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## **HIV-associated lymphoma: promising new results, but with toxicity**

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against EBV targets in tissue culture than previously believed, so it may be premature to rule out EBNA-1 as a potential target for immunotherapy.

The demonstration that EBV-specific adoptive immunotherapy established for

PTLD patients can be successfully applied to a significant number of NPC patients is a logical and important first step. The encouraging clinical results despite a number of theoretic obstacles indicate that it is time to “T” off on NPC. ■

● ● ● CLINICAL OBSERVATIONS

Comment on Spina et al, page 1891

## HIV-associated lymphoma: promising new results, but with toxicity

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Treatment of HIV-associated non-Hodgkin lymphoma with rituximab plus infusional cyclophosphamide, doxorubicin, and etoposide resulted in high complete remission and 2-year failure-free and overall survival rates but a high rate of infection.

The outlook for patients with HIV-associated non-Hodgkin lymphomas (NHLs) has dramatically improved in the era of highly active antiretroviral therapy (HAART) probably due in large part to improvements in immune status and bone marrow function. In a large trial conducted prior to the HAART era comparing low-dose methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone (m-BACOD) with standard-dose m-BACOD, the median survivals in both arms were approximately 8 months, and less than 20% of the patients were long-term survivors.<sup>1</sup> A phase 2 trial of infusional chemotherapy with cyclophosphamide, doxorubicin, and etoposide (CDE) for patients with HIV-associated NHL was conducted by the Eastern Cooperative Oncology Group. Complete remission (CR) rates

were similar for patients who received HAART (44%) and those who did not (47%). At a median follow-up time of 50 months, 47% of the patients receiving HAART, and at a median follow-up time of 78 months, 30% of those not receiving HAART, were alive. In the group that received HAART no deaths were due to treatment, while treatment-related mortality was 9% among those who did not receive HAART.<sup>2</sup>

The addition of rituximab to standard chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has improved the outlook for patients with diffuse large B-cell lymphoma (DLBCL) without HIV infection.<sup>3</sup> However, in the HIV setting, in which 60% to 70% of lymphomas are DLBCL, addition of rituximab to CHOP in a randomized trial of the AIDS Malignancy Consortium (AMC)

did not result in an improved response rate. Significantly, more grade 3/4 neutropenia was seen in the rituximab group (39%) compared with the group that did not receive rituximab (17%). Deaths due to infection occurred in 7% of the rituximab-treated group and 2% of the group who did not receive rituximab.<sup>4</sup>

In the present issue of *Blood*, Spina and

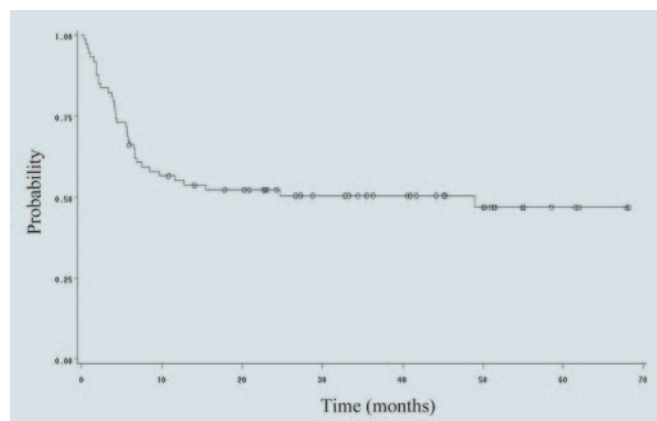
colleagues added rituximab to infusional CDE in patients with HIV-associated NHL and report a high CR rate (70%) and 2-year event-free and overall survival rates of 59% and 64%, respectively. The 2-year event-free survival rate was lower (52%; Figure 1), reflecting toxicity. Serious infections were seen in 47% of patients, including opportunistic infections in 14%. Mortality due to infection was 8%.

Although the follow-up is short in the present trial, similar results were reported with an infusional regimen of etoposide, prednisone, vincristine, and doxorubicin followed by dose-adjusted cyclophosphamide according to initial CD4 count and level of neutropenia during treatment (DA-EPOCH) without the addition of rituximab. The median follow-up time in that study was approximately 4 years.<sup>5</sup>

The AMC is currently combining DA-EPOCH with concurrent or sequential rituximab in a randomized phase 2 trial for HIV-associated lymphoma. The trial is ongoing. Clearly, the improvements in immune and bone marrow function with HAART have made more aggressive treatment of HIV-associated lymphoma possible. Whether this is due to the possibility of increased drug-dose intensity or continuous drug exposure to the tumor by infusion is unclear. For the present, it is probably safest to avoid use of rituximab with chemotherapy for HIV-associated lymphoma outside the setting of a clinical trial. ■

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Event-free survival of 74 patients with HIV-NHL treated with rituximab plus infusional cyclophosphamide, doxorubicin, and etoposide. See the complete figure in the article beginning on page 1891.