose intensity was well-detailed in Goldie and colleague's, Rationale for the use of alternating non-cross resistant chemotherapy (Goldie 1982). Goldie wrote that resistance to multiple chemotherapeutic agents may occur after exposure to a few and that alternating the treatment regimens at every cycle is most effective for a variety of cancers. Much of this analysis was based on mathematical development and a computer program. Goldie's initial hypothesis was borne-out of strategies used in older cancer studies such as, Tormey and colleague's mid-1970s breast cancer trial which "explored the possible benefits of a fixed cross-over of two non-cross-resistant chemotherapy regimens in comparison to one regimen" (Tormey 1979).

ALL TRIAL & ERROR: PAST & PRESENT CLINICAL TRIALS FOR AIDS-NHL:

Some of the first trials for AIDS-NHL which took place over ten years ago were complete disasters. In one study conducted on 25 patients with SNCC AIDS-NHL, Odajnyk and colleagues (Odajnyk 1986) administered a modified regimen of COMP. Only a few of these patients achieved CR to therapy and there was an overall median survival of 3 months. All 25 patients developed grade IV hemotologic toxicity and many of these patients died not because of their lymphoma, but because of OIs and bacterial sepsis.

A few years later, Gill and colleagues (Gill 1987) at USC conducted a NHL study in which two treatment regimens were compared on 22 patients treated and diagnosed between 1982 and 1986. Group 1 (13 patients) was administered the M-BACOD chemotherapeutic regimen and group 2 received COP-B, a highly intensive, "novel" regimen consisting of: L-asparaginase (a moderately active, non-myelosuppressive enzyme that inhibits protein synthesis), high-dose ARA-C (cytosine arabinoside) + high-dose methotrexate, vincristine, cyclophosphamide, and prednisone.

There were two reasons for testing this "novel" regimen: 1) to improve upon remission rates obtained with M-BACOD; and 2) the belief that the high-doses of ARA-C (which is known to cross the blood-brain barrier) and high-dose Methotrexate would both prevent CNS relapse. During this 5-year study in the mid-1980s, PCP prophylaxis was not routinely used and colony stimulating factors were nonexistent.

Seven of the 13 (54%) patients in group 1 attained a CR whereas only 3 of the 9 (33%) in group 2 attained a CR. It is also interesting to note that 2 of the 13 patients in group 1 had CNS progression while 6 (5 of whom had initial bone marrow involvement) of the 9 patients in group 2 developed CNS progression. The five with the initial bone marrow involvement developed severe neutropenia, with a drop in their ANC to a mean of 100. There was also a statistically significantly difference in the occurrence of OIs: 7 of the 9 (78%) in group 2 (five with PCP) vs, 1 of the 13 (8%) in group 1 (P=.01). Because this "novel" regimen (group 2) turned out to be a disaster, Gill claimed "early results with the first nine patients were poor enough to mandate an early termination of the protocol." (Gill 1987).

Because M-BACOD demonstrated some efficacy (a CR of 54%) in the Gill 1987 study, Levine and the AIDS Clinical Trials Group's (ACTG) Oncology Committee decided to study a modified m-BACOD regimen in ACTG 008. ACTG 008 designed to "ascertain if lesser dose-intensity might be associated with deceased risk of current of intercurrent infection and longer survival." (Levine 1991 b) Thus, 008 halved the doses of mylelosuppressive agents in the M-BACOD regimen from those used by Gill in 1987 and originally employed by Skarin and colleagues (Skarin 1983 a) in their seminal 1983 non-AIDS lymphoma study.

ACTG 008 Regimen (modified M-BACOD) Standard M-BACOD (used by Gill and Skarin)

Bleomycin (B) 4 mg/m2, day 1, IV 4 mg/m2, day 1, IV

Doxorubicin (A) 25mg/m2, day 1, IV 45 mg/m2, day 1, IV

Cyclophosphamide 300 mg/m2, day 1, IV 600 mg/m2, day 1, IV

Vincristine sulfate (O) 1.4 mg/m2, day 1 IV (not to exceed 2mg) 1.0 mg/m2, day 1, IV

Dexamethasone (D) 3 mg/m2, days 1-5, orally 6 mg/m2, days 1-5, orally

Methotrexate (M) 500 mg/m2, day 15, IV 3000 mg/m2, day 14, IV

ARA-C (CNS prophylaxis) 50 mg. Intrathecal days 1, 8, 21, 28 NONE

Whole Brain Radiation prophylaxis or treatment -- 2400 cGY with marrow involvement -- 4000 cGY with know CNS involvement NONE

Zidovudine (AZT) 200 mg every 4 h for 1 year; starting after chemotherapy NONE

Duration of Treatment 4-6 cycles, every 28 day 10 cycles, every 21 days

(Levine 1991 b)

CNS prophylaxis was added to the regimen because CNS relapse was quite common -- in the Gill study -- in patients with systemic AIDS-associated NHL. This was one of the first NHL-AIDS studies to use ARA-C intrathecally, AZT, and PCP prophylaxis.

Of the 42 patients enrolled onto ACTG 008, 35 were evaluable for response with a mean CD4 count of 150. 16 patients (46%) achieved a complete response. Four of these 16 did relapse, but no relapses occurred in the central nervous system. The median duration of survival for all 42 patients was 5.6 months and for the 35 evaluable patients it was 6.5 months. The 16 complete responders, however, had a median survival of 15 months.

Even with this modified (less-myelosuppressive) regimen, 61% of the patients had their ANC fall below 1000 and 21% experienced an ANC below 500. Nine patients (21%) had to have their therapy delayed due to their neutropenia, and over half of the patients (57%) developed neutropenic fevers. A significant number patients -- 9 (21%) of the 42 -- developed PCP even though most (81%) were on prophylaxis.

Bacterial sepsis occured in 5 of the patients, causing death in one. When this study was analyzed, only 6 of the 42 patients (14%) remained alive. Overall, 21 of the 42 (50%) patients died of progressive lymphoma. Thus, the other deaths were due to intercurrent OIs or OIs that developed after their course of treatment.

ACTG 008 investigators did conclude that this modified dose -- with CNS prophylaxis -- was somewhat more promising than the standard regimens employed previously because 1) the complete responders held their responses longer; 2) none of the responders relapsed in the central nervous system; and 3) the duration of event-free survival possibly reflected "an ability to actually administer all chemotherapy as planned, without the need for long delays in treatment due to intercurrent opportunistic infection." (Levine 1991 b).

This new, modified regimen, however, did not significantly improve the median survival (6.5 months) compared to retrospective studies using more intensive regimens where median survival rates were reportedly 5 to 7 months (Kaplan 1989). Thus, ACTG 008 did suggest for the first time that a modified, less-intensive chemotherapeutic regimen might be effective therapy for some patients and was

associated with less myelosuppression than would be anticipated with standard-dose chemotherapy.

A few years later, the ACTG Oncology Committee designed ACTG 074 to determine if GM-CSF -- a hematopoietic growth factor that directly boosts patients' neutrophils -- would allow patients to successfully receive full-dose intensive chemotherapy (Walsh 1993). ACTG 074 was a Phase I dose-escalating study of m-BACOD in combination with GM-CSF. The maximum dose level employed the same doses of doxorubicin (45 mg/m2) and cyclophosphamide (600 mg/m2) administered in the Gill 1987 and Skarin 1983 studies. The dose of methotrexate was severely reduced to 200 mg/m2, compared with 500 mg/m2 used in ACTG 008 and 3,000 mg/m2 used in the Gill study. Hence, the change from uppercase "M" to lower case "m" to reflect this modified dose.

Of the 16 evaluable patients, 8 (50%) achieved a CR. None of the cycles in level I (ACTG 008 dose) resulted in an ANC below 500 and only 25% of the cycles in level 3 (standard full-dose) resulted in an ANC below 500 or neutropenic fevers.

Investigators concluded that the administration of the GM-CSF was "probably" why there was such limited hematologic toxicity; however, constitutional symptoms due to GM-CSF (fever, fatigue, rash, chills, and shortness of breath) were "significant" (Walsh 1993). This may be explained by the fact that a GM-CSF dose of 20 mcg/kg was selected for this study, considerably higher than the current standard dose of 5 mcg/kg used for NHL patients.

