Chapter 9

Management of human immunodeficiency virus-associated lymphomas

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Introduction

Human immunodeficiency virus (HIV) infection is associated with a variety of malignancies including acquired immune deficiency syndrome (AIDS)-defining and non-AIDS-defining lymphomas. Collectively, they may be referred to as HIV-associated lymphomas. AIDS-defining non-Hodgkin lymphomas (NHL) include diffuse large B-cell lymphoma (DLBCL), Burkitt's lymphoma, primary central nervous system (CNS) lymphoma, and less commonly primary effusion lymphoma and plasmablastic lymphoma. Approximately 10% of HIV patients will develop a NHL. Non-AIDS-defining lymphomas, which have an increased prevalence in HIV-infected individuals, include Hodgkin lymphoma (HL). The risk of developing a HIV-associated lymphoma correlates directly with the degree of immune dysfunction.

Management of HIV-associated lymphomas has evolved over the years. Widespread use of antiretroviral therapy has reduced the incidence of HIV-associated lymphomas and improved the outcome of these patients. Often, HIV lymphomas have an aggressive presentation. Treatment balances the goal of achieving a complete response (CR) while managing the risk of opportunistic infections.

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Antiretroviral and supportive therapy

Concurrent use of antiretroviral therapy is associated with improved CR rates [1]. Large studies of antiretroviral therapy in patients without lymphoma show that continuous antiretroviral therapy is superior to episodic antiretroviral therapy based on reduced risk of opportunistic infection [2]. Therefore, antiretrovial therapy should be initiated or continued during chemotherapy. Drug interactions may arise from the potential of highly active antiretroviral therapies (HAART) to either inhibit or induce the cytochrome p450 system. While interactions between antiretroviral agents and chemotherapy may occur, the added benefit of an improved immune system and reduced risk of infection warrants the addition of antiretroviral therapy.

Opportunistic infection prophylaxis and use of granulocyte-colony stimulating factor (G-CSF) support for febrile neutropenia are mandatory with all rituximab-based chemotherapy regimens in HIV-associated DLBCL. Patients should be screened for hepatitis B infection and antiviral prophylaxis initiated as appropriate.

Systemic human immunodeficiency virus-associated non-Hodgkin lymphoma

In the past, HIV associated with NHL generally had a poorer prognosis. However, with the development of antiretroviral therapy, treatment outcomes and prognosis have improved significantly to be more in line with non-HIV-associated NHL. Factors that are associated with poor prognosis in patients with HIV-associated NHL include the lack of achievement of a complete remission, the presence of a high International Prognostic Index (IPI) score, and Burkitt subtype [3].

Indolent HIV-associated NHL is relatively less common. This entity can sometimes be managed by initiating antiretroviral therapy. The majority of HIV-associated NHLs are aggressive and treated depending on the histological subtype. Prior to the development of antiretroviral therapy, low-dose chemotherapy was believed to be superior to standard-dose chemotherapy because of increased toxicity with the standard dose therapy. In a large randomized trial, 198 patients with HIV-associated NHL were randomized to receive standard dose methotrexate, bleomycin,

doxorubicin, cyclophosphamide, vincristine, and dexamethasone, with folinic acid and GM-CSF to stimulate white cell production (mBACOD), compared with low-dose mBACOD. Standard-dose mBACOD was found to be as efficacious as low-dose mBACOD, with slightly higher hematologic toxicity in patients undergoing standard-dose mBACOD. These patients had a median CD4 count of 100 cells/ul with 75–80% having CD4 count less than 200 [4]. The tolerance of chemotherapy may have improved with effective antiretroviral therapy. We will comment on the management of DLBCL, Burkitt's lymphoma, and primary effusion lymphoma.

Diffuse large B-cell lymphoma

Prior to antiretroviral therapy, DLBCL was the most common subtype of HIV-associated lymphoma. In the post-HAART era, DLBCL accounts for 25–30% of HIV-associated lymphomas. These lymphomas tend to be aggressive in presentation with involvement of extranodal sites. Often they are of germinal center B-cell biology expressing CD10 and Bcl 6, which are markers of germinal center differentiation. The activated B-cell subtype of DLBCL expresses Bcl2 and MUM1. Cellular immunity may be associated with different DLBCL subtypes. The germinal center subtype of DLBCL is typically encountered in HIV patients with preserved CD4 counts while the ABC subtype is associated with CD4 counts <100/ul. Myc gene overexpression is seen in ~20% of HIV-associated DLBCL.

