8 Human Immunodeficiency Virus-Related Lymphomas

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8.1 Background

The acquired immunodeficiency syndrome (AIDS) was first described in 1981, in individuals with certain opportunistic infections (OI), Kaposi sarcoma, and central nervous system (CNS) lymphomas. Three years later the clinical spectrum of non-Hodgkin lymphomas (NHL) in the populations at risk of AIDS was first described [1, 2]. Since the introduction of combined antiretroviral therapy (cART) in the mid-1990s, the incidence of lymphomas, which formerly accounted for 2–3% of newly diagnosed AIDS patients, has decreased and outcomes have improved [3]. Simultaneously, a shift toward histologies that occur at higher CD4 lymphocyte counts, such as Burkitt lymphoma and classical Hodgkin lymphoma (cHL), was observed [4–7]. The increasing proportion of long-term survivors of lymphoma has raised the possibility of developing certain non-AIDS-defining solid tumors, especially those related to the lifestyle and viral infections in HIV-infected patients.

8.2 Epidemiology

The risk of lymphoid tumors in HIV disease is highly linked to the CD4+ T-cell count [8, 9]. The incidence of NHL has decreased approximately 80% in the cART era, with the greatest decrease occurring among those NHLs that develop in association with advanced immune depletion, such as AIDS-related primary CNS lymphoma [10]. The proposed explanation for this decline is the ability of cART to prevent depletion of CD4+ T-cells, thus decreasing the risk of such tumors. In contrast, those lymphomas that occur at higher CD4+ T-cell counts, such as Burkitt lymphoma, have not changed substantially in incidence since the introduction of cART [8]. The overall relative increase in risk for lymphoma still ranges between 10- and 20-fold higher than in the general population. This risk is similar to that for lymphomas arising in individual with immunosuppression of other origins. cHL incidence has increased since the introduction of cART, further illustrating the complex interaction of immune status with lymphoid malignancy [11]. cHL has 10- to 20-fold higher risk in comparison with the general population, but this increased risk is not

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consistently observed across cHL subtypes, and there has been a shift over the cART era in subtype presentation. In the pre-cART era, mixed cellularity cHL accounted for the majority of cases. In the cART era, there has been a shift so that there is nearly equal presentation of mixed cellularity and nodular sclerosing cHL [12]. Lymphoma is currently the most frequent malignancy among HIV-infected individuals and a frequent neoplastic cause of death in these patients [13].

The diagnosis of AIDS precedes the onset of NHL in less than 50% of the patients, and the simultaneous diagnosis of NHL and HIV positivity is currently relatively frequent. The geographic distribution of NHL lymphomas is similar to the geographic spread of HIV infection, and the incidence is similar for all risk groups for HIV infection.

8.3 Pathogenesis

Although AIDS-related lymphomas are usually of B-cell origin as demonstrated by immunoglobulin heavy-chain gene rearrangement studies, they have also been shown to be oligoclonal, polyclonal, and monoclonal in origin. Although HIV is a risk factor for a variety of cancers, it does not appear to be directly implicated in lymphomagenesis. HIV indirectly creates an environment in which chronic antigen stimulation, cytokine dysregulation, and coinfection with oncogenic viruses, such as the Epstein-Barr virus (EBV), are involved, within the setting of genetic abnormalities and impaired immune surveillance. All these factors can lead to the emergence of monoclonal B cells. Impaired T-cell immunity toward EBV is strongly implicated in lymphomagenesis, especially in some aggressive lymphomas such as the immunoblastic and plasmablastic subtype [14, 15].

Infection by human herpesvirus 8 (HHV-8) or Kaposi sarcoma herpesvirus (KSHV) is frequently observed in HIV-infected patients with primary effusion lymphoma (PEL) [16], and the combined presence of EBV and HHV-8 appears to be unique to PEL [17]. Other lymphoproliferative disorders in HIV-infected patients involving HHV-8 include multicentric Castleman disease (MCD) and HHV8-positive plasmablastic lymphoma (PBL) [18].

