Non-Hodgkin's Lymphoma

The use of highly active antiretroviral therapy (HAART) and effective prevention and treatment strategies for opportunistic illnesses (OIs) have dramatically increased survival for people with HIV disease. As a result, there is a growing focus on serious complications that may arise during the course of illness, including AIDS-associated malignancies (cancers). Current AIDS-defining malignancies include Kaposi's sarcoma (KS), primary central nervous system (CNS) lymphoma, systemic non-Hodgkin's lymphoma (NHL), and invasive cervical cancer. This article will review systemic NHL.

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What Is Non-Hodgkin's Lymphoma?

Lymphoma is a cancer characterized by rapidly dividing, abnormal lymphocytes, which are white blood cells that comprise part of the immune system. One type of lymphoma, Hodgkin's disease, has a unique appearance under the microscope, as well as a typical clinical course and treatment. All other types are collectively termed non-Hodgkin's lymphoma. Only NHL is currently considered to be an AIDS-defining illness, though there is accumulating evidence that Hodgkin's disease may also occur with increased frequency in HIV-infected individuals.

While HAART has reduced the rate of OIs in people with HIV, its overall effect on the incidence of NHL is not clear. NHL occurs in approximately 5–10% of HIV positive individuals, typically late in the course of their disease. Due to this late presentation, NHL is the AIDS-defining diagnosis in only 3% of AIDS cases, but eventually accounts for up to 16% of AIDS-related deaths.

Although the precise cause of NHL is unknown, multiple studies have shown that compared with the general population, HIV positive individuals have a 200- to 600-fold increased risk of developing NHL, particularly the more aggressive subtypes. This much higher incidence in the HIV positive population is attributed to two main causes. The first has to do with altered immune function. Reduced numbers of functional CD4 cells in people with HIV leads to impaired immune surveillance, or failure to recognize and destroy abnormally multiplying cells. In addition, there is evidence that several lymphocyte-signaling molecules—such as interleukin 6 (IL-6), interleukin 10 (IL-10), and

chemokine receptor 5 (CCR5)—play a role in the development of NHL in people with HIV, possibly due to abnormal stimulation of cell proliferation (rapid reproduction or replication).

The second main cause of increased NHL in people with HIV has to do with the role of viruses. Continuously multiplying HIV constitutes a chronic (long-term) stimulus for proliferation and activation of lymphocytes. Over time, this constant lymphocyte hyperactivity may progress to an unchecked, cancerous state. In addition, HIV viral genes have been found to integrate into the DNA (genetic material) of human macrophages, another type of white blood cell, thereby inducing these immune cells to overproduce signals that stimulate lymphocytes. Finally, other viruses—such as Epstein-Barr virus (EBV, the cause of mononucleosis) and human herpesvirus 8 (HHV-8, associated with KS)—also have been implicated in certain subtypes of NHL, though their exact roles remain unclear.

NHL Classification

Although the malignant, or cancerous, cell type in NHL may be either B cells (lymphocytes that produce antibodies) or T cells (lymphocytes that attack infected or cancerous cells directly), the overwhelming majority of NHL in people with HIV is of the B cell type.

Traditionally, the different types of NHL have been classified according to the Working Formulation proposed in 1982, which categorizes lymphomas according to the appearance of the malignant cells (small-cleaved vs large), their growth pattern in lymph nodes (follicular vs diffuse), and the aggressiveness with which they multiply and spread (low, intermediate, or high grade). Thus, a low-grade, follicular, small-cleaved B cell lymphoma would have a more indolent, or slow, course than an intermediate-grade, diffuse (widespread), large cell lymphoma.

Over the past two decades, new technologies have enabled more sophisticated characterization of malignant lymphocytes beyond simply describing their appearance under the microscope. Specifically, immunophenotyping and flow cytometry are techniques that identify specific marker molecules, such as CD4 and CD20, found on the cell surface of lymphocytes. By identifying the specific surface marker signatures of various lymphomas, and also by detecting certain chromosomal (genetic) abnormalities specific to these lymphomas, it is now possible to tease apart types of NHL which previously had been lumped together due to their similar appearance under the microscope, but which are actually separate disease entities with different clinical courses and prognoses. Thus, the new Revised European-American Lymphoma Classification and World Health Organization (REAL/WHO) system now includes 23 subtypes of B cell and T cell NHL.