While there is no standard of care for HIV-associated DLBCL, the literature has supported the use of combined modality chemoimmunotherapy while balancing toxicities from immune suppression (Table 9.1). Rituximab was first thought to be contraindicated in patients with HIV-associated NHL based on a randomized study comparing rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (RCHOP) with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) alone. In the rituximab arm, treatment-related infection occurred in 13 of 99 patients (14%) compared with 2 out of 51 (2%) patients treated with CHOP alone [5]. Most deaths resulted from bacterial infections and occurred early during treatment, after the first or second cycle of chemotherapy, and were higher in patients with CD4 counts <50 [5].

Chemotherapy	Phase	Sample size	ORR	CR	OS	Infection rate	HAART
DR-COP	II	40: DLBCL N=39 Other N=1	67.5%	47.5%	67.5% 47.5%	40%	Yes
DA-R-EPOCH	II	48: DLBCL N=35 BL N=16	88%	73%	70% at 2 yr	27%	PRN
SC-EPOCH-RR	II	33: DLBCL N=33	94%	91%	68% at 5 yr		
R-CHOP	II	52: DLBCL N=36 BL N=9 Other=7	89%	77%	75% at 2 yr	Na	Yes
R-CDE	II	74: DLBCL N=52 BL N=21	75%	70%	64% at 2 yr	37%	Yes

Table 9.1 Common chemotherapy for human immunodeficiency virus-associated diffuse large B-cell lymphoma. BL, Burkitt's lymphoma; CI, confidence interval; CR, complete response; DLBCL, diffuse large B-cell lymphoma; HAART, highly active antiretroviral therapy; IV, intravenous; ORR, overall response rate; OS, overall survival; PET, positron emission tomography; PO, oral; PRN, as needed. Data from [6–10].

Chemotherapy regimen	Ref
Rituximab 375 mg/m^2, IV, day 1	[9]
Pegylated liposomal doxorubicin 40 mg/m^2, IV, day 1	
Cyclophosphamide 750 mg/m^2, IV, day 1	
Vincristine 1.4 mg/m^2, capped at 2 mg, IV, day 1	
Prednisone 100 mg, PO, day 1–5	
Every 3 weeks x 6	
Rituximab 375 mg/m^2, IV, day 1	[7]
Etoposide 50 mg/m^2/day, CI, day 1–4	
Doxorubicin 10 mg/m^2/day, CI, day 1–4	
Vincristine 0.4 mg/m^2/day, no cap, CI, day 1–4	
Cyclophosphamide 750 mg/m^2, IV, day 5	
Prednisone 60 mg/m^2/day, PO, day 1–5	
Dose adjustment based on hematologic and neurotoxicity	
Every 3 weeks x 6	
Rituximab 375 mg/m^2, IV, day 1 and day 5	[10]
Etoposide 50 mg/m^2/day, CI, day 1–5	
Doxorubicin 10 mg/m^2/day, CI, day 1–5	
Vincristine 0.4 mg/m^2/day, CI, day 1–5	
Cyclophosphamide 750 mg/m^2, IV, day 5	
Prednisone 60 mg/m^2/day, PO, day 1–5	
Dose adjustment based on hematologic and neurotoxicity	
Every 3 weeks, 2 cycles then interim PET. If PET negative, total 3 cycles. If PET positive, total 6 cycles	
Rituximab 375 mg/m^2, IV, day 1	[6]
Doxorubicin 50 mg/m^2, IV, day 1	
Vincristine 1.4 mg/m^2, capped at 2 mg, IV, day 1	
Cyclophosphamide 750 mg/m^2, IV, day	
Prednisone 40 mg/m^2/day, PO, day 1–5	
Every 3 weeks x 6	
Rituximab 375 mg/m^2, IV, day 1	[8]
Doxorubicin 12.5 mg/m^2/day, CI, day 1–5	
Etoposide 60 mg/m^2/day, CI, day 1–5	
Cyclophosphamide 187.5–200 mg/m^2/d, CI , day 1–5	
Prednisone 60mg/m^2, PO, day 1–5	
Every 4 weeks x 6	

Several trials have since supported the safety and tolerability of rituximab in this population. Rituximab plus chemotherapy was well tolerated with a reported 70% CR across multiple studies and 2-year OS of 60–70% [5–8]. A randomized Phase II study AMC-034 of dose-adjusted etoposide, doxorubicin, cyclophosphamide with vincristine, and prednisone, in combination with rituximab (DA-EPOCH-R) either concurrently or weekly for 6 weeks demonstrated the importance of concurrent rituximab. The concurrent arm demonstrated a 73% CR versus 55% CR in the sequential arm [7]. Infusional cyclophosphamide, doxorubicin, and etoposide (iCDE) with rituximab showed similarly high CR and 2-year OS rates (70% and 64%, respectively) [8]. Substitution of doxorubicin with liposomal doxorubicin did not improve outcomes [9]. A meta-analysis of 19 prospective trials demonstrated that the addition of rituximab primarily benefits patients with CD4 counts >50 [1]. In patients with CD4 counts <50, rituximab may be held until CD4 counts improve with HAART therapy.