A randomized, 30 patient study by Kaplan and colleagues (Kaplan 1991) at SFGH documented the benefits of adding GM-CSF to standard chemotherapy regimens. Patients receiving CHOP were randomized to receive GM-CSF (10 to 20 mcg/kg/day) on days 1 to 10 (early GM-CSF) or on days 4 to 13 (delayed GM-CSF) or nothing at all (control group). Patients in the delayed group vs. control groups had a higher mean nadir of the ANC (0.89 vs, 0.36 x 10 (9)/L; p = .009), a shorter mean duration of neutropenia (1.3 vs. 4.9 days; p = .02). and fewer chemotherapy cycles complicated by neutropenia and fever (27% vs. 67%; p = .001). The CR rate was 70% for the delayed group and 67% for the control group.

Initially, p24 antigen levels went down below baseline in all groups. However, in the third week after chemotherapy p24 levels rose to 243% of baseline values in the patients receiving GM-CSF (p = .01). This rise suggested viral replication, however, no effect of change in HIV activity on clinical outcomes was significant.

The next logical step was to build on the questions answered and on the knowledge gained from ACTG 008, ACTG 074 and SFGH study and put that together in a Phase III randomized controlled trial. Hence, the birth of ACTG 142: modified m-BACOD vs. standard dose m-BACOD with GM-CSF.

ACTG 142 was a four-year study -- one of the longer ACTG studies -- which accrued 198 patients of its target 250. The DSMB closed the study in September 1994 because it found no "statistically significant difference" between the treatment arms and accruing more patients was unlikely to have changed this.

While there were no significant differences in the treatment arms, we did learn some things from this trial. It was the largest treatment trial of AIDS NHL patients in history.

Disease Characteristics at Entry for Patients in ACTG 142

Gp 1: standard M-BACOD + GM-CSF Gp 2: low-dose m-BACOD

Stage I/II 37% 29%

Stage III/IV 63% 71%

Extranodal 84% 77%

Median CD4 Count 103/mm3 100/mm3

Results of Treatment for Patients on ACTG 142 (N=188)

Gp 1: standard + GM-CSF Gp 2: low- dose p. value

Complete Response 37/74 (50%) 35/77 (46%) ns

Relapses after CR 7/37 (19%) 8/35 (23%) ns

Time to progression 22 weeks 28 weeks ns

Overall med. survival 31 weeks 34 weeks ns

Time to gr 3 or 4 toxicity 12 weeks not reached .004

gr 4 neutropenia (mean) 36% cycles 22% cycles .007

NHL = cause of death 24 patients 36 patients ns

AIDS = cause of death 20 patients 12 patients ns

(Kaplan 1995 b)

What have we learned from ACTG 142? How will this improve our standard of care?

* ACTG 142 compared the results from: (1) ACTG 008, a 42 patient phase II study which -- for the first time -- halved the standard-dose of M-BACOD for AIDS NHL, and 2) ACTG 074, a phase I study, which administered escalating doses of m-BACOD with GM-CSF to 17 patients.

* You can get the same response rates if you give less (half) chemotherapy. This is not the case with most cancers where the rule is to blast the tumor with as much chemotherapy as possible. Severely immunosuppressed AIDS patients can't handle and thus shouldn't be given the standard high doses we use for non-HIV NHL and other cancers.

Interestingly, the rationale for using m-BACOD as the most effective regimen for treating patients with AIDS-NHL was called into question in 1993 (while ACTG 142 was open and accruing patients) when a 1,138 patient, 7 year ECOG/SWOG non-AIDS NHL study (Fisher 1993 b) was published. This study compared first, second and third generation NHL chemotherapy regimens: CHOP vs. m-BACOD vs. ProMACE-CytaBOM vs. MACOP-B. The rationale for this large study was to "compare CHOP with the

third generation regimens" in a multicenter randomized setting for the evaluation of response rates, time to treatment failure, survival and toxicity.

Much to everyone's amazement or chagrin, the first generation and old standard CHOP came out on top. While there were no statistically significant differences seen in response rates or survival, CHOP was found to be much less toxic. When fatal (grade 5) and life-threatening (grade 4) toxicities were compared, there was significant differences between groups (p = 0.001): CHOP (32%) and ProMACE-CtyaBOM (32%) vs. m-BACOD (59%) and MACOP-B (49%). Moreover, only having to take four agents cuts down on the administration time and overall cost. Thus, Fisher and colleagues concluded, "CHOP remains the best available treatment for patients with advanced-stage intermediate-grade or high-grade NHL."

Even though the 1,138 NHL patients did not have AIDS, many AIDS oncologists wonder if these results would hold for AIDS-associated NHL. Kaplan, however, warns this analysis does not directly apply to ACTG 142 because much higher doses of methotrexate were used in SWOG/ECOG's m-BACOD arm compared to ACTG 142 (Lawrence Kaplan, personal communication).

THE $64,000 QUESTION: WHAT MATTERS MOST? THE MOST EFFECTIVE CHEMOTHERAPEUTIC REGIMEN? OR, DO TREATMENT OUTCOME AND SURVIVAL ALL DEPEND ON THE PATIENT'S PROGNOSTIC FACTORS?

This debate concerning optimal therapy for AIDS-NHL can be discussed ad nauseum, but we must ask whether the real issue might be that response rates and survival are primarily based on a patient's prognostic factors regardless of what treatment regimen is used.

A number of studies have suggested that the patient's CD4 count at diagnosis, prior OI history and Karnofsky score are more important than the treatment regimen in predicting how well one will "tolerate" and thus respond to chemotherapy. This is best documented by comparing the results of two separate AIDS-NHL studies conducted by clinicians from the French-Italian Cooperative Study Group (Tirelli 1992; Gisselbrecht 1993).

Tirelli and colleagues (Tirelli 1992) studied 37 AIDS-NHL patients with "poor prognosis." They had median CD4 counts of 35 (range 2 - 556), poor performance status, and/or prior OIs. They were administered almost the same regimen used in ACTG 008. However, the steroid prednisone was substituted for dexamethasone, teniposide was added, methotrexate was only administered intrathecally as CNS prophylaxis instead of ARA-C, and AZT was administered during these cycles vs. waiting until after chemotherapy.

In 29 evaluable patients, only 14% showed a CR. Of the 8 non-evaluable patients who received only one dose of chemotherapy, 2 died of toxicity, 4 died of OIs, and 2 were lost to follow-up. 44% of the patients on study had intercurrent OIs and of the 20 patients who were taking their AZT, 8 (40%) had to stop it because of the toxic effects on the bone marrow.

The median survival of the treated patients was only 3.5 months. There was no significant difference in survival with those who achieved a CR vs. NR (P = 0.25). Investigators concluded that a CD4 count of less than 100 was significantly related to shorter survival (p = 0.05).

Tirelli and colleagues from the French-Italian Cooperative Study Group believed this be an unsuitable regimen for the patient population they were studying and even called into question the results from ACTG 008 in a Letter to the Editor of

the Journal of the American Medical Association (JAMA) (Tirelli 1992 b). They claimed: the CR of 14% and median survival of 3.5 months in their study vs. the CR of 46% and median survival of 6.5 months was so discordant because their NHL patients were of poor prognosis and the patients with poor prognosis were "excluded" from ACTG 008.

Levine, on behalf of the ACTG 008 team, replied in a letter that was published next to Tirelli's in JAMA (Levine 1992 b). Levine replied that:

* "This is not true." Patients with poor prognosis were not excluded from the study.

* 22 out of 42 of the patients on 008 met Tirelli's definition of "poor prognosis." And 23% (5/22) of them achieved a CR.

* The use of marrow-toxic AZT in combination with chemotherapy, and the use of eight vs. four cycles of chemotherapy in his [Tirelli's] series may have contributed to the poor results that were obtained."(Levine 1992 b)

A colleague of Levine's and co-investigator on 008 believes this analysis to fundamentally flawed and agrees with Tirelli's initial analysis that the CD4 count is the major predictor of outcome. In fact, the reasons stated above are probably not why there was such discordance in the result, but the fact that the median CD4 counts of the patients' in these studies (150 in 008 vs. 35 in Tirelli's) is probably the reason.