Most common among the HIV positive population are the more aggressive (intermediate- and high-grade) subtypes such as Burkitt's lymphoma, diffuse large cell lymphoma, immunoblastic lymphoma plasmacytoid, and anaplastic large B cell lymphoma. Only the high-grade, more aggressive forms of NHL are considered AIDS-defining, though individuals with HIV may have an increased risk of low-grade NHL as well.

Clinical Presentation

The most common symptoms heralding the onset of NHL in people with HIV are the so-called B symptoms, which consist of unexplained fevers, drenching night sweats, weight loss (more than 10% of normal body weight), and fatigue. If lymphoma cells take hold and grow in the peripheral lymph nodes, such as those in the neck or groin, the individual may begin to notice painless, firm, enlarging lumps in these areas. As noted above, people with HIV tend to develop the more aggressive, high-grade subtypes of NHL. For this reason, approximately two-thirds of individuals already have widely spread (late-stage) disease at the time of diagnosis, with up to 90% presenting with extranodal lymphoma (i.e., lymphoma that has progressed beyond the lymph nodes).

The most frequently involved extranodal site (in up to 33% of people) is the bone marrow, where white and red blood cells and platelets (cells that assist in blood clotting) are produced. When lymphoma cells infiltrate the bone marrow, they displace the normal precursors of white cells, red cells, and platelets, leaving no room for normal blood cell development. As a result, a person presenting with bone marrow involvement may have a low white blood cell count (contributing to increased risk of infection), a low red blood cell count (anemia, contributing to fatigue and breathlessness), and/or a low platelet count (contributing to easy bruising or bleeding).

The gastrointestinal tract (stomach and intestines) and liver are involved in approximately one-quarter of NHL cases, leading to symptoms such as bloating, abdominal pain, loss of appetite, nausea and vomiting, constipation or diarrhea, and jaundice (yellowing of the skin and whites of the eyes). Lymphoma in the rectum may occur, and present as a local mass or pain on defecation. A work-up (thorough diagnostic examination) of any new rectal mass in a person with HIV, especially if other systemic symptoms are present, should include a biopsy (removal of tissue for study) prior to excision (total removal) to rule out the possibility of lymphoma.

Central nervous system (CNS) involvement is found in approximately 20% of HIV positive people with NHL at the time of diagnosis. In these cases, malignant lymphocytes typically are found within the cerebrospinal fluid (CSF) in the meninges, the membranes that encase the brain and spinal cord. CNS involvement is frequently asymptomatic, but a person may experience headaches, back pain, nausea, and sensitivity to light, similar to the symptoms of infectious meningitis (inflammation of the meninges). In cases of more aggressive CNS involvement, lymphomatous masses may become

implanted in the meninges, or they may invade the brain itself, leading to more significant symptoms such as altered mental status and facial weakness or paralysis. [Ed. note: CNS involvement in NHL is distinct from primary CNS lymphoma, which originates as a mass in the brain or spinal cord and is usually associated with the Epstein-Barr virus. Unlike NHL, primary CNS lymphoma generally does not occur in people with more than 50 CD4 cells/mm^3.]

NHL Diagnosis and Staging

Typically, a person with HIV/AIDS might present to a health-care provider with some combination of the symptoms described above, for example, intermittent fevers and night sweats, fatigue, abdominal bloating, and an enlarged lymph node in the neck. The diagnosis of NHL is made with a needle biopsy of the lymph node, followed by microscopic examination and flow cytometric analysis of the tissue sample by a pathologist (a specialist who identifies diseases by examining cell and tissue samples).

If a needle biopsy does not reveal the presence of lymphoma, the node should be excised (removed) and examined to definitively rule out lymphoma. If there is no enlarged lymph node readily visible for biopsy, imaging studies may be done, such as a chest x-ray or a computed tomography (CT) scan of the chest and abdomen. If imaging reveals enlarged internal lymph nodes or masses, then a biopsy is performed guided by CT or ultrasound.