8.4 Pathology

Traditionally, human immunodeficiency virus (HIV)-associated lymphomas have been categorized as follows: (1) aggressive B-cell lymphomas (diffuse large B-cell lymphoma [DLBCL], Burkitt lymphoma [BL], aggressive B-cell lymphoma with *MYC* and *BCL-2* and/or *BCL-6* rearrangements, PBL, and PEL), (2) primary central nervous system lymphoma (PCNSL), (3) classical HL, and (4) DLBCL arising in HHV-8-associated MCD [19]. The revised WHO classification of tumors is agnostic to HIV status [20]. Importantly, the updated classification is informed to some extent by molecular features relevant to treatment. For example, advances in treatment may soon include specific therapies according to DLBCL subtype. Definitive phase III clinical trials of lenalidomide and ibrutinib in activated B-cell subtype DLBCL are ongoing and may inform a new standard of care for this disease. Studies sponsored by the US National Cancer Institute to determine feasibility of combining these agents with chemotherapy in patients with HIV on cART are ongoing, positioning patients with these diseases to be availed of new therapeutics as defined by phase III trials in the background population.

DLBCL is still the most frequent NHL subtype. Most cases are of the germinal center variant assessed by immunohistochemistry methods [21, 22], whereas the frequency using digital multiplexed gene expression remains to be validated [23, 24]. Burkitt lymphoma (BL) is the second subtype in frequency and is similar to sporadic BL with variable association with EBV [25]. The high-grade B-cell lymphomas with *MYC* and *BCL-2* and/or *BCL-6* rearrangements (also known as dual hit or triple hit according to the presence of two or the three rearrangements) account for 5–10% of cases with DLBCL and are highly aggressive with poor response to standard therapies [26]. Primary DLBCL of the central nervous system (CNS) that are truly

AIDS-related occur at CD4+ T-cell levels of less than 50/mm^3, and essentially 100% are EBV positive [20, 27]. In the cART era, primary DLBCL in CNS are rarely seen. Among patients with over 100 CD4+ T-cell cells/mm^3, the occurrence of PCNSL in over 23,000 HIV-infected patients is not documented [6, 28].

PEL is a very aggressive malignancy, being first reported in the oral cavity of HIV-infected individuals. Subsequently, it has been shown to occur in other sites as well as in conjunction with other immunodeficient states. PEL comprises about 4% of all HIV-related NHL and usually involves patients with advanced immunosuppression, with a CD4 count less than 150 cells/mm^3 and a history of prior AIDS-defining illnesses. The immunophenotype of these lymphomas resembles that of plasma cells. More than 80% of cases are EBV positive, and approximately half have been shown to have the *MYC* translocation [29].

Lymphomas arising in HHV-8-associated MCD are very rare lymphomas and mainly occur in HIV-positive patients [30]. They are difficult to distinguish from PEL. Characteristically, they are HHV-8 positive but EBV negative, express IgMλ cytoplasmic immunoglobulin, and appear within the setting of MCD in the lymph nodes involved.

While not considered to be an AIDS-defining malignancy, cHL is increased in incidence in HIV-infected individuals and may surpass AIDS-NHL in frequency in some populations, especially in those with longer life expectancies and better immunological control with cART. In the pre-cART era, in contrast to non-immunosuppressed patients, HIV-related cHL was accompanied by EBV infection in close to 90% of cases, and the mixed cellularity or lymphocyte-depleted forms comprised a larger number of cases [31]. In populations where cART is widely available, these differences are much less pronounced [12].

8.5 Clinical Presentation, Diagnosis, and Staging

In the pre-cART era, the clinical setting of patients with AIDS-related lymphoma was very different from that of non-HIV patients and was characterized by advanced-stage disease and frequently extranodal involvement, including unusual sites. Currently the clinical picture resembles that of non-HIV-infected patients, especially for the lymphoma subtypes associated with improved CD4+ lymphocyte counts, although a trend to more disseminated disease and extranodal involvement still persists [32].

