# Cancer Rising

Lymphoma is in the stars for more and more longtime HIVers. It's an immune-cell thing. But you can brighten your horoscope with early detection, fast treatment and sheer will.

January 1, 2001 By Lark Lands, PhD

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The sun-dappled glade redolent with redwood and rhododendron is a far cry from the sterile hospital cubicle where Thom Weyand endured hours of intravenous chemotherapy for non-Hodgkin's lymphoma (NHL), an AIDS-defining cancer. Weyand's name is inscribed in that lush, hushed sanctuary -- in the Circle of Friends granite at the heart of the National AIDS Memorial Grove in San Francisco's Golden Gate Park -- but as a benefactor rather than one of the 700-plus dead from AIDS whose names are also etched there. Weyand, the grove's executive director, enjoys that distinction because the chemo successfully battled his NHL. But it was no sure thing at first, in November 1999. "Finding a growth between my right armpit and chest was scary enough, but hearing the diagnosis was devastating," he says. "I have always lived a healthy lifestyle, and if there was one ailment I never expected to have to face, it was cancer." Unfortunately, Weyand is one of an increasing number of HIVers facing the Big C. A recent Danish study found that NHL now accounts for 16 percent of AIDS diagnoses, up from only 4 percent in 1994.

Asked why NHL rates are on the rise among HIVers, lymphoma expert Alexandra Levine, MD, at the University of Southern California (USC) and medical director of the USC/Norris Cancer Hospital in Los Angeles, says, "The simple explanation is that HAART prolongs survival long enough to allow for the development of lymphoma. Throughout HIV disease, B lymphocytes [antibody-producing immune cells] are constantly being stimulated in response to the virus. Since this results in the B cells' continuous proliferation, there's an increased chance that an error will eventually occur in their cellular DNA. Such errors can lead to a growth, or survival, advantage for a given B cell, resulting in a tumor or malignancy that we call lymphoma." And even HAART-takers with an undetectable viral load can't rest easy. "Because the drugs don't fully eradicate HIV," Levine says, "a low level of B-cell stimulation still occurs."

Compounding this chronic B-cell cranking is the Epstein-Barr virus (EBV) that's quietly been resting in most people's B cells since childhood but starts reproducing when immune function is lowered. EBV is thought to be a coconspirator in the development of half of all NHL in the body (systemic lymphoma) and almost all primary CNS lymphoma (the type that is isolated in the brain).

And for long-term survivors, those two risk factors are added to the effects of HAART-boosted (but not perfected) immune function and prophylactic drugs: Enough protection to prevent deaths from opportunistic infections (OIs), but not enough to stop cancers that can occur with an immune

system that's only moderately impaired. It's a happy hunting ground for this cancer of the lymphatic system, that network of organs (including the lymph nodes, bone marrow, spleen, thymus and tonsils) and vessels (carrying lymph fluid and lymphocytes) that provide immune armor.

**KNOW YOUR SIGNS**

Left untreated, this sometimes-fatal cancer can spread quickly, making early diagnosis important. Alas, many PWAs go undiagnosed until NHL is relatively advanced. In part, that's because the only signs many people initially experience are the so-called B symptoms: unexplained fever, drenching night sweats, and/or weight loss (there may be others) The fact that the B's could be caused by a number of OIs as well as by HIV itself can fool both patients -- who, having lived with such problems off and on for years, may simply shrug at the same-old same-old -- and their doctors. Levine emphasizes vigilance in reporting to your doc and testing to determine whether such symptoms are NHL.

Based on location and spread, lymphomas can be diagnosed as being one of four stages, ranging from the very limited stage I to the widespread stage IV. (Weyand was relieved to learn that his was stage I, for which the survival stats are better.) The lymphoma will also be graded as either high-, intermediate- or low-grade, depending on how quickly the cancerous cells are growing.