Positron emission tomography (PET) direct approaches are being explored in HIV-associated DLBCL. Short course EPOCH-R therapy, based on a PET-directed approach where PET negativity after two cycles results in a limit of the total chemotherapy cycles to three rather than the conventional six cycles, was studied. The 5-year OS was 68% in this population [10].

The addition of radiotherapy has not been evaluated in HIV-associated DLBCL. Practically, DLBCL is a radiosensitive disease therefore radiotherapy to sites of primary bulky disease can be considered.

The overall data support concurrent rituximab with EPOCH or conventional chemotherapy in the HAART era. Dose reductions are undertaken for CD4 counts <200 and rituximab may be held if CD4 count is <50. An ongoing AIDS Malignancy Consortium (AMC) trial is investigating the additional benefit of vorinostat to the R-EPOCH backbone.

Central nervous system prophylaxis

Prospective studies on the use of CNS prophylaxis in HIV-associated DLBCL is not available. In the HIV-negative population, the risk of CNS relapse ranges from 1 to 10%. In patients >60 years of age, the risk of

CNS relapse is increased if lactate dehydrogenase (LDH) is elevated, Eastern Cooperative Oncology Group (ECOG) performance status is >1, and there is a >1 extranodal site of disease involvement [11]. In particular, kidney and adrenal involvement is an associated with a heightened risk of CNS relapse [11,12]. In patients <60 years of age, the frequency of CNS relapse approached 5–10% with age-adjusted IPI (aaIPI) of 2 or 3 [13]. Based on this data, CNS prophylaxis may be offered to patients with testicular, kidney or adrenal involvement, or patients with elevated LDH, ECOG performance status >1, and >1 extranodal site of disease.

Human immunodeficiency virus-associated Burkitt's lymphoma

Burkitt's lymphoma is an aggressive lymphoma representing 30% of HIV-associated lymphomas; Epstein Barr virus (EBV) is positive in 30% of these cases. The majority of HIV-associated Burkitt's lymphomas have plasmacytoid differentiation characterized by medium-sized cells with abundant basophilic cytoplasm, eccentric nucleus, and often a centrally located prominent nucleolus.

Intensive chemotherapy regimens have been investigated in HIV-associated Burkitt's lymphoma (Table 9.2). The LMB86 regimen was evaluated in 63 patients who all had stage IV disease with CNS or bone marrow involvement [14]. The study demonstrated a 2-year OS and disease-free survival (DFS) of 47% and 68%, respectively [14]. Seven (11%) treatment-related deaths occurred. Low CD4 count <200 and ECOG performance >2 were identified as poor prognostic factors [14]. Patients with low-risk factors had good outcomes with 2-year OS of 60% versus 2-year OS of 12% in patients who had two or more risk factors [14]. The combination of cyclophosphamide, doxorubicin, vincristine, methotrexate, etoposide, ifosfamide, and cytarabine (CODOX-M/IVAC) demonstrates a CR rate of 70% and 3-year OS and DFS of 52% and 75%, respectively [15,16]; adding rituximab to this regimen (R-CODOX-M/IVAC) was also studied in a Phase II trial. Preliminary results from 22 patients with 17 months of follow-up showed a 1-year OS of 86% with four patients (14%) taken off the study for toxicity or progression. In a trial conducted in parallel in Spain and Germany involving 81 patients, an intensive regimen B-ALL/

Chemotherapy	Phase	Sample size	ORR	CR	OS	Infection rate	HAART
LMB86	II	63: BL = 63		70%	41% at 2 yr	18%	Yes

Table 9.2 Common chemotherapy for human immunodeficiency virus-associated Burkitt's lymphoma (continues overleaf).