An excisional lymph node or tissue biopsy is required for the diagnosis of HIV-related lymphomas. Morphologic, cytogenetic, and molecular studies should be performed to obtain a high-precision diagnosis, and the biologic material should be stored for future studies. Assessment of EBV and HHV-8 virus in lymphoma cells is highly recommended. Diagnoses based exclusively on fine needle aspiration of tumor masses should be avoided. Certain confounding factors such as HIV-related reactive lymphadenopathy and an increased incidence of infections may make the interpretation of 18 F-fluorodeoxyglucose positron emission tomography (FDG-PET) scans more difficult than in the HIV-negative population, especially in patients with detectable HIV viral loads. Gadolinium-enhanced magnetic resonance imaging (MRI), ^{201}thallium single-photon emission computed tomography (^{201}Th-SPECT), or FDG-PET scan, combined with cytology, flow cytometry, and a polymerase chain reaction (PCR) method to detect EBV-DNA in cerebrospinal fluid (CSF), are helpful for the diagnosis of PCNSL and to differentiate between PCNSL and cerebral toxoplasmosis. Immediate definitive diagnosis with stereotactic biopsy, as is the standard of care in the non-HIV setting, is essential to optimize therapeutic outcome. In the pre-cART era, biopsy was delayed or even omitted in patients presenting with ring-enhancing brain lesions. A presumptive lymphoma diagnosis was made for those not responding to a short course of anti-toxoplasma treatment. This is no longer a justified practice.

The Ann Arbor/Cotswolds and the Lugano [33, 34] staging systems are commonly used for patients with NHL and HL. HIV viral load and CD4 lymphocyte count should be added to the usual procedures to assess the stage. Serologic studies for hepatitis B and C virus,

cytomegalovirus, EBV, *Toxoplasma*, and varicella-zoster are also highly recommended. A detailed HIV history including assessment of prior opportunistic infections (OI), general immune function, antiretroviral treatment history, and HIV control should be obtained. Additionally, cardiac function should be assessed in selected cases with either a cardiac multigated acquisition (MUGA) scan or an echocardiogram before treatment planning.

8.6 Prognostic Factors

The prognosis of HIV-infected individuals with lymphoma is determined by patient-, lymphoma-, and HIV-specific factors [35]. The significance for each of these factors has varied over the last three decades due to changes in antiretroviral and lymphoma-directed therapy, improved supportive care, and a shift in the incidence and biology of lymphoma.

Since effective HIV control has become achievable, adequate lymphoma-directed therapy is possible in the contemporary cART era, and survival is now similar to that observed in immunocompetent patients. Hence, the International Prognostic Index (IPI) [36] and age-adjusted IPI have been extensively validated and remain reliable predictors of outcomes in HIV-related aggressive NHL. Similarly, the International Prognostic Score (IPS) [37] has shown prognostic relevance in HIV-associated cHL, although this prognostic significance was not observed in all studies. With regard to the impact of HIV-related factors on survival, low CD4 counts have been implicated as predictors of poor survival in several studies, while other reports have not found this association, especially in the cART era [38].

Composite scores including patient-, lymphoma-, and HIV-related factors have been developed. Of these, the combined AIDS-related lymphoma IPI (ARL-IPI) score for patients with DLBCL, which consists of prior history of AIDS, baseline CD4 count, and viral load, and the age-adjusted IPI is a better predictor of survival than the age-adjusted IPI alone [39]. Of note, in this analysis, the 5-year overall survival (OS) was 78% for the low-risk group, which is similar to outcomes described in HIV-negative patients with DLBCL. The prognostic value of other biologic parameters (e.g., germinal center vs. activated B-cell phenotype, EBV, or Bcl-2 expression) is less consistent and varies among the different studies.