When the French-Italian Cooperative Group tested an intensive chemotherapeutic regimen in NHL patients with "good prognosis" and "low risk", they observed the exact opposite. Gisselbrecht and colleagues (Gisselbrecht 1993) tested the modified regimen, LNH 84, on 141 chemotherapy-naive NHL patients with an Eastern Cooperative Oncology Group (ECOG) performance status less than 2 and no active OIs. PCP prophylaxis was intsituted as well as AZT after chemotherapy was ended.

Of 136 patients evaluable for response, 89 (65%) acheived a CR with a median survival of 9 months. And, of those 89 patients, only 21 (24%) relapsed during the entire observation period.

This study clearly validated past data analyses from Kaplan's group in 1989 (Kaplan 1989) that determined that a patient's CD4 count, more than any other prognostic factor, most strongly predicted treatment outcome and survival. Hence, patients in the LNH84 study with a CD4 count less than a 100 were found to have a poorer response to therapy and marketly shorter survival than those who had a CD4 count above 100 ($p = 0.0001$). In fact, those patients with a CD4 count above 100, no "B" symptoms, a good performance status, and nonimmunoblastic lymphoma had a 50% probability of survival at 2 years.

CNS PROPHYLAXIS; YES, NO, ALWAYS?

There has never been a randomized controlled study conducted that proves the benefits of prophylaxis for CNS lymphoma and thus, a "controversy revolves around the use of prophylactic intrathecal antitumor therapy" (Scadden 1994 c). It has, however, been documented that many patients with systemic NHL who respond to therapy subsequently have central nervous system relapse. This was apparent early on in the Gill 1987 study where 8 of 12 patients (67%) who were not prophylaxed with either intrathecal ARA-C or methotrexate relapsed in their central nervous system (Gill 1987). And, none of the 35 patients in ACTG 008 who

were prohylaxed with intrathecal ARA-C relapsed in their central nervous system (Levine 1991 b).

The use of intrathecal ARA-C or methotrexate as prophylaxis has led some clinicians, such as USC's Alexandra Levine, to state that it should be "mandatory" (Levine 1992 a). Other clinicians, such as UCSF's Lawrence Kaplan, says that "there is not a shred of data in the literature" that documents that ALL patients with systemic disease require CNS prophylaxis and "challenges" Levine to come up with data proving that ALL systemic AIDS- NHL patients really need CNS prophylaxis (Lawrence Kaplan, personal communication). Kaplan contends that only those with lymphoma involving the bone marrow, epidural area (outermost part of the brain and spinal cord), sinus disease, or patients with SNCC (category "J") histology need be prophylaxed with either intrathecal ARA-C or methotrexate.

If the patient has lymphomatous involvement of the meninges (regardless of marrow involvement or histology), they should be treated with whole brain radiation and intrathecal ARA-C or methotrexate ( sometimes alternating) until no malignant cells are found in the cerebral spinal fluid. In addition, many clinicians and some treatment protocols for AIDS-NHL require that patients receive PCP, MAI, and antifungal prophylaxis (ECOG protocol: E1494). HOW TO TREAT PRIMARY CNS-NHL

Initial therapy given to patients with "suspected" primary CNS AIDS-NHL is anti-toxoplasmosis therapy for 7 to 14 days with pyrimethamine and sulfadiazine or clindamycin (Scadden 1994 c). This empiric therapy is often instituted before a tissue biopsy is taken. If the patient worsens after day 5 or fails to improve after day 14, s/he will most likely be required to undergo one of several neurologic procedures including ultrasound guided stereotactic biopsy, or craniotomy in order to obtain a definitive tissue diagnosis (Irwin 1993). Therapy might be withheld if the patient does not consent to one of these procedures. As one radiation oncologist said, "No meat, no treat!"

The importance of early diagnosis of AIDS PCNS NHL before severe neurolohgical complaications arrise has been stressed. Once toxoplasmosis is ruled out, a brain biopsy should be performed in order to initiate therapy (Lawrence Kaplan, personal communication).

Optimal therapy, however, for AIDS PCNS lymphoma has yet to be defined (Levine 1992). Radiation therapy to the brain with steroids and aggressive OI prophylaxis is now the present standard of care. It is effective for the palliative relief of neurological symptoms, butmay not be curative. In fact, no randomized trials have been performed to evaluate whether radiation therapy has a beneficial effect on survival (Scadden 1994 c).

Nisce and colleagues (Nisce 1992) used whole brain radiation to treat 25 men with AIDS-CNS NHL between 1987 and 1991. 24 out of 25 of these patients previously had at least one OI. The whole brain was treated with a total dose ranging from 30 to 40 Gy over 3 to 4 weeks. If a response was obtained, patients received an additional "boost" to the tumor bed consisting of approximately 14 Gy over one week.

Of the 25 patients, 24 were evaluable for response. 19 of the 24 patients (79.2%) exhibited improvement in their neurological manifestations. None of the patients who responded had a recurrence of their neurological dysfunction.

The mean survival time of these patients studied was 4.8 months (range, 1 to 18 months). While mean survival time was slightly higher in these patients who underwent radiation therapy compared to the survival times of 1 to 2 months seen in patients who go untreated, Nisce and colleagues concluded, "although relatively high doses of radiation were delivered, our aim is not to alter survival time but to improve quality of life." (Nisce 1992).

Realizing that there is little difference in survival whether or not one undergoes radiation therapy has made many patients -- and their physicians -- decide to forgo treatment. According to David Scadden of Harvard Deaconess Medial Center:

..the approach at our center is based upon the underlying health status of the patient and active involvement of patient and family in the decision making process. Patients with prior AIDS complications that significantly compromise their quality of life often prefer steroids alone or pain medications only (Scadden 1994 c).

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## EXPERIMENTAL TREATMENTS

During the past ten years scientists have made few advances in developing experimental treatments for AIDS-NHL. Only a handful of experimental treatment options have been studied over the years. The rest of the time has been spent attempting to perfect the recipe for the "ultimate chemotherapy cocktail." There is nothing wrong with attempting to perfect the standard of care and working with the basics, however, much time may have been lost in this pursuit.

Nevertheless, there are now a number of experimental treatments in clinical development. Some are still variations on the old chemo cocktail while others are part of new pathogenesis-based therapeutic approaches. Below are detailed descriptions of these therapies and the status of their clinical development.

### CDE CONTINUOUS INFUSION: A KINDER, MORE GENTLER APPROACH?

There are now attempts to boost response rates, lower toxicity and extend survival with a 96 hour continuous infusion of the combination chemotherapeutic regimen of cyclophosphamide, doxorubicin, and etoposide(CDE). Presently, the Eastern Cooperative Oncology Group (ECOG) of the National Cancer Institute (NCI) is accruing for E1492, a phase II trial of Cyclophosphamide, Doxorubicin and Etoposide (CDE) with ddI and G-CSF for AIDS non-Hodgkin's lymphoma.

The initial rationale for this study was based on several single-institution phase I/II trials (Sparano 1993 a, b) run by Einstein's/Montefiore's Joe Sparano. In one of the initial studies (Sparano 1993 a), these three drugs (CDE), were given to 21 patients receiving a 96-hour continuous infusion who were followed for a median of 21 months. 13 (62%) achieved a complete response (CR) and 5 (24%) achieved a partial response (PR). The median survival was 18 months calculated by the Kaplan-Meier method.

These patients had a mean CD4 count of 87 and extranodal disease in 19 of 21 patients (90%). This regimen resulted in a significant decrease in patients' CD4 counts: 98 pre, 37 post (n= 8). There was a high rate of grade IV neutropenia which complicated 38% of the cycles, and fevers were associated with 21% of the cycles. Dose reduction was required in 47% of the total cycles and for 79% of patients who received at least two cycles (Sparano 1993 b).

Sparano and colleagues then completed a follow-up pilot study which included the antiviral ddI (to stabilize the CD 4 count) and G-CSF (Sparano 1994). 6 of 8 patients (75%) achieved a CR, with a median CD4 count of 120 at baseline. While on treatment, the mean decrease in CD4 count was only 29 as compared with a drop of 61 CD4s in the prior cohort treated with CDE alone. Patients in this study also showed a trend toward higher leukocytes (p = 0.06) and neutrophils (p =0.16).