**IN THE HOUSE OF TREATMENT**

With systemic lymphoma, intravenous (IV) infusions of chemotherapy are necessary, both to treat affected areas and to prevent spread. The regimen that your doc will choose for you, and how long it's continued, will depend on many things, including the stage and grade of the cancer, your current health status, and, ultimately, the response to the chemo -- by both the cancer and your body. Luckily, there are now a number of options that may send lymphoma packing. CHOP (cyclophosphamide, hydroxydaunomycin/ doxorubicin, vincristine/ Oncovin and prednisone) was once standard and is still often used. Trials show complete remission (tumor disappearance) in about one-third of those treated. But Levine was the first to report more success with a low-dose regimen of m-BACOD (a tongue-tripping combo of methotrexate, bleomycin, Adriamycin, cyclophosphamide, Oncovin/ vincristine and dexamethasone). This combo has made tumors vanish in almost half of those treated, with the majority of those (70 percent) not experiencing relapse. Standard doses cause substantial additional toxicity without improving results.

Another possibility being studied is continuous IV infusion of cyclophosphamide, doxorubicin and etoposide (CDE), given over four days, and repeated every 28 days until complete remission is achieved. Results have generally been similar to m-BACOD's, but the drawbacks are substantial -- hospitalization during therapy, the insertion of a central catheter to administer the drugs, and the need to discontinue HAART during treatment to avoid severe mucous-membrane inflammation.

Perhaps most promising is EPOCH (etoposide, prednisone, Oncovin/vincristine, cyclophosphamide and hydroxydaunomycin/doxorubicin) being studied at the National Cancer Institute. Results to date have been striking, with a complete remission in 94 percent of those with CD4s above 100 and half of those with CD4s below 100. So far, no one with a complete remission has relapsed.

During chemo, antiretroviral therapy must be stopped, so viral loads have skyrocketed and CD4s plummeted. But HAART is restarted after the chemo is completed, and numbers mostly rebounded to starting points within six to 12 months. With most chemo regimens, it is safe to continue HAART because the combo causes neither excess toxicity nor problematic drug interactions. One notable exception is AZT (Retrovir), which, when combined with chemo, can cause severe bone-marrow suppression.

Other experimental therapies include monoclonal antibodies (rituxan/ Rituximab is currently being studied with CHOP), pegylated L-asparaginase (promising results in one trial) and liposomal anthracyclins such as Doxil or Daunoxome. Inhibitors of angiogenesis -- which stop the new blood vessels needed for growing cancer cells -- are, Levine says, “promising.” None are approved for HIVers with NHL, but some are available for other indications and/or through clinical trials.

For HIVers with primary CNS lymphoma, treatment has traditionally involved corticosteroids followed by whole-brain radiation (with or without chemo). Results have generally been only a several months’ boost in survival, although radiation can greatly improve symptoms -- an important goal for many. But there may be new hope from a surprising quarter: hydroxyurea, used in some HAART combos and approved for ovarian cancer, may reduce tumors by suppressing EBV. Karen Slobod, MD, of St. Jude Children’s Research Hospital in Memphis, Tennessee, has reported substantial reduction of brain tumors in two HIVers given varying doses of the drug. Positive results included improvements in strength, vision and ability to walk. Although one patient died later of unrelated causes, the autopsy showed no remaining tumor. The other patient continues to do well a year after starting treatment. Studies are needed to confirm this approach (one is now ongoing at St. Jude’s), but there’s an encouraging possiblity that this inexpensive oral agent might be effective in low, relatively safe doses. Other researchers say that immune boosting with HAART and therapies such as interleukin-2 might also hold promise.

**EASY ON THE SIDE EFFECTS**

Meanwhile, anything to make the current chemotherapies better, safer and more tolerable is worth standing in line for. Chemo’s side effects are notoriously nasty -- nausea, vomiting, fatigue, diarrhea, hair loss, peripheral neuropathy, mouth sores, jaw pain, constipation, swollen or sensitive gums and, worst of all, bone-marrow suppression. The danger posed when bone marrow’s cell-producing ability is zapped was underlined for *POZ* readers last summer by the death of contributing editor Stephen Gendin, whose white blood cells plummeted only three days after his first round of chemo, leaving him with no defenses against infection (see "He Died of Old AIDS," *POZ*, October 2000).