Similarly, a composite score for HIV-related HL developed in six European countries includes two parameters independently associated with OS: CD4 counts <200 cells/mm^3 and IPS >2. A retrospective multicenter study of 229 advanced HIV-HL patients who had received ABVD plus cART showed CD4 cell counts <200/mm^3 to be an independent adverse prognostic factor for PFS and OS [40].

8.7 Treatment of HIV-Related Lymphomas

8.7.1 General Principles

In the cART era, the treatment of the specific subtypes of HIV-related lymphomas is similar or identical to that used for lymphomas arising in non- immunosuppressed patients, but the treatment recommendations are mostly based on evidence from phase II trials, retrospective series, or expert opinion [3, 41]. In addition, several specific aspects should be considered, being the concomitant antiretroviral therapy and the prophylaxis and eventual treatment of opportunistic infections (OI) the most relevant.

8.7.2 Diffuse Large B-Cell Lymphomas

Several phase II studies conducted in Europe and the USA have shown promising results with the combination of the anti-CD20 monoclonal antibody rituximab with chemotherapy schedules, such as CHOP (R-CHOP) [42] or infusional regimens such as CDE (cyclophosphamide, doxorubicin, and etoposide) (R-CDE) [43] or EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) (R-EPOCH) [44].

Although the only phase III trial comparing CHOP vs. R-CHOP showed negative results for overall and progression-free survivals, the response was superior for R-CHOP [45]. The lack of survival benefit was attributed to the high treatment-related mortality of 36% for patients with a CD4 count <50 cells/mm^3 in the R-CHOP group and the lower than expected response rate in the whole group compared with that observed in other trials using R-CHOP. Despite these results, most contemporary trials use rituximab as part of the treatment, but some restrict its use in patients with CD4 counts <50 cells/mm^3. In the AMC034 trial, rituximab was given either consecutively with EPOCH or sequentially (weekly with six doses after completion of chemotherapy). In this "pick-the-winner" phase II trial, only the concurrent arm reached the predefined endpoint, with a CR rate of 73% (71% for DLBCL) versus only 55% in the sequential arm. With concurrent R-EPOCH, the 2-year OS reached 70%, similar to that achieved with R-CHOP or R-CDE regimens.

Based on the evidence from two-pooled clinical trials of 150 patients and a meta-analysis of pooled individual patient data for 1546 patients from 19 prospective clinical trials showing improved overall survival with the infusional EPOCH regimen and with rituximab, many experts and cooperative groups, especially in North America, have adapted six cycles of chemoimmunotherapy with R-EPOCH as their standard initial regimen for the treatment of HIV-positive patients with DLBCL [46]. However, there is no prospective randomized controlled trial comparing the R-EPOCH regimen to others, and in Europe the most used regimen is R-CHOP. Encouragingly, outcomes with initial therapy for HIV-DLBCL are close to those similarly treated for HIV-negative patients in the current era [47]. Of note, preliminary reports from the randomized CALGB phase III trial comparing dose-adjusted EPOCH-R and R-CHOP in the HIV-unrelated setting reported no difference in event-free survival [48, 49]. However, the dose adjustment in the HIV setting is substantially different compared to the phase III approach, limiting the ability to apply those results to the HIV setting.