The ECOG study will give these three drugs intravenously over 96 hours (4 days) through two portable pumps (referred to as a "fanny pack"). Treatment will be repeated every 28 days for a maximum of 8 cycles (8 months). The targeted accrual is 49 (45 evaluable) patients.

In accordance with E1494, Johns Hopkins' Richard Ambinder, vice-chair of ECOG's AIDS Committee, received funding through NCI's Cancer Therapeutics Evaluation Program (CTEP) to do a nested pilot study on the potential role of steroids in suppressing the cytotoxic immune response (CIR) to EBV tumor antigen in AIDS lymphoma. Ambinder believes that chemotherapy regimens that contain steroids (i.e., prednisone) actually inhibit the CIR to EBV. He will use ten patients from this trial and 10 patients from a Miami lymphoma study using chemotherapy and prednisone.

THE REBIRTH OF MGBG: BACK OFF THE SHELF FOR ANOTHER TRY

Methyl-glyoxal-bis guanylhydrazone (Mitoguazone or MGBG) is thought to have a unique mechanism which causes interference with polyamine biosynthesis. Polyamines are thought to be important in the stabilization of DNA. MGBG has been around since the early 1960s but has yet to be approved by the FDA for any malignancy. Over the past 15 years, MGBG has shown antitumor activity in patients with a number of cancers including head and neck, endometrial, prostate, Hodgkin's disease and non-AIDS NHL (Perry 1983; Knight 1983; Slayton 1986).

When it was initially tested in patients in the 1960s and 1970s, MGBG was administered daily and sometimes weekly. Severe toxicities included mucositis, vasculitis, myopathy, painful skin lesions, anorexia and significant weight loss (Freireich 1962; Knight 1979). This caused the drug to be put back on the shelf for a number of years until clinicians realized that changing to a once every two week schedule with a modified dose -- or using it in combination with other chemotherapeutic agents -- would alleviate some of the most extreme toxicities.

Combination regimens using MGBG (e.g., the MIME regimen consisting of MGBG + Ifosfamide + Methotrexate + Etoposide) have induced excellent response rates in non-AIDS patients with refractory Hodgkin's and NHL (Cabanillas 1987).

MGBG is now being tested in phase II studies in AIDS patients with relapsed or refractory NHL. It has been suggested that MGBG might be best suited for these NHL patients because of its long half-life (the amount of time the active drug stays in the body), its ability to penetrate into the cerebrospinal fluid [CSF], and its relative lack of marrow toxicity (Levine 1995). Results from a small 31 patient phase II study of MGBG in relapsed or refractory AIDS NHL (median CD4 count = 83) are recently published. Of 25 evaluable patients, there have been 2 CRs (8%), 5 PRs (20%) and one patient with stable disease for over 10 months (Levine 1995). Clinical benefit was observered in terms of weight gain (43%) and improved performance status (33%). 24% of the patients demonstrated an increase in their CD4 counts. Thrombocytopenia, which occured in 16% of the patients was the only notable hematologic toxicity. Other side effects included flushing (84%)and mucositis (29%).

If all goes well with the current multicentered phase II study, MGBG will be brought to the FDA in 1996 as an NDA for second-line treatment of AIDS-NHL. This will be the first time that an agent will be submitted for licensure specifically to treat an AIDS lymphoma.

## IMMUNE MODULATORS AND CYTOKINE INHIBITION

### Anti-IL-6 (Interleukin-6) strategies

It has long been postulated that cytokine production and dysregulation play an important role in the development of NHL. Because a number of studies have demonstrated that large cell diffuse and immunoblastic lymphomas express high levels of the lympho-stimulatory cytokine IL-6, researchers have been considered down-regulation of this cytokine as a possible treatment for NHL.

IL-4 is a protein that has been shown to inhibit IL-6 in vitro. te Velde and colleagues (te Velde 1990) demonstrated this inhibition in KS cells in 1990 and Herndier documented its inhibition in HIV-associated large cell lymphoma in 1995. (Herndier 1995). IL-4 is secreted by antigen-activated CD4 cells and stimulates the growth and differentiation of B cells (Schwab 199). Moreover, in studies at Schering-Plough Research Institute, administration of murine IL-4 to immunocompetent and nude mice cause marked inhibition of murine tumors including, sarcoma, B16 melanoma, and Lewis lung (Kaplan, ACTG IL-4 concept sheet).

Because of this pre-clinical data, Kaplan and colleagues proposed a study of IL-4 to be conducted through the ACTG. However, Schering-Plough has refused to give drug for this study and told Kaplan that they never again want to work with the ACTG (Lawrence Kaplan, personal communication). Some investigators have mentioned that they were apprehensive to use IL-4 as a front-line therapy. So, this protocol was designed with two separate arms: one as up-front therapy in good-prognosis, stable patients with a window of opportunity, and another for patients who have relapsed standard combination chemotherapy.

IL-4 is presently being tested in an ACTG study for AIDS-KS; another conducted by Gill and colleagues at USC recently closed. In neither study has IL-4 induced more than a handful of responses (Miles & Gill, personal communication). In fact, although Miles does not believe that this drug is very active against KS, he has been struck by its apparent antiviral activity. Thus far, patients in the ACTG study have shown a marked decrease in their p24 antigen level and an approximate 70% drop in the viral bDNA levels (Steven Miles, personal communication). The dose-limiting toxicity of IL-4 has been neutropenia, which can be regulated with G-CSF.

An anti-IL-6 monoclonal antibody (BE-8) was recently studied in 11 patients with AIDS-NHL in France by Emile and colleagues (Emile 1994). Patients with immunoblastic and large-cell diffuse lymphomas were analyzed for tumor response and effects on their IL-6 levels.

BE-8 was able to neutralize the IL-6 levels in 9 of the 11 patients. However, only 5 patients experienced a stabilization of their NHL and one achieved a PR. A clear, beneficial effect was seen in the lymphomas associated with fevers and wasting; these patients showed a mean body weight increase of 1.4 kilograms. The major toxicities noted were moderate thrombocytopenia and some neutropenia.

The fact that BE-8 did not induce a significant response rate in these patients (no CRs) has led Emile and colleagues to believe that the "growth of malignant

cells may be [only] partially IL-6 dependent" but that neutralizing IL-6's effects can "completely abrogate B clinical symptoms" (Emile 1994).

IL-2 (Interleukin-2) Caliguri and colleagues at Roswell Park Cancer Institute in Buffalo have been administering daily low-dose subcutaneous injections of IL-2 in order to extend patients' responses to chemotherapy and in the hope that it will help normalize patient's immune function by raising T cells and lowering viral load. In turn, this rise in T cells might help fight off EBV which targets B cells.

Their phase I study -- in which IL-2 was given to patients who achieved a response from chemotherapy -- enrolled 5 patients with NHL along with 5 others who had KS (Bernstein 1994). Only one of the 5 NHL patients has relapsed thus far. The major toxicity noted from IL-2 was the usual lethargy and fevers. Patients did have an increased CD4s and there was no significant increase in their viral load. The fact that IL-2 therapy was not detrimental to these patients' immunologic functions in this phase I study is reassuring in light of the fact that Clifford Lane's IL-2 HIV study noted that therapy appeared too toxic in patients who had less than 100 CD4s at baseline (Kovacs 1995).

A larger phase II study of IL-2 in NHL patients who have achieved a marked response to chemotherapy will be conducted in a multi-center trial run through the NCI's cooperative group CALGB (Cancer and Leukemia Group B). The primary objectives of this study are to ascertain if IL-2 can prolong tumor response and survival.

Immunotoxin Therapy

Immunotoxin therapy consists of using a monoclonal antibody directed toward a cell surface antigen (such as B cell markers CD19 or CD22). This antibody is linked ("conjugated") to a toxin (e.g., the à chain of ricin) and then the antibody toxin complex binds to the receptor on the cell surface and is taken up by the cell. If all goes as planned, the toxin will kill the cell, hopefully with minimal toxicity to neighboring cells or those which come along to clean up the mess.

Anti-CD22

Kaplan and colleagues at SFGH are presently accruing patients with AIDS-NHL for phase I/II trial of Ricin à-chain conjugated anti-CD22 (IgG-RFB4-dga). This antibody is intended to kill B-cells via their CD22 surface antigen. Both chemotherapy naive and those with relapsed and refractory disease are eligible. A small number of patients have been enrolled and are tolerating therapy. One refractory patient with a gastrointestinal lymphoma has already achieved a CR and another has had a PR. This study, however, has been slow to accrue due to the low rate of CD22 positivity among screened tumors making this particular immunotoxin impractical for most patients (Lawrence Kaplan, personal communication).

