Lymphoma: Death Rates Still High, but Cancer May Be Predicted

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Despite the effectiveness of antiretroviral (ARV) therapy, HIV-positive people diagnosed with non-Hodgkin's lymphoma (NHL) face a significantly higher risk of death compared with HIV-negative individuals diagnosed with the same malignancy. While these data, presented by a team of California researchers on Monday, February 9, at the 16th Conference on Retroviruses and Opportunistic Infections, are sobering, the results from a study conducted by National Cancer Institute (NCI) and Mayo Clinic investigators are highly encouraging and suggest that it may be possible to predict lymphoma two to five years before it develops.

NHL and Prognosis

Previous studies suggest ARV therapy has virtually leveled the NHL playing field for people with HIV, with survival rates on par with those seen in HIV-negative individuals. However, according to Michael Silverberg, MD, of Kaiser Permanente Northern California, many of these studies had small sample sizes and simply didn't have the necessary numbers to pinpoint differences between both groups of patients diagnosed with this cancer of the immune system.

To evaluate two-year survival rates in a much larger study, Silverberg's group compared outcomes among 268 HIV-positive and 8,203 HIV-negative Kaiser Permanente patients diagnosed with lymphoma between 1996 and 2005—years in which combination ARV therapy was widely available.

The majority of cases diagnosed with NHL were advanced (state III or IV) in 53 percent of the HIV-positive individuals and 47 percent of the HIV-negative patients. Among the HIV cases, 62 percent had diffuse large B cell lymphoma (DLBCL) and 16 percent had Burkitt's lymphoma, compared with 38 percent and 1.6 percent, respectively, among the HIV-negative cases (DLBCL and Burkitt's have always been the most common forms of NHL in HIV-positive individuals).

More than half—59 percent—of the HIV-positive individuals with NHL died within two years, compared with 29 percent of the HIV-negative patients with NHL. In other words, HIV status was associated with a nearly five-fold increase in the risk of death within two years. Even among patients with lymphoma in its earliest stage (stage I), the death rate was significantly higher: 58.6 percent of patients with stage I NHL were dead within two years, compared with 17 percent of HIV-negative patients with stage I NHL.

Significant differences were apparent regardless of age at the time of diagnosis, gender, race, NHL type and among those who received chemotherapy within the first four months of diagnosis. With respect to race, differences were most apparent among Hispanics and Asian/Pacific Islanders—63.8 and 88.9 percent among Hispanics with HIV and a lymphoma diagnosis died within two years, compared with 26 and 28.7 percent of HIV-negative Hispanics and Asians, respectively.

Predicting NHL

While the California researchers rightfully concluded that further research is very much needed to advance management and therapeutic approaches for NHL in HIV-infected patients, a team of NCI and Mayo Clinic investigators may have stumbled upon the next best thing: predicting a risk of lymphoma by measuring levels of specific protein molecules.Immunoglobulins or monoclonal proteins are produced in excess by B cells in people with multiple myeloma, a form of cancer similar to certain types of lymphoma, notably the DLBCL variety common among people living with HIV. These proteins are composed of two types of smaller molecules, one called a heavy chain and the other called a light chain. There are five types of heavy chains and two types of light chains: kappa and lambda.

Measuring levels of kappa and lambda light chains in the blood, as well as the ratio between the two, is vital to diagnose and manage multiple myeloma. In patients with active myeloma, levels of free light chains are higher than normal.

To determine if measuring free light chain levels in people with HIV—as a marker of abnormal B cell function—may signal a higher risk of lymphoma, Eric Engels, MD, of the NCI and his colleagues conducted an analysis involving 66 HIV-related NHL cases and matching HIV-positive NHL-free controls. Blood samples obtained up to five years before an NHL diagnosis were evaluated for levels of immunoglobulins, monoclonal proteins and free light chains.

Levels of immunoglobulins and monoclonal proteins, before the onset of NHL, did not predict B cell problems or a heightened risk for cancer.

Conversely, levels of kappa and lambda free light chains were well above the normal reference ranges among the NHL patients before diagnosis. In fact, two to five years before NHL was found, both light chains were significantly higher than those of patients in the controls who remained free of NHL.

Levels of both kappa and lambda free light chains were elevated in lockstep, meaning that the ratio between the two did not change. In patients with certain types of myeloma, the level of one free light chain may increase while the other does not, which can help determine the type of myeloma causing disease.

A confounding issue in this particular study was that a high number of the HIV-positive patients were not on ARV therapy before their lymphoma diagnosis—about 90 percent. In addition, many had very low CD4 counts at the time of their NHL diagnosis. It is not clear to what extent the degree of immune suppression, free light chain levels or a combination of both was predictive of

NHL. That said, Engel’s group concluded that “free light chains may be a sensitive marker of B cell activation and dysfunction and could identify HIV-infected persons at increased non-Hodgkin’s lymphoma risk.”