After the pathologic tissue diagnosis of NHL is made, the clinical stage of the disease must be determined. More advanced stages portend a worse prognosis (prospect of recovery and survival) and require more aggressive treatment. The Ann Arbor staging system is a scheme initially devised for staging Hodgkin's lymphoma, but it applies to NHL as well. It is based on the concept that lymphoma cells spread first through the lymphatic system to various lymph node groups, and from there to extranodal organs. Thus, there are four stages that correspond to increasingly distant spread of disease and worse clinical prognosis:

Stage I refers to NHL found in only one lymph node region—for example, an enlarged neck lymph node—but no other disease.

Stage II refers to disease involving two or more lymph node regions on the same side of the diaphragm (the large sheet of muscle that separates the chest cavity from the abdominal cavity), for example, enlarged lymph nodes in both the neck and chest.

Stage III disease involves lymph node groups on both sides of the diaphragm, for example, in the neck and groin.

Stage IV refers to widely spread disease that involves other organ systems, such as the CNS, the bone marrow, or the gastrointestinal tract.

To determine disease stage, several tests are performed at the time of diagnosis. CT scans of the chest, abdomen, and pelvis help to determine the extent of involvement of lymph nodes and extranodal organs. A bone marrow biopsy is performed to look for malignant lymphocyte infiltration. Under local anesthesia, a biopsy needle is inserted into the posterior iliac spine (the back of the pelvis) and a small amount of marrow is withdrawn and examined under a microscope for the presence of malignant lymphocytes. Similarly, a lumbar puncture (spinal tap) is performed to look for CNS disease. Again under local anesthesia, a needle is inserted into the space surrounding the spinal cord at the level of the lumbar spine, and a small amount of CSF is withdrawn and examined microscopically for the presence of malignant cells.

The blood level of lactate dehydrogenase (LDH) is checked, as this enzyme, produced by rapidly dividing lymphocytes, provides a prognostic index that reflects disease burden (i.e., how extensively the lymphoma has spread). Also, uric acid levels are checked, because this byproduct of lymphocyte proliferation can potentially cause kidney failure. Finally, all patients undergo basic blood tests to determine levels of white and red cells and platelets, as well as to assess liver and kidney function.

Two other tests are typically performed at the time of diagnosis, but these are done for treatment-related reasons rather than for staging purposes. The first is a functional imaging study, either a gallium-67 scan or positron emission tomography (PET). For these tests, the individual is first injected with a harmless radioactive substance that is taken up by cells with very high metabolic rates, including rapidly dividing malignant lymphocytes. These areas of uptake then light up on the scan, showing the location of the lymphoma. The gallium-67 or PET images complement the CT scans and serve as a useful baseline for disease location.

Often after NHL is treated, repeat CT scans reveal residual masses in lymph nodes or extranodal organs. This does not necessarily mean that treatment has failed. In some cases, although all the malignant lymphoma cells have been eliminated, residual scarring and swelling remain, which a CT scan cannot differentiate from actual lymphoma. Here lies the utility of a functional study. When the gallium-67 or PET scan is repeated, the masses noted on the CT scan can be checked for radioactive uptake. If these areas continue to light up, as they did in the baseline functional study, then the residual masses indeed represent

One of the most promising new approaches to NHL treatment is the use of immunotherapy.

persistent lymphoma. On the other hand, if the masses do not light up, then the residual areas noted on the CT scan can safely be regarded as simple scarring, not persistent disease.

The second test that may be performed for treatment purposes is an echocardiogram (ECHO), a noninvasive imaging method that uses ultrasound to visualize the chambers of the heart and to ensure normal contractile function. One class of chemotherapeutic drugs used to treat NHL—the anthracycline class, specifically doxorubicin (Adriamycin)—can cause cumulative damage to heart muscle. For this reason, a baseline ECHO is done prior to initiation of therapy (see below). While it is often acceptable to forgo an ECHO in young, otherwise healthy individuals, this study is essential in older people and those with known cardiac disease, or whenever there is doubt regarding a person's baseline cardiac function.

