evidence that imatinib fails to significantly reduce BCR-ABL kinase activity in these cells at clinically achievable concentrations, although the precise mechanism for this remains elusive.[7] Possibilities include transporter proteins that affect intracellular drug concentrations such as OCT-1, P-glycoprotein, and ABCG2 or high levels of kinase active BCR-ABL protein. In this case, more potent inhibitors that are not substrates for these transporters should be able to eliminate MRD. However, yet another scenario is conceivable. CML stem cells may express BCR-ABL but they may not depend on it, relying on exogenous growth and survival signals, such as cytokines and interactions with stroma. Elimination of such dormant cells would require stem cell–directed rather than BCR-ABL–specific approaches. Whatever the precise mechanism of disease persistence, elimination of residual disease may be central to the long-term success of imatinib therapy of CML. ■

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CLINICAL OBSERVATIONS

Comment on Straathof et al, page 1898

"T"-ing off on nasopharynx cancer

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Nasopharyngeal carcinoma (NPC) is the most frequent Epstein-Barr virus (EBV)–associated malignancy worldwide. In this issue, Straathof and colleagues take aim at EBV-associated NPC showing that adoptive immunotherapy with EBV-specific T cells expanded in vitro can be successfully administered to NPC patients and is associated with potential therapeutic efficacy.

Epstein-Barr virus (EBV) immunotherapy has proved its mettle in stem cell transplantation where donor T cells are stimulated with autologous EBV-immortalized B cells in vitro and then transferred into the patient to prevent or treat uncontrolled proliferation of EBV-infected B cells, or so-called posttransplantation lymphoproliferative syndrome (PTLD). In these cases, EBV gene products expressed in the malignant B cell are ideal tumor-associated antigens marking tumor cells for killing by EBV-specific cytotoxic T cells (CTLs). It is not known which cell populations in the polyclonal T-cell mixture are responsible for therapeutic efficacy, but $CD8^+$ CTLs specific for the latent infection viral antigens expressed in immortalized B cells are presumed to be important.

Successfully applying this therapeutic approach to EBV-associated NPC is not without potential issues. The most obvious problem is a significant mismatch between the repertoire of $CD8^+$ CTLs and the pattern of EBV gene expression in NPC. EBV-immortalized B cells express 9 latent infection viral proteins—6 nuclear proteins (EBV nuclear antigens; EBNAs) and 3 latent membrane proteins (LMPs)—and CTLs stimulated in vitro by EBV-infected B cells most frequently recognize EBNA-3A, -3B, or -3C. However, NPC cells usually express only EBNA-1, LMP1, and LMP2, so these tumor cells fail to express the EBNA-3 targets recognized by most of the therapeutic CTLs. LMP1 is expressed in only 65% of the tumor cells and is not a very immunogenic protein, and LMP1-specific CTLs are uncommon. LMP2A protein is detected in only 50% of tumor cells, but LMP2A-specific T cells are a subdominant population following the EBNA-3s. EBNA-1 is important for maintenance of the viral episome, protein can be detected in every tumor cell, and it would be an ideal tumor marker. However, the EBNA-1 glycine-alanine repeat region has a potential immune evasion mechanism that prevents proteosome-dependent degradation and efficient presentation of EBNA-1 peptides through the HLA class I pathway, so that EBNA-1–specific CTLs fail to efficiently kill EBV-infected B cells in tissue culture.

Effective therapy also requires that the therapeutic T cells migrate to the tumor. The mucosal location and infiltrating T-cell milieu typically associated with NPC may provide additional obstacles for transferred effector T cells. NPC patients also present different logistic issues versus transplant patients. T cells from transplant donors can be prepared ahead of time, but this head start is not available for NPC patients.

The results reported by Straathof and colleagues show that these logistic problems can be overcome, and EBV-specific T-cell populations can be successfully generated for treatment of NPC patients. Cells were safely administered, and there was a trend for improved outcomes among the treated patients. These results are extremely encouraging since the protocol involved no significant alteration from the transplant patients. As expected, EBNA-3s were the dominant targets of the transferred T cells so that the bulk of the T cells may not have been expected to target the NPC tumor cells. The LMP2A-specific T cells represented less than 10% of the transferred T cells, so that specific manipulations to increase LMP2A-specific T cells may increase efficacy. The number of EBV-specific or LMP2A-specific T cells in the peripheral blood of treated patients did not significantly change, suggesting that a "full" lymphocyte pool may inhibit the in vivo amplification of the transferred EBV-specific T cells. The authors suggest that gentle immunodepletion prior to adoptive transfer may result in longer duration and efficacy of the EBV-specific T cells. An intriguing correlation was the best clinical response in a patient with a strong EBNA-1–specific response in the T-cell preparation. Recent studies indicate that EBNA-1–specific CTLs may have more effector activity

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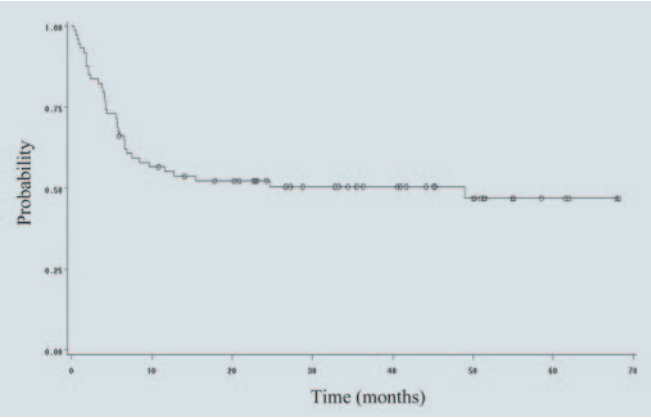
Treatment of HIV-associated non-Hodgkin lymphoma with rituximab plus infusional cyclophosphamide, doxorubicin, and etoposide resulted in high complete remission and 2-year failure-free and overall survival rates but a high rate of infection.

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.[1] 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.[2]

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.[3] 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.[4]



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.

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.[5]

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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