Several areas of uncertainty remain unsolved due to lack of solid information: first, the treatment of patients in localized stages (I or II non-bulky), for which chemoimmunotherapy with six cycles of R-CHOP or R-EPOCH is generally preferred to three to four courses followed by radiotherapy; second, the use of rituximab in patients with a low CD4 count (<50/mm^3), in whom there are recent trends to use rituximab irrespective of the CD4 count, except in patients with history of prior or ongoing OI and a low likelihood of adequate HIV control with cART due to poor adherence; and third, the concurrent or sequential use of cART during chemotherapy. Possible benefits of concurrent cART include better HIV control leading to fewer infectious complications and AIDS-defining events [50], but these benefits could be counterbalanced by drug-drug interactions leading to either increased toxicities or possible underdosing, resulting in either the emergence of HIV or lymphoma resistance. Although there is no formal consensus, most groups tend to use the concurrent option, except if a short-term chemotherapy schedule is used. Given the availability of newer antiretroviral agents, such as the HIV integrase strand transfer inhibitors that have very little relevant drug-drug interactions, there is little reason to suspend cART while administering cancer chemotherapy, including with the DA-EPOCH-R regimen.

8.7.3 Burkitt Lymphoma

Prior to the advent of effective cART, all HIV NHL, including Burkitt lymphoma, were treated with CHOP-like therapy. Outcomes were dismal. The current therapy of BL in HIV-infected patients is similar or identical to that used in non-immunocompromised patients, based on specific short-term immunochemotherapy regimens. These regimens include rituximab combined with intensive chemotherapy schedules based on high-dose cyclophosphamide and methotrexate, among other cytotoxic drugs (e.g., hyper-CVAD, CODOX-M/IVAC, LMB86, B-ALL/NHL 2002, or BURKIMAB) [51–53]. Although the results

are similar to those observed in BL arising in the general population (overall survival of 70–80%), the toxicity (especially mucositis and infections) is higher in HIV-infected patients [54].

In a very different approach from the intensive regimens mentioned above, the US National Cancer Institute has developed effective risk-adapted Burkitt lymphoma therapy based on the EPOCH-R regimen. For low-risk patients (defined as normal LDH, ECOG performance 1–2, stage I–II, and mass <7 cm), the "short-course EPOCH-RR" regimen has shown favorable results. This involves a short course of EPOCH (without dose adjustment: all patients receive a fixed dose of 750 mg of cyclophosphamide) with a double dose of rituximab [55]. Dunleavy et al. reported on 11 patients with HIV infection and BL (none presented CNS involvement) having an excellent OS at 73 months of 92%, which remains unchanged in further updates. In a larger expanded effort, the preliminary report at a median follow-up of 25 months of the first 77 patients of a US National Clinical Trials Network trial of risk-adapted DA-EPOCH-R showed progression-free survival of 87% and overall survival of 88% for all patients. There was no evidence that the 20 HIV+ patients outcome was different that the non-HIV patients [56]. The final results in over 100 patients are expected to be reported soon.

8.7.4 Aggressive B-Cell Lymphoma with MYC and BCL-2 and/or BCL-6 Rearrangements

There is limited experience on treatment of this poor-prognosis subgroup of patients in the HIV setting. The most reasonable option is to mimic the experience of non-immunocompromised patients, in whom the DA-EPOCH-R schedule seems to be the most promising immunochemotherapeutic approach [57].

8.7.5 Plasmablastic Lymphoma

Currently there is no standard of care with respect to chemotherapy in PBL in patients with HIV due to the rarity of the condition and to the fact that most studies have been retrospective in nature. In some studies, the DA-EPOCH regimen offered better results than CHOP, while in others the CODOX-M/IVAC was also superior than CHOP. In any case, the median survival of these patients is short, ranging between 5 and 17 months, making new therapeutic approaches necessary. New drugs such as vorinostat, bortezomib, or ibrutinib in combination with chemotherapy targeting the non-germinal phenotype and oncogenic viruses seem promising, and prolonged survival has been observed in individual cases or short series [58, 59].

8.7.6 Primary Effusion Lymphoma

The optimal treatment for HIV-PEL is undefined. Many patients with HIV-related PEL receive standard combination chemotherapy regimens such as CHOP, but the response is poor (50% CR and median overall survival of 6 months). The use of infusional regimens (CDE or EPOCH) or intensive regimens with high-dose methotrexate could provide better results. The benefit of autologous hematopoietic stem cell transplantation (HSCT) in patients in first CR is uncertain.