NHL Treatment

The approach to treating NHL in people with HIV largely depends on its grade and stage. As previously noted, the overwhelming majority of NHL in people with HIV consists of intermediate- to high-grade aggressive disease. Accordingly, the majority of existing data, and most of the discussion in this article, pertain to this type of disease rather than low-grade NHL, which is relatively less common in people with HIV.

Briefly, low-grade NHL has a more indolent nature and is associated with longer survival. Paradoxically, because low-grade NHL cells grow and divide more slowly, they are relatively resistant to chemotherapy, which kills only rapidly dividing cells. Stage I or II low-grade NHL, which is localized by definition, can be treated with radiation therapy. Radiation produces up to a 50% relapse-free survival rate at 10–15 years in the HIV negative population. Treatment for stage III or IV low-grade NHL ranges from simple observation, to single agent chemotherapy, to full-strength combination chemotherapy.

Localized stage I or II intermediate- or high-grade disease historically has been treated only with local radiation therapy. In this procedure, a radiation oncologist (cancer specialist) carefully maps out and marks the region of the body that contains the lymphoma, and this field is then irradiated using a machine resembling an x-ray scanner that emits a strong beam of radiation. Daily sessions last approximately 15 minutes, and the full course is given over a period of 3–4 weeks. More recent studies have shown that combining radiation with chemotherapy leads to improved response and survival rates. Thus, the current standard of care for stage I or II intermediate- and high-grade NHL is radiation therapy along with a short course of combination chemotherapy, typically the CHOP regimen.

Favorable prognostic factors in HIV positive NHL patients include a CD4 cell count greater than 100 cells/mm³, age below 35 years, a normal LDH level, early disease stage at diagnosis, good performance status, no history of a prior AIDS-defining illness, use of HAART, and an adequate initial response to therapy.

The CHOP regimen consists of four drugs: ***c***yclophosphamide (Cytoxan, Neosar), ***h***ydroxydaunorubicin (doxorubicin), vincristine (***O***ncovin), and ***p***rednisone. CHOP is typically given every three weeks. On the first day of each 21-day cycle, cyclophosphamide, doxorubicin, and vincristine are infused intravenously (into a vein) over several hours. Prednisone is given orally on days 1 through 5. Over the next three weeks, the patient is monitored for signs of infection and for significant drops in blood cell counts, and side effects such as nausea are treated until the cycle repeats.

While the optimal treatment for stage I and II NHL consists of three cycles of CHOP along with radiation therapy, treatment for stage III and IV disease relies on chemotherapy alone, since the lymphoma is too widespread to be included in a radiation treatment field. Over the years, multiple studies in the HIV negative population have investigated a variety of chemotherapy regimens, but none have been shown to improve upon the survival benefits of CHOP. Thus, the current standard of care for stage III and IV intermediate- to high-grade NHL in people with HIV consists of six cycles of CHOP. However, the question as to whether other regimens are more effective in this population is still under investigation. (See Clinical Trials on page 49 of this issue for currently enrolling studies.) Occasionally, the six cycles of CHOP are followed by a course of local radiation therapy to sites of residual disease. If CNS involvement is documented or strongly suspected, another chemotherapeutic agent—either methotrexate or cytarabine (Cytosar-U, DepoCyt)—is infused intrathecally into the CSF (similar to a lumbar puncture) once weekly for four weeks.

Treatment Toxicities and Complications

The most common side effects of treatment are the toxicities caused by chemotherapy and radiation. With respect to CHOP, the main toxicities of cyclophosphamide include bone marrow suppression (resulting in low white and red blood cell and platelet counts), nausea and vomiting, hair loss, and (rarely) urinary bladder inflammation.

Toxicities of doxorubicin include bone marrow suppression; nausea and vomiting; hair loss; irritation of the gastrointestinal mucosa (mucous membranes); and cumulative, dose-related heart muscle damage. The lifetime dose of doxorubicin cannot exceed a specific limit, beyond which there is a serious risk of heart failure.

The main toxicity associated with vincristine is peripheral neuropathy, which can manifest as numbness or tingling in the hands and feet. Prednisone's side effects include bloating, fluid retention, sleep disturbances, psychosis, elevated blood sugar, and gastritis (inflammation of the stomach lining).

