The advent of antiretroviral therapy (ART) led to substantial improvements in the outcome for patients with HIV-associated lymphoma (1–5). Whereas a diagnosis of aggressive lymphoma in the setting of HIV was a likely fatal complication in the pre-ART era, this was no longer the case after the widespread institution of ART because of improved HIV control, reduced opportunistic infections, and improved lymphoma treatment. Presently, most patients with HIV-associated diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), and Hodgkin lymphoma (HL) can be cured of their disease with optimal treatment (3,4,6,7).

In this edition of the Journal, Gopal and colleagues examine a cohort of more than 23,000 HIV-positive patients from the Center for AIDS Research Network of Integrated Clinical Systems (CNICS) (8). They provide insights into temporal changes in presentation and outcome of patients with a diagnosis of lymphoma in the United States since the start of the antiretroviral era. The study presents several interesting findings. Over the 14-year duration studied, which the authors divided into three time periods, the age at diagnosis of HIV-associated lymphoma steadily increased and the proportion of patients with nonwhite, nonblack ethnicity rose, reflecting the shifting demographics of the epidemic. In addition, over these time periods, patients were less immune-compromised, as measured by CD4 lymphocyte count and HIV loads.

One of the notable messages from the study is that over this 14-year period, there were compelling shifts in the relative incidences of different lymphoma types—while the proportion of cases of BL and HL increased, DLBCL and primary central nervous system lymphoma (PCNSL) cases decreased. This shift in the pathobiology of tumor types, which has occurred since the advent of ART, reflects the concomitant preservation of immune function at the time of lymphoma diagnosis. Tumors that are virally driven and characterized by adverse biology such as PCNSL occur in patients with advanced immune suppression and very low CD4 counts. Thus, the availability of ART has decreased the proportion of patients in low CD4 strata and the incidence of PCNSL. On the other side of the coin, ART has increased the proportion of patients in higher CD4 strata where tumors with more favorable biology such as BL and HL occur, as demonstrated in the Gopal et al. study (Figure 1) (8). Others have reported similar trends, but this study specifically examines these changes since the advent of ART (9,10).

One would expect the shift toward more biologically favorable and curable lymphomas to translate into improved clinical outcome over the 14-year time period. Interestingly, this was not the case. In particular, patients with DLBCL had a 5-year survival of 44.1%, compared with 68.7% for all patients with DLBCL in the Surveillance Epidemiology and End Results (SEER) database. Our own group and others (including a multicenter study by the AIDS Malignancy Consortium) have reported that patients with HIV-associated DLBCL and BL have equivalent survivals to the HIV-uninfected population in the ART era (2,3,6,11). The CNICS cohort reflects a diverse HIV-positive population under routine care across the United States, and the poorer results reported in this observational study suggest that heterogeneous factors, such as social setting, access to optimal oncologic and infectious disease care, and disparate approaches to lymphoma management, may all impact survival.

In conclusion, because HIV-associated lymphomas are potentially as curable as those arising in HIV-negative patients, it is critical that they be approached with the same care as HIV-negative cases. The outcome of the CNICS cohort suggests that various factors may compromise treatment, and these should be identified. As in the case of HIV-negative lymphoma, tumor histogenesis plays an important role in survival of HIV-associated DLBCL. Patients with the non-GCB subtype have a substantially worse outcome than their GCB counterparts after standard therapy (2,12). Future studies in HIV lymphoma should focus on better identifying non-GCB tumors and other tumors with adverse biology and including these in clinical trials of targeted treatment (13). For example, studies that investigate novel agents to target driver pathways such as the B-cell receptor cascade are ongoing and show promise (14).

References

12. Lenz G, Wright G, Dave SS, et al. Stromal gene signatures in large-B-cell lymphoma (DLBCL) toward lymphomas with a more favorable biology such as centroblastic DLBCL (DLBCL-CB), Burkitt lymphoma (BL), and Hodkin lymphoma (HL). cHL-MC = classical Hodgkin lymphoma mixed cellularity type; EBV = Epstein–Barr virus; HHV8 = human herpes virus 8; IB = immunoblastic; PL = plasmablastic lymphoma.

Figure 1. A model for the histogenesis of HIV-associated lymphoma. Since the advent of antiretroviral therapy (ART), there has been a pathobiologic shift away from virally driven and poor prognosis lymphomas such as primary central nervous system lymphoma (PCNSL), primary effusion lymphoma (PEL), and immunoblastic diffuse large B-cell lymphoma (DLBCL-IB) toward lymphomas with a more favorable biology such as centroblastic DLBCL (DLBCL-CB), Burkitt lymphoma (BL), and Hodkin lymphoma (HL). cHL-MC = classical Hodgkin lymphoma mixed cellularity type; EBV = Epstein–Barr virus; HHV8 = human herpes virus 8; IB = immunoblastic; PL = plasmablastic lymphoma.

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