Chemotherapy regimen	Ref
Cytoreductive = COP	[14]
Vincristine 2 mg, IV, day 1	
Cyclophosphamide 300 mg/m^2, IV, day 1	
Prednisome 60 mg/m^2, PO, day 1–7	
Induction	
COPADM1	
Vincristine 2 mg, IV, day 1	
Methotrexate 8 g/m^2, IV, day 1	
Cyclophosphamide 500 mg/m^2, IV, day 2–4	
Doxorubicin 60 mg/m^2, IV, day 2	
Prednisone 60 mg/m^2, PO, day 1–7	
COPADM2	
IDEM with vincristine 2 mg, IV, day 1, day 6	
Cyclophosphamide 1000 mg/m^2, IV, day 2–4	
Prednisone 60 mg/m^2, PO, day 1–7	
Consolidation = CYVE x 2	
Etoposide 200 mg/m^2, IV, day 2–5	
Cytarabine 50 mg/m^2, IV, day 1–4, 12 hours before high-dose cytarabine	
Cytarabine 3 g/m^2, IV, day 2–5	
Maintenance – 4 cycles	
Sequence 1	
Vincristine 2 mg, IV, day 1	
Methotrexate 8 g/m^2, IV, day 1	
Cyclophosphamide 500 mg/m^2, IV, day 2–3	
Doxorubicin 60 mg/m^2, IV, day 3	
Prednisone 60 mg/m^2, PO, day 1–5	
Sequence 2 and 4	
Etoposide 150 mg/m^2, day 1–3	
Cytarabine 100 mg/m^2, SC, day 1–5	
Sequence 3	
Vincristine 2 mg, IV, day 1	
Cyclophosphamide 500 mg/m^2, IV, day 223	
Doxorubicin 60 mg/m^2, IV, day 3	
Prednisone 60 mg/m^2, PO, day 125	

Chemotherapy	Phase	Sample size	ORR	CR	OS	Infection rate	HAART
R-CODOX-M/ IVAC	II	81: BL N=81	90%	80%	72% at 4 yr	32% cycle A 13% cycle B *11% mortality in induction	Yes
DA-R-EPOCH	II	19: BL N=19			100% at 6 yr	NA	No

Table 9.2 Common chemotherapy for human immunodeficiency virus-associated Burkitt's lymphoma (continues overleaf).

Chemotherapy regimen	Ref
Prephase	[17]
Cyclophosphamide, 200 mg/m^2, IV, day 1–5	
Prednisone, 60 m/m^2, IV, day 1–5	
Cycle A	
Rituximab 375 mg/m^2, IV, day 7	
Vincristine 2 mg, IV, day 8	
Methotrexate 1500 mg/m^2, CI, day 8	
Ifosfamide 800 mg/m^2, IV, day 8–12	
Dexamethasone 10 mg/m^2, IV, day 8–12	
Teniposide 100mg/m^2, IV, day 11–12	
Cytarabine 150mg/m^2, IV q 12 hour, day 11–12	
Cycle B	
Rituximab 375 mg/m^2, IV, day 28	
Vincristine 2 mg, IV, day 29	
Methotrexate 1500 mg/m^2, CI, day 29	
Cyclophosphamide, 200 mg/m^2, IV, day 29–33	
Dexamethasone 10 mg/m^2, IV, day 29–33	
Doxorubicin 25 mg/m^2/day, IV, day 32–33	
Cycle C	
Rituximab 375 mg/m^2, IV, day 49	
Vindesine 3 mg/m^2, no cap, IV, day 50	
Methotrexate 1500 mg/m^2, CI, day 50	
Dexamethasone 10 mg/m^2, IV, day 50–54	
Etoposide 250 mg/m^2/day, CI, day 53–54	
Cytarabine 2000 mg/m^2, IV q 12 hour, day 54	
<55 yo A/B/C x 2, ≥A/B x 3	
Rituximab 375 mg/m^2, IV, day 1	[18]
Etoposide 50 mg/m^2/day, CI, day 1–4	
Doxorubicin 10 mg/m^2/day, CI, day 1–4	
Vincristine 0.4 mg/m^2/day, no cap, CI, day 1–4	
Cyclophosphamide 750 mg/m^2, IV, day 5	
Prednisone 60 mg/m^2/day, PO, day 1–5	
Dose adjustment based on hematologic and neurotoxicity	
Every 3 weeks x 6	

SC-EPOCH-RR	II	11: BL N=11	90% at 6 yr	NA	No

Table 9.2 Common chemotherapy for human immunodeficiency virus-associated Burkitt's lymphoma (continued). BL, Burkitt's lymphoma; CI, confidence interval; CR, complete response; HAART, highly active antiretroviral therapy; IV, intravenous; ORR, overall response rate; OS, overall survival; PET, positron emission tomography; PO, oral. Data from [14,17,18].