The side effects of local field radiation depend on the area being irradiated, but generally include local skin and mucous membrane inflammation, gastrointestinal distress (e.g., diarrhea), and possibly bone marrow suppression.

Tumor lysis syndrome (TLS) is another concern when starting chemotherapy, especially in people with stage III or IV lymphoma and a heavy disease burden. The rapidly dividing malignant lymphocytes are often exquisitely sensitive to chemotherapeutic drugs, and many millions of these cells may die and rupture, or lyse, in the first hours of chemotherapy. Like all cells, lymphocytes contain high levels of potassium, phosphorus, and uric acid. These products are released into the bloodstream in large amounts when the lymphocytes rupture, potentially leading to electrolyte disturbances that can cause irregular heartbeat, kidney failure, and death if left untreated.

In people with a heavy disease burden at diagnosis, measures should be taken before and during chemotherapy to avoid TLS. Allopurinol (Zyloprim), a drug that inhibits the production of uric acid, may be started a few days before chemotherapy. During chemotherapy, copious intravenous fluids are given to wash out and rapidly eliminate the accumulating TLS products. Bicarbonate is also sometimes given to alkalinize the blood and urine, facilitating elimination. Finally, in people at high risk for TLS, blood electrolyte levels are checked frequently to monitor and rapidly correct any abnormalities.

Immune suppression due to chemotherapy is perhaps the treatment-related issue that has received the most attention in people with HIV. As described previously, one of the major side effects of most chemotherapeutic agents is bone marrow suppression, which may cause a drop in levels of white blood cells, specifically neutrophils that fight infection. Neutropenia (low neutrophil count) following chemotherapy results in greater vulnerability to infection, especially in HIV positive people who are already immunocompromised. Thus, in the pre-HAART era, up to 50% of NHL deaths in people with HIV were attributable to treatment-related OIs. To address this problem, several clinical trials were performed comparing the standard CHOP regimen with less immunosuppressive, reduced-dose chemotherapy regimens. These studies demonstrated that lower chemotherapy doses indeed caused less neutropenia and were just as effective in terms of survival.

The HAART era has brought a return to full-dose chemotherapy regimens such as CHOP for people with HIV. HAART increases CD4 cell counts, reduces HIV viral load, decreases the risk of OIs, and often leads to immune reconstitution. Because of these immune-boosting effects, rates of OIs in people on HAART who receive full-dose chemotherapy have decreased dramatically. Thus, the current standard of care is to integrate HAART with full-dose chemotherapy as early as possible in the treatment of NHL, while keeping in mind possible antiretroviral toxicities. For example, AZT (zidovudine, Retrovir) can suppress the production of neutrophils to such an extent that it may be preferable to substitute another anti-HIV drug for the duration of chemotherapy.

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Several other measures may be taken to minimize the risk of infection. Immediately after the completion of chemotherapy, subcutaneous injections of granulocyte colony-stimulating factor (GCSF, filgrastim, Neupogen) may be given. GCSF is a natural hormone that stimulates the production of neutrophils. Regular use of GCSF in people with HIV after chemotherapy for NHL helps to reduce the incidence of neutropenia and fever, as well as the length of hospital stays. It also allows for fewer reductions in chemotherapy doses and fewer treatment delays. Antibiotic prophylaxis (preventive treatment) against *Pneumocystis carinii* pneumonia (PCP) also should be provided to all HIV positive individuals receiving chemotherapy for NHL. Antimicrobial prophylaxis against *Mycobacterium avium* complex (MAC) should be given to those with CD4 cell counts below 50 cells/mm^3.

Prognosis for NHL

Large retrospective studies in the general population have identified several key factors that determine good response to therapy and favorable overall prognosis. These factors, which comprise the International Prognostic Index (IPI), include age below 60 years, LDH enzyme levels within normal limits, early disease stage, no more than one site of extranodal disease, and a good overall performance status (ability to carry out activities of daily life). In the HIV *negative* population, stage I NHL and a favorable IPI is associated with a five-year overall survival rate of 94%. Stage II NHL and one poor IPI risk factor is associated with a five-year overall survival rate of 70%. Stage I or II NHL with three poor IPI risk factors reduces the five-year overall survival rate to 50%. Stage III and IV NHL have a five-year overall survival rate of 50%, but this drops with additional poor IPI risk factors.