A similar anti-CD22 monoclonal antibody has been studied in non-AIDS NHL. Of 22 patients evaluated after one month of therapy, one had achieved a CR and 6 achieved a PR (Shen 1988). Dose-limiting toxicities included edema (swelling) and aphasia (difficulty in speech and understanding).

ANTI-CD19

Scadden and colleagues (Scadden 1994a) have completed a trial using another immunotoxin, Anti-B4-blocked Ricin (Anti-B4-bR) with combination chemotherapy in patients with AIDS-NHL. Anti-B4-bR is the murine (mouse) monoclonal antibody Anti-B4 which targets CD19 with a modified ricin (à and chain) dimer. This therapy was given over a 7 day continuous infusion after patients have responded to two cycles of either CHOP or m-BACOD.

45 patients (mean CD4 = 146) enrolled in the study and 26 of them -- after responding to the chemotherapy -- went on to receive Anti-B4-bR therapy. Although there has not been enough time to evaluate all patients, a substantial number of patients who had a CR are holding their CR. At least 20% of the patients who had only a PR after their chemotherapy, have gone on to achieve a CR. At least four patients have also developed anti-mouse antibody (HAMA) or anti-ricin antibody (HARA). The grade III or greater toxicities included fever, myalgias (muscle pain), fatigue, nausea and vomiting, central line thrombosis (blood clotting), and elevated liver enzymes.

This study was an extension of the phase I Anti-B4-bR monotherapy study conducted by Tulpule and colleagues (Tulpule 1994) on 9 refractory NHL patients. Given over a 28 day continuous infusion, only one patient achieved a CR and another achieved a solid partial remission of a liver lesion. One other patient had a "mixed" response and all others (67%) progressed on therapy.

According to Scadden, Anti-B4-bR monotherapy does not seem to be that effective. In combination with chemotherapy, however, there is synergy; even in some patients who are multi-drug resistant. The Anti-B4-bR may sometimes augment the chemotherapy and push a patient from a PR to a CR and also hold the durability of that patient's CR (David Scadden, personal communication). A pilot study of 28-day Anti B4-bR infusion with CHOP is underway in anticipation of a randomized, phase III trial comparing this combination therapy approach with chemotherapy alone.

RADIOIMMUNOTHERAPY

Straus and colleagues at Memorial Sloan-Kettering are conducting a phase I-II study of 131I-LL2 murine IgG antibody in refractory patients with AIDS and non-AIDS NHL. Similar to the other immunotoxins, 131I-LL2 is a murine (mouse) monoclonal antibody that is targeted to bind to the cancerous B cells by way of the CD22 antigen. However, radioactive iodine (131I) is used is used as the toxin instead of ricin. Because the iodine is radioactive, 131I-LL2 is a radioimmunotherapy. Not only might this monoclonal antibody have therapeutic, cell killing capabilities, it can also be used for imaging of the tumor. Tumor imaging (which is like a tumor scan) may be useful to determine the presence of occult tumor sites in the body.

TOPOISOMERASE 1 INHIBITORS

Camptothecins are a class of compounds believed to have special activity against topoisomerase-I, an enzyme involved in DNA replication, by interfering with topoisomerase function. The most well known of the camptothecins is topotecan, produced by Smith Kline-Beecham. Topotecan inhibited the HIV-1 long terminal repeat (LTR) (Crumpacker 1993) and has also been shown to have antitumor activity in a number of cancers (Slichenmyer 1993). SmithKline and Lawrence Kaplan recently designed a protocol using topotecan in patients with AIDS-NHL. Kaplan's SFGH site will be used as well as two more (yet to be determined) sites around the country (Lawrence Kaplan, personal communication). [Topotecan will also be entering a phase I study against progressive multifocal

leukoencephalopathy (PML), the aggressive neurological OI linked to infection by JC virus.]

UCLA's Steven Miles has designed a protocol for a phase II study of 9-aminocamptothecin (9-AC) for patients with AIDS-NHL which will soon open throughout the ACTG. 9-AC -- licensed by the NCI -- is the sister compound of topotecan. It has shown antitumor activity in mice (Supko 1992) and in humans with solid tumors (Dahut 1994).

This 9-AC study will probably be a two-arm study for both initial treatment and for refractory patients. If patients do not achieve at least a 25% response to therapy after their first cycle, they will be removed from study and offered other standard treatments.

ANTI-EBV STRATEGIES

Lyerly and colleagues at Duke University have designed a protocol for a phase I, 5 patient study of cellular adoptive immunotherapy using EBV specific T cells for refractory or recurrent EBV-expressing AIDS-NHL. Patients with EBV-positive NHL will first undergo leukapheresis to isolate white blood cells that will be used to grow anti-EBV cytotoxic T lymphocytes (CTLs). These anti-EBV-CTLs will be grown and stored while the patient undergoes standard combination chemotherapy. If the patient achieves anything less than a CR, he/she will have their grown anti-EBV-CTLs reinfused into their body for a total of four 30-60 minute infusions every two weeks. Patients then will receive intravenous IL-2 infusions on the day of therapy and for four days afterwards.

Such a novel anti-EBV strategy as this has been used with some success to treat non-AIDS NHL patients by Papadopoulous and colleagues (Papadopoulos 1994) at Memorial Sloan-Kettering (MSKCC) and by Heslop and colleagues (Heslop 1994) at St. Jude's Children's Research Hospital.

Following up on Papadopoulos' successful adoptive immunotherapy using infusions of untreated donor lymphocytes in patients without AIDS who developed EBV-associated NHL after bone marrow transplantation, O'Reilly and colleagues at MSKCC have designed a phase I study of EBV-specific T cells for the treatment of EBV-associated NHL in patients with AIDS, transplant recipients, or other immunodeficiency disorders (Susan Krown, personal communication).

In this study, patients with AIDS-associated EBV-positive NHLs will receive infusions of EBV-specific cytotoxic T-cells from a related, histocompatible donor. These cytotoxic cells are generated in the laboratory by culturing EBV-infected donor B cells with purified donor T cells, and then expanding the T cells in culture with IL-2. These expanded EBV-specific T cells are then reinfused into the patient without prior chemotherapy.

In a similar study, Scadden and colleagues at Deaconess Medical Center in Boston will be conducting a phase I trial of adoptive transfer of allogenic or haplodentical peripheral blood mononuclear cells (PBMCs) to patients with refractory or relapsed AIDS-related NHL. Each patient will receive approximately 2-8 X 106 cells/kg of mononuclear cells weekly for 4 weeks. Patients will also receive 30 million units of interferon three times weekly. Patients must be on an approved antiviral and will be watched closely for the development of graft-versus-host-disease.

Ambinder and colleagues at Johns Hopkins Oncology Center are currently enrolling for a pilot study of 5-Azacytidine (5-AC) given as a 7-day continuous infusion

in HIV positive patients with relapsed or refractory EBV-associated lymphoma. 5-AC is an analogue of cytidine which has been in clinical trials since 1967. This analogue inhibits DNA methyltransference, causing a block in cytosine methylation in newly replicated DNA (Chabner 1990). Until recently, 5-AC was most well known as a treatment for sickle cell anemia (Dover 1985).

5-AC is able to reverse the methylation of viral transcriptional regulatory elements in tumors and thus results in the expression of the EBNA-2,-3A, 3B, and 3C antigens (Masucci 1989). Because these antigens are targeted by cytotoxic T cells in virtually everyone studied, the tumors might then be destroyed by a preexisting "tumor-specific" cellular immune response.

COMBINATION THERAPY FOR PCNS NHL

ECOG has implemented the multi-centered/multi-cooperative group study E 1493, a Phase II trial of sequential chemotherapy and radiotherapy for AIDS-related primary central nervous system (PCNS) lymphoma.

E1493 is a trial of the standard chemotherapeutic regimen CHOD (Cyclophosphamide, Doxorubicin, Vincristine and Dexamethasone) followed by radiation therapy to the brain for the treatment of AIDS-related primary central nervous (CNS) lymphoma.