Antiviral medications targeting HHV-8 (e.g., valganciclovir, ganciclovir, or cidofovir) have been concomitantly used with chemotherapy in some cases, with long-term remissions having been reported. Other approaches are being preclinically evaluated. They include brentuximab vedotin, proteasome inhibitors, anti-endothelial vascular growth factor (VEGF), and other inhibitors of angiogenesis and HHV8 replication (valproate, HIV-protease inhibitors, nelfinavir, and ganciclovir).

8.7.7 Primary CNS Lymphoma

Profound immunosuppression (CD4 cells <50/mm^3), EBV detection in lymphoma cells from virtually all patients, and high aggressive histology (frequently immunoblastic) are the hallmarks of this lymphoma and must be considered for

treatment decision making [60]. The introduction of cART has not only led to a decline in the incidence of PCNSL but also a modest improvement in OS. However, outcomes remain dismal with few patients alive 2 years after diagnosis. Importantly, many patients who develop AIDS-PCNSL in the current era are previously undiagnosed and/or untreated for their HIV and can be salvaged immunologically. Since essentially 100% of AIDS-PCNSL are EBV+, immune recovery with cART and reconstitution of EBV-specific immunity may confer a therapeutic benefit in this setting. Therefore, rapid diagnosis of CNS lesions in HIV-infected patients is critical for optimal care. In the pre-cART era, there was an algorithm to begin anti-toxoplasmosis therapy and then to re-evaluate after 2 weeks of therapy. If the lesion worsened, it was presumed to be lymphoma. In the cART era, this approach should not be considered a reasonable medical practice.

The therapeutic approach recommended in immunocompetent patients with PCNSL includes upfront induction chemotherapy with high-dose methotrexate and cytarabine followed by consolidation with whole-brain radiotherapy or further chemotherapy with or without autologous HSCT. This treatment is not well defined in HIV-infected patients. A retrospective cohort of 13 patients treated with high-dose methotrexate-based therapy in whom HIV control was achieved with cART showed all patients free of lymphoma and high functional status with a median follow-up of 50 months [60, 61]. A trial of high-dose methotrexate with rituximab and cART is ongoing at the US NCI, with encouraging initial results [49]. Results reported using the combination of whole-brain radiotherapy and cART suggest poor long-term outcomes and late neurotoxicity (leukoencephalopathy) complicating around 20% of cases, suggesting chemotherapy approaches may be preferred. Importantly, HIV-related PCNSL can largely be prevented by early HIV diagnosis and treatment.

8.7.8 Classical Hodgkin Lymphoma

The ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) chemotherapy regimen with concurrent cART has been evaluated in retrospective studies in patients in advanced stages of HL, showing CR rates over 80% and EFS and OS probabilities of 75–85% [62, 63]. These results were similar to those achieved in HIV-negative patients [64]. The German HIV study group evaluated the incorporation of the BEACOPP regimen with concurrent cART to the treatment in patients with HIV-related HL. Patients with early favorable HL received two to four cycles of ABVD followed by involved-field radiation; patients with early unfavorable disease were treated with four cycles of BEACOPP baseline or four cycles of ABVD; and patients with advanced HIV-cHL received six to eight cycles of BEACOPP baseline. In patients with advanced HIV infection, BEACOPP was replaced by ABVD. The CR rate for patients with early favorable, early unfavorable, and advanced-stage cHL was 96%, 100%, and 86%, respectively, and no significant differences were observed in overall survival among the three (95.7%, 100%, and 86.8%, respectively) [65].

Taken together, a stage-adapted treatment approach is feasible and effective in HIV-related cHL. Two cycles of ABVD followed by 20 Gy involved-field (IF) radiotherapy (RT) can be regarded as standard treatment for early favorable cHL, while four cycles of ABVD followed by 30 Gy IF-RT may be considered the standard of care for patients with early-stage unfavorable cHL. For advanced stages, six cycles of ABVD or BEACOPP may be equally considered. However, ABVD is most commonly used for advanced HIV-cHL in many parts of the world.