NHL2002 resulted in a CR rate of 80%, with 9% treatment failures, 11% deaths during induction, and 7% deaths in remission [17]. The 4-year OS was 72% [17]. Bone marrow involvement and CD4 count <200 were prognostic for OS and PFS [17]. ECOG performance of >1 was the only parameter influencing death during induction. Contrary to other experiences, age was not a prognostic factor for death during induction, CR, OS, PFS, or DFS [17]. In 11 patients with Burkitt's lymphoma and HIV infection treated at the National Institutes of Health (NIH) with a short course EPOCH and double-dose rituximab (SC-EPOCH-RR), the OS and PFS were 90% and 100%, respectively at 73 months of follow-up [18].

Primary effusion lymphoma

Primary effusion lymphoma is a rare B-cell neoplasm presenting as serous effusions in the pleural, peritoneal. or pericardial cavity without detectable tumor masses and universally associated with human herpesvirus-8 (HHV-8). Sometimes, secondary solid tumor masses can be seen in the pleura. Most cases are co-infected with EBV. The disease is extremely aggressive with median survival of 6 months and 1-year OS of ~40%. In a retrospective analysis of 28 patients, the median survival was 6.2 months after treatment with chemotherapy regimens, which included CHOP, high-dose methotrexate and iCDE [19]. Poor performance status and lack of antiretroviral therapy at diagnosis were predictors for poor survival [19]. Primary effusion lymphomas often have CD30 expression.

Rituximab 375 mg/m^2, IV, day 1 and day 5	[18]
Etoposide 50 mg/m^2/day, CI, day 1–5	
Doxorubicin 10 mg/m^2/day, CI, day 1–5	
Vincristine 0.4 mg/m^2/day, CI, day 1–5	
Cyclophosphamide 750 mg/m^2, IV, day 5	
Prednisone 60 mg/m^2/day, PO, day 1–5	
Dose adjustment based on hematologic and neurotoxicity	
Every 3 weeks. 2 cycles then interim PET. If PET negative, total 3 cycles. If PET positive, total 6 cycles	

In vitro experiments using primary effusion lymphoma cell lines and primary tumors demonstrate the ability of brentuximab vedotin, an anti-CD30 monoclonal conjugated antibody, to decrease cell proliferation, induce cell cycle arrest, and trigger apoptosis [20].

Case reports of patients treated with high-dose therapy and ASCT, allogeneic stem cell transplant (ALSCT), and adjunctive antiviral therapy are variable [21–23]. One patient managed with a reduced intensity conditioning with melphalan and fludarabine plus ALSCT from a matched HIV-negative sibling achieved a sustained remission for 31 months post-transplant [21]. In contrast, another patient managed with an ASCT relapse post-transplant [22]. Another case report describes the use of ganciclovir in conjunction with chemotherapy with a 2-year ongoing complete remission [23]. In the absence of prospective trials or large retrospective review, EPOCH- or CHOP-like regimens may be used.

Stem cell transplant in relapsed or refractory human immunodeficiency virus-related lymphoma

HIV patients with relapsed NHL can also benefit from high-dose chemotherapy followed by stem cell transplantation. The use of ASCT for HIV-related lymphoma was first published in a case report in 1996. The experience was notable for an increased risk of opportunistic infections. Since HAART development, feasibility of ASCT for HIV-associated NHL and HL has improved with demonstrated efficacy in early-stage and

chemosensitive disease. Across several trials, stem cell mobilization was effective [24–27]. A retrospective analysis from the European Group for Blood and Marrow Transplantation (EBMT) Lymphoma Working party of 68 patients with relapsed lymphoma showed a non-relapse mortality of 7.5% at 12 months [28]. Not achieving complete remission or having chemotherapy-resistant disease at ASCT was associated with worse PFS and OS. A subsequent EBMT study reporting matched case control study of HL and NHL patients undergoing ASCT stratified by HIV status showed similar relapse rates, PFS, and OS. There was a slight increase in non-relapse mortality at 1-year in HIV-positive patients versus HIV-negative patients (8% versus 2%, respectively) that did not reach statistical significance [29].