Both combination chemotherapy regimens and whole brain radiation have been used separately for the past twenty years with some success in treating AIDS and non-AIDS-related lymphoma. While radiation is most commonly used, it doesn't usually shrink or kill the tumor completely. It mostly helps with a relief in the symptoms caused by the lymphoma. Chemotherapy is used less often because most patients can not tolerate extensive cycles (courses of treatment) because their immune system is so depleted.

However, data suggest combining both treatment regimens in non-AIDS-related CNS lymphoma might improve response rates as well as increase survival (DeAngelis 1992).

Patients will be treated with both modalities sequentially (first the chemotherapy, then the radiation) to determine: 1) the response rates and overall survival; 2) the toxicity associated with this sequential combination; 3) the impact on the quality of life from taking this regimen.

All patients will receive one cycle of the chemotherapy regimen CHOD. In the days after chemotherapy, patients will start taking the granulocyte colony stimulating factor, G-CSF, to boost low white blood cell levels which leave the body vulnerable to infection. About a week later, patients will begin radiation therapy to the brain which will be given five days a week for approximately four weeks.

Patients will only receive this chemotherapy infusion once (on the first day for one hour) at the beginning of the trial and then never again. It is thought that this first dose is the strongest and most effective way of killing the cancer cells and shrinking the tumor. If patients are found to have cancer cells in their spinal fluid, they will receive intrathecal chemotherapy with Cytarabine (injected into the space surrounding the spinal cord) twice weekly until those cells have disappeared.

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CURRENT OPINIONS IN AIDS-RELATED LYMPHOMA FROM PHYSICIANS, CLINICIANS + RESEARCHERS

Over 30 AIDS and non-AIDS oncologists, radiation oncologists, clinicians, primary care physicians, and laboratory researchers who have worked in the field of AIDS lymphoma for the past 13 years were interviewed by telephone or in person. They were all asked about their work and how they felt about the current state of AIDS-related lymphoma research. Many were asked about their recent or forthcoming articles which provide a basis for our limited understanding of the pathogenesis and the treatments used on patients with AIDS-NHL. They were asked questions germane to their expertise in three broad areas: 1) pathogenesis; 2) diagnosis and prognostic factors; and 3) treatments -- the standard of care and experimental agents.

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

I. WHAT IS THE PATHOGENESIS OF AIDS-NHL?

A majority interviewed expressed that they did not have a clear picture of all the mechanisms involved in the development of AIDS NHL. Most, of course, note that it starts with a hyperactivation of B cells and immunosuppression, but from there on, most cite their favorite pathogenesis articles.

A. "How is AIDS-NHL different from non-AIDS NHL?"

Many admitted that their understanding of AIDS-NHL came directly from past experience with organ transplant patients who developed NHL . NHL wasn't something new to them like AIDS-KS. They knew that some organ transplant patients developed NHL because they were administered immunosuppressive drugs (like Cyclosporin A) in order to wipe out their T cells so they wouldn't reject the donated organ. So, it was no big surprise to see men with AIDS develop NHL (early in the 1980s) because they were also immunosuppressed due to HIV.

Some were surprised when they realized that these men were presenting with Burkitt's or Burkitt's-like NHL (Western) which was previously rare in the this country. Indeed, the NHLs that these HIV-positive patients were presenting with were much more aggressive than the non-AIDS NHLs seen previously. The high proportion of large cell lymphomas and the fact that many of these patients were presenting with grade III and IV lymphomas (with extranodal involvement) was disconcerting to many. Thus, "why did this patient population have to pick and choose this, the worst type of NHL?" Past experience told these physicians that these would be the toughest to treat. B. How central is the role of EBV in the pathogenesis of NHL?

EBV was a hot topic. There was little if no doubt that PCNS NHLs are universally EBV-positive. There is, however, a discrepancy as to the rate at which EBV is present in systemic (non-CNS) NHLs of AIDS patients. Many said that they were not sure what studies to believe, considering that reported rates range between 30-70%.

Some would have liked to have said that EBV causing hyper B cell activation was the sole reason for this occurrence of NHL, but since only about half of these cases have evidence of EBV, it is evident that something else may also play a pivotal role. All in all, most believe that EBV infection plays a very important, if not necessary role.

C. What about cytokine and oncogene dysregulation?

Again, many believed that the dysregulation of IL-6 and IL-10 have some role in the pathogenesis of AIDS-NHL. However, there is not enough information as to their exact role. Some were not sure at what point in the course of HIV disease or lymphomagenesis these cytokines become pathogenic.

The same thoughts center around c-myc activation and its 8:14 translocation. It is better to be c-myc negative, but being positive -- as seen with Rabkin's latest study -- does not assure the development of AIDS NHL.

Even though many studies conflict with each other as to the mechanisms of lymphomagenesis, one oncologist found it comforting that -- unlike AIDS-KS -- we at least have identified the B cell as the "cell of origin."

D. How do you feel about data that has come out of SFGH/UCSF documenting a significant number of polyclonal AIDS-NHLs?

Many clinicians and pathologists were divided -- and opinionated -- about the issue of polyclonal NHLs. Some boldly said that they don't believe the data at all and that they have never seen a polyclonal AIDS-NHL as long as they have been treating patients. There are a number of questions they felt unresolved centering around that data. The other sceptics said that the reason they have never seen a polyclonal AIDS-NHL is because the pathologists at their institutions were so talented that they were able to clearly identify every monoclonal NHL and all the rest are just chalked up to a B cell lymphoproliferative disorder.

Some find this data on polyclonal NHLs fascinating, and while they don't see too many, they feel obliged to mention and reference their UCSF colleagues in articles they write. These same clinicians said that if the patient has a tumor mass but is not given the definition of a monoclonal NHL by the pathologist, they are still going to use standard chemotherapeutic regimens to fight the tumor and to insure that it does not grow into a monoclonal NHL.

Some clinicians said that they do not concern themselves with the debate and that clonality is not an issue for the vast majority of patients seen day in and day out. They said that if the patient's tissue or FNA (fine needle aspirate) comes back with a positive stain, that is all that is usually needed to consider the tumor as being a B cell malignancy. It all depends on what the pathologist sees under the microscope. When the pathologist sends his/her report back, there is not a box that is checked that delineates the NHL as polyclonal or monoclonal. Assays used for determining clonality are expensive ($500.00 a pop) and are never used unless the patients tested are part of a lab based study.

A few oncologists said that this delineation (if it can be done) would prove beneficial in future pathogenesis based studies for randomizing patients.

Others suggest that histologically, polyclonal disease is virtually indistinguishable from monoclonal lymphoma. And, to stop this debate, histology should be considered the "gold standard."

Another oncologist felt that this was still a serious issue and needed to be addressed because some patients might not be offered treatment because the did not get a pathologists "monoclonal" diagnosis. He warns:

We can call them what we like, but the fact is that the patients are dying as a direct result of what you can call either a polyclonal lymphoma or an aggressive

polyclonal lymphoproliferative disorder. Whatever you call it, they are aggressive diseases. And, morphologically and histologically, they are virtually undistinguishable.

e. What do you believe may be the role of KSHV in the pathogenesis of certain HIV-associated lymphomas?

The recent discovery of the KS-associated herpesvirus KSHV (Chang 1994, Weiss 1995, Ambrozial 1995, Moore 1995) and its association with body-cavity based AIDS-associated lymphomas confirmed many researchers' intuition that undiscovered etiologic agents may trigger or participate in the pathogenesis of several AIDS-related neoplasms. However, the new agent remains to be fully sequenced and many further questions remain before it can be definitely shown to be a transforming agent either for KS or body-cavity based lymphomas. Moreover, the lymphoma tissues examined were all EBV+ and c-myc gene arrangement negative, and so many questions remain about the etiologic agents of other AIDS-associated lymphomas, for example polyclonal and EBV-negative ones. Some believe that KSHV may be a transforming virus by itself. New techniques such as the representational difference analysis (RDA) used to discover KSHV and several new hepatitis viruses may soon uncover unsuspected etiologic agents for small non-cleaved lymphomas and possibly others. This area will be certain to experience explosive growth in the coming months and years.