There is limited data on interim PET scans in HIV-cHL, but recent data from a retrospective cohort study indicate a high negative predictive value of a PET scan performed after two to three cycles of ABVD [66]. In a prospective US intergroup trial of PET-2 response adapted therapy that included HIV-infected patients, the approach was feasible, and the outcomes did not appear to be different from that of the HIV-unrelated cases [67, 68]. Recent case studies indicate that brentuximab vedotin may also be useful in HIV-positive patients with relapsed HL, and a combination of brentuximab vedotin,

doxorubicin, vinblastine, and dacarbazine is currently being investigated in a study by the AIDS Malignancy Consortium (AMC) (NCT 01771107). The AMC is also accruing patients with HIV-cHL to an NCI-sponsored trial using anti-programmed death 1 (PD1) agents (NCT 02408861).

Essential to the management of HIV-cHL is the absolute contraindication to use ritonavir and most other protease inhibitors as part of the cART regimen when vinblastine or brentuximab vedotin is used because of cyp3A4 interactions leading to severe neutropenia and neurotoxicity that can create inability to administer curative intent therapy [69].

8.7.9 Diffuse Large B-Cell Lymphoma in Patients with HHV-8 Multicentric Castleman Disease

The prognosis of MCD has dramatically improved in recent years, mainly due to the widespread use of cART and targeted therapies such as rituximab. This approach has markedly reduced the rate of progression to NHL [70]. These lymphomas are EBV unrelated, and IgM, lambda restricted. The spleen and lymph nodes are typically involved. Treatment for HHV-8 related DLBCL in these patients is poorly defined. Some cases may express CD30 providing a rationale for use of brentuximab vedotin therapeutically.

8.7.10 Treatment of Relapsed or Refractory HIV-Related Lymphomas

As most HIV-positive patients in the cART era can tolerate dose-intense multiagent regimens in first-line therapy, it seems recommendable to approach HIV-positive patients with relapsed or refractory DLBCL in a manner similar to immunocompetent patients. High-dose salvage regimens such as ICE (ifosfamide, carboplatin, etoposide), DHAP (dexamethasone, cytarabine, cisplatin), ESHAP (etoposide, dexamethasone, cytarabine, cisplatin), or GDP (gemcitabine, dexamethasone, cisplatin) in combination with rituximab appear to have similar efficacy and should be used for appropriate patients. Patients with chemosensitive disease who are transplant eligible should proceed to autologous hematopoietic stem cell transplantation (HSCT) [71–74]. In HIV-negative DLBCL, many new agents are under development, particularly inhibitors of the NF-kappa B pathway and B-cell receptor signaling, but experience in HIV-positive patients is lacking. The AMC in collaboration with the Cancer Therapy Evaluation Program at the US NCI is currently developing a study of ibrutinib in HIV-DLBCL.

Effective therapeutic options for patients with relapsed or refractory BL are limited, and the only reasonable option is to administer rescue immunochemotherapy followed immediately by autologous HSCT. The new approaches under development in HIV-negative individuals seem promising and will hopefully be translated to HIV-infected patients in the near future.

Patients with relapsed or refractory HIV-related cHL should be considered early for high-dose chemotherapy and autologous HSCT if chemosensitive relapse is achieved [71–74]. Peripheral blood stem cells can be effectively mobilized [75], and the results are similar to those shown in immunocompetent patients [71–76]. As mentioned previously immunotherapy approaches with brentuximab vedotin and anti-PD1 agents are being or will soon be incorporated in clinical trials in relapsed or refractory HIV-related cHL.