Primary central nervous system lymphoma

Primary central nervous system lymphoma (PCNSL) represents 15% of HIV-associated NHL. Comparatively, PCNSL occurs in 1% of all NHL. PCNSL is an AIDS-defining illness and commonly CD4 count is <200/ul at diagnosis [30]. In patients with AIDS, 20–30% of the CNS lesions are found to be primary CNS lymphoma with toxoplasmosis and progressive multifocal leukoencephalopathy accounting for many of the remaining cases. EBV has a pathogenetic role in these lymphomas and can be a reliable diagnostic marker [31]. Diagnosis is made through a combination of imaging by computed tomography (CT) or magnetic resonance imaging (MRI), toxoplasmosis serologic testing with an empiric trial of antibiotics, evaluation of EBV DNA in the cerebrospinal fluid (CSF), CSF cytology, or early brain biopsy.

PCNSL has an aggressive clinical course with a median survival of less than 2 months. Optimal therapy for PCNSL is unknown. CNS-penetrating regimens containing high-dose methotrexate, steroids, and antiretroviral therapy are recommended. In a small series of 15 patients treated with high-dose methotrexate intravenously at a dose of 3 g/m^2 every 14 days with leucovorin rescue, 47% of patient showed a CR with a median survival of 19 months [32]. Radiation therapy has historically been incorporated into the treatment. In a retrospective analysis of 111 patients with HIV-related PCNSL, those who received whole brain

radiation therapy had improved outcomes [33]. Since PCNSL occurs in the context of significant immunosuppression, patients can succumb to opportunistic infections. Monitoring the efficacy of the antiretroviral regimen is needed in the hope that enhancing the immune system may augment the response to therapy.

Other types of non-Hodgkin lymphoma

Rare cases of indolent lymphomas such as follicular lymphoma and mucosa-associated lymphoid tissue (MALT) lymphoma have been observed in patients with HIV infection. Rare cases of peripheral T-cell and NK T-cell lymphoma have also been described in case reports.

Human immunodeficiency virus-associated Hodgkin lymphoma

The relative risk of HIV patients to develop HL is higher than in the general population. In contrast to HL of the general population, HIV-associated HL is associated with EBV in 80–100% of cases. The IPS for a patient with advanced HIV-associated HL defined the following adverse risk factors: age over 45, male gender, stage IV disease, low albumin, anemia, lymphopenia, and leukocytosis. In patients with HIV-associated classical HL (cHL) 80% present with advanced stage disease and 70–96% present with B symptoms, defined by fevers over 100.4°F/38°C for 3 consecutive days, weight loss >10% body weight in 6 months, and drenching night sweats. These risks factors are similar for non-HIV-associated cHL.

In the post-HAART era, several chemotherapy regimens have been studied including ABVD, Stanford V, and BEACOPP [34–37]. However, the OS rates for Stanford V and BEACOPP did not compare well to ABVD despite inclusion of earlier stages in those studies. In a series of 62 patients with HIV and advanced stage HL treated with six to eight cycles of ABVD and HAART, 87% of patients achieved a CR and 5-year OS rate of 76% [37]. A large retrospective study of 224 patients demonstrated that HIV status did not influence OS and PFS for HL [38]. While BEACOPP demonstrated an improved CR compared to ABVD, only 66% of the BEACOPP-treated patients completed therapy compared with 82% in the ABVD trial [35,37]. In addition, 25% of the BEACOPP-treated patients died during

chemotherapy [35]. However, the use of a risk-adapted strategy for HL was reported with excellent results. In this study of 108 patients, early favorable patients received ABVD and 30 Gy of involved field radiation, early unfavorable patients received four cycles of BEACOPP or ABVD and 30 Gy IFRT, and advanced stage patient received six to eight cycles of BEACOPP. Patients with advanced HIV infection received ABVD. The CR rates for patients with early favorable, early unfavorable, and advanced stage HL were 96, 100, and 86%, respectively. The 2-year OS was 90.7% with no significant difference between early favorable (95.7%), early unfavorable (100%), and advanced HL (86.8%) [39]. As the use of 20 Gy and 30 Gy doses of RT proved equally effective in HIV-negative early stage HL, the lower dose of 20 Gy RT should be given in early stage HIV-associated HL [40].

Two cycles of ABVD followed by 20 Gy IFRT can be regarded as standard treatment for early favorable HL. In early stage unfavorable HL, four cycles of ABVD followed by 30 Gy IFRT is considered the standard of care. Patients with advanced stage HL should receive six cycles of ABVD [39].

Incorporation of novel agents such as brentuximab vedotin are being investigated in HIV-associated cHL. Results of the frontline use of brentuximab vedotin and AVD in HIV-negative and HIV-associated HL are highly anticipated.

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