II. HOW DO YOU DIAGNOSE NHL AND WHAT PROGNOSTIC FACTORS DO YOU THINK IMPACT ON TREATMENT OUTCOME AND SURVIVAL?

There was consensus from most all who were interviewed regarding the diagnosis of NHL.. Many said that even though most of these NHLs are extranodal, a swollen asymmetrical lymph node is still going to be something to makes one think that its NHL. This is true especially when the patient has classic "B" symptoms that have lasted for a while and remain unexplained.

A. How important is a definitive diagnosis?

For systemic lymphoma, the patient will first have to have some sort of x-ray, CT scan or MRI. If the oncologist believes it to be a lymphoma, then a tissue biopsy or a fine needle aspirate is mandatory. It was thought that justifying a biopsy in the cases of systemic NHL was not too problematic especially when the procedures are not so invasive.

A few oncologists and radiation oncologists felt that asking a patient with supposed PCNS NHL (after toxoplasmosis was ruled out) was necessary in order to deliver treatment. As one oncologist said, "I don't like having to demand one. I try to explain to them that so much radiation to the brain will be extremely detrimental unless it really is NHL. If I really have to get pushy, I use the classic line No Meat, No Treat'."

Interesting, a number of oncologists recalled the problems with neurologists at their institution -- and cite Dana Farber Cancer Center as a classic example -- who refused to conduct brain biopsies on AIDS patients suspected of having PCNS NHL. Some were not sure if such reticence was due to AIDSphobia or homophobia. Others feel that some advanced patients may be too fragile to undergo such an invasive procedure.

B. Why are all these AIDS patients presenting with stage IV NHLs? Isn't there some way of finding these lymphomas at stage I level when they are more treatable?

Most said that it would be opportune to get these patients before they were at stage IV, but in the setting of HIV disease that is probably not possible. As one oncologist said, "These things just appear and at random sites all over the body. They are highly aggressive and can double in size in 24 hours. Short of giving someone an MRI everyday, there is not a great deal one can do to for early detection. The best advice from most was to be aware of the classic "B" symptoms and to monitor how long they last. If they don't go away within a week, "get them to a doctor for a thorough check-up and have him/her rule out all other possible OIs first."

C. What are some of the most severe prognostic factors?

A majority of opinions were in synch with the current literature that mentions CD4 count below 100, prior OIs and extranodal disease (especially bone marrow involvement). Some believe that having all poor prognostic factors means that the patient will not respond well to therapy and will thus have short survival. A few felt that it would soon be important to start stratifying patients to various therapies based on these three prognostic factors. In addition, patients that initially present with such poor immune function will have trouble with the chemotherapy itself and if neutropenia sets in, it will further delay treatment.

III. WHAT DO YOU CONSIDER AS THE PRESENT STANDARD-OF-CARE TREATMENT REGIMEN?

Opinion was divided as to whether to use CHOP or m-BACOD, either in high doses with growth factor support or in modified doses. It all seemed to depend upon what the physician was most comfortable using. One even said that he prefers his special regimen which he refers to as "CHOP-LITE."

Even though opinion was divided, there were still some who remained optimistic about successfully treating NHL, saying that in some cases "it is curable, and that's a lot more than you can say for other cancers." Some did not find it problematic nor get depressed over the fact that while they would cure a patient of his/her NHL, that same patient still had the HIV ravaging his body.

A. What are your thoughts about the outcome of the ACTG 142 study?

Most were familiar with the various ACTG studies that have led us to the basic understanding that low-dose/modified regimens will work just as effectively as high dose regimens in this patient population. Nevertheless, some say that it all depends on the patient population (e.g. approximately 20 patients out of 45 with CD4 counts above 200 are still alive after ? + years). They would still like to attempt to administer the largest and most effective doses to patients that can truly handle them. Since it seems as thought the first two cycles are the most important (and will predict how well one responds), it might be helpful to get as much "bang-for-your-buck" as possible.

Some did not expect to see a significant difference in the arms, but realized that this large phase III study was needed. It was also the largest study completed on patients with AIDS NHL and the data base that has been built up will help for years to come. B. How important is it now to design a study that would look at low-dose m-BACOD vs. low-dose CHOP?

There are many who would like to see such a study done. But in reality, they said, "it is completely unfeasible." These sentiments came from most of the investigators of ACTG 142 who spent 4 years of their lives attempting to accrue approximately 200 patients. They basically said that AIDS-NHL studies don't

accrue well -- worse than cancer studies in general. Also, many community physicians and oncologists are not all that concerned with the ultimate standard-of-care studies.

C. What is your belief on CNS prophylaxis?

Almost everybody said that they empirically initiated CNS prophylaxis in all patients just because it was the "safe" thing to do even though there were no hard-core data proving its effectiveness. A few others were more cautious about routinely prophyaxing all patients and said it only needs to be done on those with lymphoma involving the bone marrow, epidural area (outermost part of the brain and spinal cord), sinus disease, or patients with SNCC (category "J") histology.

D. Do you feel that a non-AIDS oncologist is fully capable of treating an AIDS patient with NHL?

Most said that it all depended on the oncologist and also what city he/she practiced in. Those in San Francisco felt that there were some excellent community doctors who could give good, adequate care. But, if the oncologist was not in a cosmopolitan city and if he/she did not see that many patients with AIDS it could be detrimental to patient. They feared that the oncologist would not know the intricacies of AIDS and treat the patient with high-dose regimens meant for non-AIDS NHL patients. Also, they were skeptical as to whether or not this oncologist knew that supportive care (prophylaxing with everything possible) was necessary in immunocompromised patients with low CD4s. In major cities the oncologist might not have to play such an intensive role in the management of the patient because of the hope that the primary care physician would be looking out for those things.

IV. WHAT ARE YOUR THOUGHTS ABOUT SOME OF THE EXPERIMENTAL TREATMENTS THAT ARE PRESENTLY IN THE CLINIC?

Almost all said that chemotherapy -- what we have to offer in 1995 -- is simply not effective enough, especially in such an immunocompromised patient population with poor bone marrow reserve.

One oncologist said that while this is true, he was taught that chemo was supposed to be his friend and it was up to him to make it work for -- in whatever way -- for his/her patients.

Some hoped that their various potential new treatments would work for their patients whether it was a cytokine modulator or an anti-EBV agent. Others remained more doubtful because: 1) we still don't have a clear picture of the pathogenesis of AIDS-NHL; and 2) targeting one aspect (i.e., IL-6 or ras) of lymphomagenesis would simply not be effective enough.

Most believed that these experimental agents and approaches would have to be used in combination with chemotherapeutic regimens. They thought that if you could do as much damage to the tumor as possible, such agents might then be able to wipe the rest of it away and hold the response, thus impacting on survival.

There was a great deal of skepticism around a number of treatments. The prolonged 96 hour CDE regimen is thought by some to be too cumbersome and too awkward and that it would not boost response rates that much over what has been seen previously with m-BACOD. The defense to that argument has been, "yes, we might not have significantly higher response rates, but so far we have shown

that survival is twice as long as standard regimens. " The retort to that, "we will see how CDE fares after the multi-institutional phase II trial is completed and followed."

A few clinicians are also skeptical about using IL-2. Even though it is only given to those patients who initially respond to chemotherapy, some don't feel that it will be effective or worth the additional flu-like symptoms which are present with lymphoma itself. After seeing that Cliff Lane's IL-2 data documented a negative effect on patients with CD4s below 100, some clinicians warn that these NHL patients (many with CD4s under 100) will be harmed. The investigators using IL-2 for AIDS-NHL and KS said they did not see any negative virologic effects in their 10 patient phase I study. It will be important to monitor this now that IL-2 is going to be used for AIDS-NHL in an NCI multi-institutional study.

There are some who are pleased to see that MGBG has had some success in AIDS-NHL patients who are refractory or who have relapsed. Clinicians do feel that it has definite antitumor activity and are thrilled that they have seen very little neutropenia. With a large pool of competent AIDS-oncologists pushing their phase II trial along, many believe that MGBG will soon be on the market and suitable for second line therapy. At present time, there is really no second line therapy to speak of.

Most say that MGBG will have to be used in combination with other agents. This analysis stems from the fact that many do not feel that monotherapy for NHL has been -- or ever will be -- effective.