In HIV-infected patients with NHL and cHL submitted to high-dose therapy and autologous HSCT, adequate CD34+ cells are usually collected at the first mobilization attempt [75]. Tolerance to myeloablative chemotherapy is good, and engraftment kinetics is comparable to that of HIV-negative patients, also with similar regimen-related and infectious complications during the period of aplasia. The use of G-CSF as well as anti-infective prophylaxis is strongly recommended after transplant, with antibacterial, antifungal, and antiviral prophylaxis being

advisable. Trimethoprim-sulfamethoxazole is used to prevent *Pneumocystis jirovecii* pneumonia but has to be withheld from the day of stem cell infusion until engraftment due to its known hematologic toxicity. Aerosolized pentamidine is a good option for this prophylaxis. Antiretroviral therapy is usually given along the HSCT program. The CD4+ cell count decreases after high-dose chemotherapy with the nadir at approximately 3–6 months after transplantation and subsequently recovers to pretransplant levels within the first year. The thymus-dependent pathway of T-cell reconstitution after autologous HSCT has been demonstrated to be as efficient as in HIV-uninfected individuals [74, 76].

Recent reports support allogeneic HSCT in HIV-infected persons as a standard of care when the underlying hematologic malignancy can benefit from this procedure [77, 78]. In one reported case, not only was leukemia cured, but there has been an inability to detect residual HIV infection, suggesting that the patient may even be cured by transplantation owing to a donor graft homozygous for a deletion 32 mutation in the CCR5 HIV co-receptor [77]. There are some special considerations in management. It is essential to have a multidisciplinary patient care team with expertise in antiretroviral therapy as well as in allogeneic HSCT. Patients will benefit from maintenance of cART throughout the transplant process, but special precaution must be taken with potential interactions with immunosuppressive and anti-infectious agents [78].

8.7.11 Antiretroviral and Supportive Therapy

Current literature is lacking for definitive clinical guidance on how best to combine cART and anticancer agents in patients with HIV and hematological malignancies [79, 80], and therefore until this information is available, communication among oncohematologists, infectious disease physicians, and pharmacologists is crucial to guide treatment decisions. Given that there is general consensus on the concurrent administration of cART and chemotherapy, the selection of the cART schedule is of paramount importance. The prior cART schedule, the sensitivity of the HIV strand, the possible coexistence of hepatitis B or C, and the type of chemotherapeutic and anti-infectious agents should be considered for choosing the most appropriate cART regimen. Although individualized cART is sometimes necessary, the most recommended schedule should include integrase inhibitors (raltegravir or dolutegravir) combined with nucleoside/nucleotide reverse transcriptase inhibitors such as lamivudine (3TC)/abacavir or emtricitabine (FTC)/tenofovir alafenamide (TAF). Most once-daily single-tablet formulations and the use of protease inhibitors and cobicistat should be avoided due to their frequent pharmacologic interactions, as well as disoproxil fumarate (TDF) if renal toxicity is expected. If there is coinfection with hepatitis B virus, the cART should preferentially include FTC/TAF or FTC/TDF as an alternative.

The general supportive measures used in non-immunocompromised patients with lymphomas such as prophylaxis and treatment of tumor lysis syndrome or infections during neutropenia and the use of colony-stimulating factors and transfusion, among others, are fully applicable to HIV-infected patients.

Primary and secondary anti-infectious prophylaxis should be administered according to the CD4+ counts and the previous history of OI. *Pneumocystis jirovecii* prophylaxis is recommended for all patients. Systematic prophylaxis against CMV is not recommended, but careful PCR monitoring of CMV blood levels should be performed in all patients with CD4+ counts lower than 100/mm^3, and preemptive therapy should be administered accordingly.

In the current era of HIV medicine, planning optimal cancer therapy requires that the HIV infection be evaluated as a comorbid condition and not as the primary disease. If the prospects for long-term successful management of the HIV infection are favorable, then cancer management can often proceed as it would for any patient with similar performance and malignant disease characteristics.

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