The prognosis for NHL in people with HIV is worse than that for the HIV negative population because the former

generally present with high-grade, aggressive, late-stage disease. Favorable prognostic factors in HIV positive NHL patients include a CD4 cell count greater than 100 cells/mm^3, age below 35 years, a normal LDH level, early disease stage at diagnosis, good performance status, no history of a prior AIDS-defining illness, use of HAART, and an adequate initial response to therapy.

Unfortunately, even among those who initially have a complete response to NHL therapy (up to 70% in people with HIV), 25% experience relapse (return of illness) within six months. In the pre-HAART era, this translated into an average survival period of 5–8 months. Since the introduction of HAART and the return to full-dose chemotherapy, several studies looking at various regimens have found improved average survival times, ranging from 18 months to as long as 53 months, though such results have not been consistently borne out in larger clinical trials.

For those who relapse or do not respond to initial treatment, the prognosis is grim. A variety of more potent, experimental chemotherapy regimens have been investigated, but these are associated with significantly increased toxicities. Whether such therapies in conjunction with HAART will improve the outlook for HIV positive people with relapsed or refractory (treatment-resistant) NHL is not yet known.

On the Horizon

Clearly, the poor prognosis of NHL in people with HIV demands continued exploration of new treatments. One of the most promising approaches is the use of immunotherapy. The most well-known and effective of these—already widely used in the HIV negative population—is rituximab (Rituxan), a human/mouse hybrid antibody that targets the CD20 antigen found on the surface of up to 95% of NHL lymphocytes. Studies reported in 2002 demonstrated that in the HIV negative population, the addition of rituximab to CHOP increased the complete response rate as well as overall survival in elderly patients. A similar large trial in people with HIV has recently been completed and results are expected to be presented later this year.

Variations on the anti-CD20 antibody theme are also in development. Tositumomab (Bexxar) and ibritumomab tiuxetan (Zevalin) are anti-CD20 antibodies linked to radioactive agents. When they bind to malignant lymphocytes, their radioactivity helps to destroy the cells. At present, their use in individuals with HIV remains investigational.

Another novel tactic for treating NHL in people with HIV is the use of high-dose chemotherapy followed by autologous (self-derived) bone marrow transplantation, or auto-BMT. The first step in this procedure is the collection of stem cells—bone marrow precursor cells that give rise to all white and red blood cells and platelets—from a patient. After the stem cells are collected and stored, the patient receives extremely high doses of chemotherapy aimed at eradicating the lymphoma. The chemotherapy doses are so strong that the bone marrow is completely destroyed, leaving the person with no means of producing white and red blood cells and platelets. Normally this would lead to the patient's rapid demise, but auto-BMT allows the individual's previously stored stem cells to be reinfused, after which they reconstitute the bone marrow and begin to produce new white and red cells and platelets. The strategy of auto-BMT therefore enables the use of much higher doses of chemotherapy than would otherwise be tolerated. The procedure already is commonly used in HIV negative patients. Recent small studies in people with HIV have demonstrated that this approach is also feasible in this population, and may extend survival times.

Other novel therapies are showing promise. Interleukin 12 (IL-12), a cytokine, or immune system signaling molecule, has been shown to induce the production of interferon-gamma and tumor necrosis factor-alpha (TNF-alpha), two other cytokines that stimulate immune system cells to attack and destroy cancerous cells. Synthetic polyamine analogs are another class of signaling agents that interfere with normal cellular function and induce programmed cell death. Bryostatin-1 is yet another antitumor agent that induces programmed cell death, in this case by interfering with the cellular processing of cancer-causing genes.

Numerous other experimental agents are undergoing intense laboratory and clinical investigation. With time, the most effective of these will expand the armamentarium used to combat NHL in people with HIV, in the hope of extending and enhancing the lives of those who are battling this serious illness.

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