A. Do you believe in a window-of-opportunity for AIDS patients with NHL?

This has been a contentious debate. One that has divided clinicians planning trials. Some feel that it is OK to give a patient an experimental treatment as long as you believe it is moderately effective and as long as you closely follow that patient. If he/she does not show a response within the first or second cycle, he/she should be immediately removed from the study and offered the "best" available treatment. Those in that camp do not feel that all patients should receive experimental therapies and that it might depend on a host of prognostic factors. They feel that an experimental treatment must be given its best available chance to show activity. If it is not working, then switch. But, to give it to a patient who has failed everything else and on death's-door does not give the agent of a fighting chance. However, salvage trials for refractory patients are often the first studies of new cancer drugs in humans.

There are also those that do not feel a patient has time to waste on a bogus pathogenesis based therapy. They are also concerned that some new chemotherapy agents might cause multi-drug resistance. It this occurs, you have blown your chance to give them standard agents that might not work.

Because this debate has become such an issue, many protocols have an up-front arm and a relapse/refractory arm. Likewise, protocols are now being designed which allow investigators at certain sites to choose which population(s) they feel most comfortable using the agent in.

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CLINICIAN'S RESPONSE

by David T. Scadden, M.D.

Lymphomas are a reminder that the immune system is a war machine generally disciplined, but capable of fearsome destruction if control breaks down. The highly sophisticated defender that is the immune system must have the power to quickly unleash or reign in cell growth in order to respond to infection or injury. Command over immune cell growth is largely located in T cells whose failings are too well know accompaniment of HIV infection. As these control cells loose their grip, it not only allows infections to have their day, but also disturbs the usual between forces in the remaining parts of the immune network. Now, when viruses are capable of turning on B cells arise or when other growth can signals reach the B cell, the usual dampening effect of the T cell is absent and B cell growth can go unchecked. Part of the immune system has become an enemy and it has completely escaped the bounds its immune cell colleagues normally impose. When these lymphoma cells begin to run amuck there is little time before they wreak severe havoc. Help must come quickly and help must come from the outside. Help can mean cure.

The nature of help against lymphoma is limited to chemotherapy and radiation at present. Unlike the completely foreign organism which cause opportunistic infections, lymphoma resembles its normal cell counterparts in all but a small number of ways. This means that the drugs which are used to poison the tumor cells are often toxic to normal cells causing significant side effects. When the immune system is already ailing, withstanding these toxic effects is all the more difficult. Striking a balance between ill and beneficial effects has been the challenge which only recently appears to have given way. Through the commitment of many, a recent study detailed in this text (ACTG 142), has provided guidelines for safer use of chemotherapy. Now we can begin to pursue in earnest the next generation of questions.

All of the questions will truly require the effort of a "we" to address. There are somewhat natural alliances which have formed such as between clinical researchers who are finally formalizing ties to efficiently test the questions of new types of chemotherapy drugs and drugs for those patients whose tumors do not respond or relapse. Overlapping interests have also grouped some clinical and laboratory investigators and now the National Cancer Institute has facilitated sharing of reagents among them so questions regarding the molecular dimensions of tumors can be explored. Other alliances have taken dedicated efforts like between activists and clinical investigators that have shaped the questions, often galvanized the efforts and brought needed attention from industry and government. These groups must be extended to incorporate the immunologists and virologists and gene therapists to begin to explore ways in which advances can be furthered. The recent identification of novel virus sequences (the KS virus) in lymphoma reawakens the whole area of virus induced lymphoma. The potential of biologic, immune-based therapies (cytokines, antibodies or cells) has only begun to be tested and surely at least one weapon of the immune war machine can be wrestled back to serve as an ally.

But, most important alliances will be forged in the community. These alliances must be between the communities at risk, service organizations and health providers to improve awareness of increasingly common complications of HIV and to shore up the support for those afflicted by it. Primary care providers and patients should serve as advocates for improved care and education. Investigators need to be involved in outreach of these groups to be sure that the lessons of what of what has been learned are not squandered and the potential of what is to come is not neglected. Activists must help keep the changing health care delivery climate from undermining people's ability to participate in clinical studies or receiving emerging therapies. Government must remember our shared interest in this problem with continued support. Those

affected by lymphoma must remember the power they to make a difference for themselves by being informed and by seeking a partnership with their care providers. Embodied in this volume is knowledge that informs hope and action for us all.

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## UPDATE ON LAST YEARS' KS PROJECT RECOMMENDATIONS

Much of last year was spent seeking implementation of the policy recommendations proposed in TAG's July 1994 KS PROJECT Report. Individual meetings were set up with NIH Directors Samuel Broder (NCI), Anthony S. Fauci (NIAID), and William E. Paul (OAR) to go over the recommendations and to ask for their support in working with each other (and their respective staffs) in order to implement some of these changes. All were initially receptive to various recommendations. In December of 1994, the three directors organized a meeting to go over the recommendations, pin-point what were germane to each institute and asked for a coordinated effort in solving some of the fundamental shortcomings the Institutes had in targeting AIDS-related malignancies on a basic and clinical science level. Below is an overview of the progress to date.

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.

Due to the hiring freeze at the NIH, and a government-wide effort to reduce the number of Federal advisory committees, it has become apparat that the DRG will not be able to assemble a separate study section for AIDS-related malignancies. The need for qualified reviewers in the DRG still remains an issue in light of the fact that OAR's Paul is in favor of having institutes increase the pool of money they use for investigator-initiated AIDS grants (R01s).

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.

The NCI recently issued a request for application (RFA) for an AIDS Malignancy Consortium. This consortium will act as a mini-clinical trials network that will study novel agents in Phase I and Phase II trials. The 2 million dollars per year that has been allocated for this RFA is problematic if 8 to 10 sites are to be reasonably funded. Broder and NCI's Ellen Feigal have assured us and others that there is the possibility of putting more money into this consortium after its first year if circumstances warrant. A number of experienced AIDS oncologists (over 20 of them) have recently submitted their applications for which only 8 to 10 will be chosen. Thus, there are those out there who are willing to do the work and who have the patients. While the NCI's AIDS Malignancy Consortium will be a separate entity, it is the hopes of many at the OAR and in NIAID that the ACTG will be able to play a vital part in signing onto protocol and using their sites to accrue patients. The collaborative relationship the NEI's SOCA has with the ACTG (where each SOCA protocol get an ACTG number) is a model that might prove useful for having both institutes work together

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

The ACTG Oncology Committee remains a separate core committee which conducts its protocol negotiations through the ACTG's Complications of HIV Research Agenda Committee (RAC). The leadership of this RAC is thus far collegial and remains committed to the Oncology Committee agenda. Likewise, the Immunology RAC has expressed interest in assisting the Oncology committee with immunologic assays that will be run through its Advanced Technology Laboratory (ATL).

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.

The Cancer and Leukemia Group B (CALGB) and the Southwestern Oncology Group (SWOG) have both taken ECOG's lead in setting up AIDS committees or group and are soon to open their own AIDS-related malignancy protocols. Moreover, each groups has opened a few of ECOG's protocols at their respective institutions.

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.

The OAR, through its AIDS Research Evaluation Working Group and its Area Review Panels, is presently investigating the AIDS-malignancy efforts of both the NCI and NIAID. They are also aware of the NCI AIDS Malignancy Consortium RFA and are making recommendations regarding how both institutes might best collaborate. In addition, the Bishop-Calabresi committee report on the future of NCI is expected to contain recommendations regarding NCI's AIDS research portfolio.

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.

The NCI recently funded (through a targeted RFA) a number of major institutions around the country to conduct serum and tissue banking of AIDS-related malignancies.

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.

The NCI will hold its first KS Workshop on June 5-6, 1995 . This two-day conference will bring together the major basic scientists and clinicians working on KS in the US to discuss pathogenesis, the current standard of care and experimental treatments. 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 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..

In an effort to teach non-AIDS oncologist and primary care physicians about treatment options for AIDS-related malignancies, the NCI's CTEP awarded ECOG a marketing grant for its three new AIDS trials. The grant will be used for physician and patient brochures, and for exhibits at major AIDS and cancer conferences.

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?

The recent discovery and confirmation of the presence of a new herpesvirus in cells from AIDS- and non-AIDS-KS patients will generate new research approaches which may assist in the prophylaxis and treatment of AIDS-KS.

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