The lesson here: Beware. Gendin’s physician, Howard Grossman, MD, says that preventive antibiotics used with G-CSF (Neupogen) to boost white blood cell counts might help prevent infections and reduce the risk of chemo complications. Levine recommends that Neupogen be started on the second or third day after chemo begins and emphasizes that patients with a fever above 101 degrees should immediately call doc.

Lymphoma licker Weyand strongly seconds the Neupogen recommendation. Of Gendin’s fate, he

says, “There but for the grace of God could I have gone -- and did go part-way 10 days after my first chemo, when my plummeting white blood cells resulted in pneumonia.” After that, 10 daily Neupogen shots after each chemo cycle helped.

“Being on chemo is bad enough without needlessly risking death,” he says. “It was like living a half-life. I functioned fair enough for day-to-day tasks, but my neuropathy worsened, and my life’s energy, desires and joys were minimal. After it was over I was left exhausted and depressed.”

Something that might have improved Weyand’s chemo course is nutrient supplementation. But choices must be made carefully, according to Kedar Prasad, PhD, a professor of radiology and director of the Center for Vitamins and Cancer Research at the University of Colorado Health Sciences Center in Denver. “Most of the benefit from chemo and radiation,” he says, “comes from the cell-destroying free radicals that those therapies create. But free radicals are countered by glutathione, an antioxidant. Nutrients that raise glutathione levels in normal cells -- especially N-acetyl-cysteine (NAC) and alpha-lipoic acid -- will also raise them in cancer cells, possibly protecting those cells against the chemotherapy or radiation. So they should not be taken for a week before and throughout cancer therapy.”

But Prasad stresses that all antioxidants are not alike, a fact he says many physicians misunderstand. “Some people have extrapolated the findings on the protective effects of glutathione to the other antioxidants, and that’s just not valid,” he says. "In fact, not only do high doses of A, C, E and carotenoids *not* protect the cancer cells, they actually inhibit their growth without affecting the growth of normal cells." Prasad recommends a specific nutrient protocol both during and after cancer therapy. Preliminary results from studies at several universities show that such nutrients may improve chemo’s outcome and quality of life. And with all the research that shows that good nutrition is tied to lower cancer rates overall, keeping those nutrients coming in might actually help prevent cancer recurrence -- or even help keep it from happening in the first place.

**AN OUNCE OF PREVENTION**

Because of their possible anti-EBV effects, a more specific prophylaxis is the use of antiherpes drugs. Although research results are mixed, a recent University of Toronto study showed that daily doses of at least 800 mg of acyclovir (Zovirax) are strongly linked to protection against NHL. That doesn’t surprise Larry Bruni, MD, a physician with a large HIV practice in Washington, DC. “After 15 years of treating more than a thousand patients with either acylovir [800 mg, three times per day] or, since its approval, valacyclovir [Valtrex, 500 mg, three times per day], I have seen only three cases of non-Hodgkin’s lymphoma,” he says. “My feeling is that Valtrex is a generally effective prophylactic against this cancer.” In those who have been successfully treated for lymphoma, he also recommends Valtrex as a prophylactic against recurrence.

According to Weyand, anything to prevent the return of the NHL monster is a big plus. One year and six chemo cycles post-diagnosis, he has been pronounced “cancer-free” but says, “I continue to come to grips with the reality that I may face a recurrence. The challenge now is to fortify my immune system so it doesn’t happen.” That’s why he’s added yoga, intense body work, plentiful

rest, group psychotherapy and nutrient supplements to his drug regimen.“It seems to be paying off,” he says. “My post-chemo shakes and depression are almost nonexistent. I am reclaiming and rebuilding my life -- and I’m glad I’m still here to enjoy the grove’s redwoods and rhododendrons.”

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