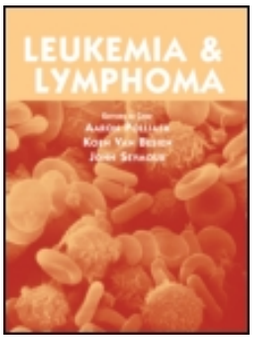

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COMMENTARY

Advancing therapeutics in human immunodeficiency virus-associated lymphoma: where to go from here?

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The outcome for patients who develop human immunodeficiency virus (HIV)-associated lymphoma has significantly improved over the past two decades. In the early years of the infection, a diagnosis of lymphoma was frequently a fatal consequence of HIV; but now, due to the availability of antiretroviral therapy as well as improved therapeutic strategies, the development of lymphoma is a curable complication in most cases. Since the widespread use of antiretroviral therapy, the proportion of patients in lower CD4 strata has fallen significantly. This has led to a shift in histologic subtype away from poor-prognosis lymphomas such as primary central nervous system lymphoma (PCNSL) and primary effusion lymphoma (PEL) (that occur in advanced immunodeficiency) toward more favorable histologies such as Burkitt lymphoma and Hodgkin lymphoma (that develop in the setting of higher CD4 lymphocyte counts) [1–3].

Patients who relapse or who are refractory to primary therapy generally have a very poor survival rate, but few studies have specifically addressed and investigated this. In this edition of ***Leukemia and Lymphoma***, Noy and colleagues from the AIDS Malignancy Consortium (AMC) report on the outcome of 88 patients with relapsed and refractory acquired immune deficiency syndrome (AIDS)-related lymphoma (ARL), and the study spans over a 10-year period [4]. While the 2-year overall survival rate of the entire population was just 35%, it is noteworthy that patients who achieved a response (complete or partial, CR or PR) to second-line therapy (various chemotherapy regimens were used) had an excellent outcome. In addition, among responders, patients who received subsequent high-dose therapy and autologous stem cell transplant did not have an improved survival over those who did not receive high-dose therapy. These results are interesting, as the role of high-dose therapy is not well established in HIV-associated lymphoma and requires further investigation. Patients with Burkitt histology had a particularly poor survival, and just 12% were alive at 1 year. Overall, the promising outcome in a subset of patients who responded to salvage therapy supports an aggressive approach to patients with relapsed or refractory HIV-associated lymphoma, just as in the HIV-negative setting.

While this report highlights the importance of improving salvage therapies in HIV-associated lymphoma, the poor survival of patients with relapsed and refractory disease (especially those with Burkitt lymphoma) emphasizes the continued need to optimize upfront management of these diseases. Regarding this, much progress has been made over the past few years. While it is now well established that the addition of rituximab to anthracycline-based regimens improves survival in patients with HIV-negative diffuse large B-cell lymphoma (DLBCL), its role in ARL has been controversial [3,5]. This stemmed from another AMC phase III randomized study of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) with or without rituximab in HIV-associated aggressive lymphoma [6]. The study demonstrated that rituximab was associated with significantly more infectious deaths but only a trend in improved tumor control, and based on these findings, the authors concluded that rituximab did not improve the outcome of HIV-associated lymphoma. However, when the AMC recently investigated the EPOCH (etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin) regimen with rituximab (R; concurrent versus sequential administration) in a randomized phase II study in ARL, they demonstrated that rituximab could be administered safely, and this was also shown in a National Cancer Institute (NCI) study [7,8]. These studies also demonstrated high efficacy of the EPOCH-R regimen and improved response rates, when compared to the earlier AMC study results where CHOP with or without rituximab was administered. Regarding Burkitt lymphoma (BL), following the widespread introduction of antiretroviral therapy, there was a significant improvement in the outcome of HIV-associated DLBCL but not BL [9]. This is likely explained by the fact that CHOP-like regimens were widely used and are known to have poor efficacy in BL, due to their inability to overcome the high proliferation rate of the tumor. Recently, regimens such as EPOCH-R have demonstrated high efficacy in BL,

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and modified R-CODOX-M-IVAC (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, etoposide, ifosfamide and cytarabine) was well tolerated in a toxicity and feasibility study [10,11].

In terms of future directions, tumor histogenesis has been shown to be an important predictor of outcome in both HIV-positive and -negative patients, and patients with the non-GCB (germinal center B-cell) subtype of DLBCL have a significantly worse survival than their GCB counterparts following standard therapy [8,12]. Therefore, future studies should focus particularly on this and other groups with adverse tumor biology, and investigate novel agents that target driver pathways. In this respect, strategies such as modulation of the B-cell receptor cascade and the nuclear factor-κB (NF-κB) transcription factor make sense and are currently under way [13,14].

Potential conflict of interest: A disclosure form provided by the author is available with the full text of this article at www.informahealthcare.com/lal.

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