The Management of HIV-Hodgkin Lymphoma

19

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Contents

19.1 Introduction

Since 1996, the availability of combination antiretroviral therapy (cART) has led to improvements in immune status among HIV-infected persons, reducing AIDS-related morbidity and prolonging survival. However, despite the impact of cART on HIV-related mortality, malignancies remain an important cause of death [1–3]. While the incidence of the two major AIDS-associated malignancies—Kaposi's sarcoma (KS) and high-grade non-Hodgkin lymphoma (NHL)—has dramatically declined in the cART era, the risk of non-AIDS-defining malignancies (NADM) such

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as Hodgkin lymphoma (HL), anal cancer, liver cancer, or lung cancer remains markedly elevated [4–6]. In patients with HIV-HL, curative-intent chemotherapy, modern cART, and supportive care have resulted in outcomes that are similar to that reported in HIV-negative HL [7–9].

19.2 Epidemiology

Compared with the general population, the incidence of HIV-HL is increased by approximately 10–15-fold with about 45–55 new cases per 100.00 person-years among HIV-infected patients [4–6, 10–18]. A summary of epidemiological studies reporting data on standardized incidence ratios is given in Table 19.1. The incidence of HIV-HL may have further increased in the decade after the introduction of cART. However, recent studies observed significant declining annual trends in hazard rate of HIV-HL in the range of −3.2% to −5% per year [19, 20].

Although in western countries patients with HIV-HL appeared to be approximately 4–5 years older than their HIV-negative counterparts, recent

Table 19.1 Studies providing standardized incidence ratios (SIR) for HL in persons with HIV/AIDS

Country	Period	*N*	HIV/AIDS	SIR	Reference
Switzerland	1985–2003	7304	HIV	17.3	Clifford [10]
				11.4 (HAART-nonuser)	
				36.2 (HAART-user)	
USA	1980–2002	31,7428	AIDS	9.4	Biggar [11]
				7.0 (1980–1989)	
				8.1 (1990–1995)	
				13.2 (1996–2002)	
France/Italy	1985–2005	8074	HIV	10.8	Serraino [12]
USA	1991–2002	57,350	HIV (initially AIDS-free)	5.6	Engels [13]
				2.8 (1991–1995)	
				6.7 (1996–2002)	
				4.5 (before AIDS)	
				15 (after AIDS)	
USA	1992–2003	54,730	HIV	14.7 (RR)	Patel [14]
				11.7 (1992–1995)	
				16.6 (1996–1999)	
				17.9 (2000–2003)	
UK	1983–2007	11,112	HIV	13.9	Powles [15]
				4.5 (1983–1995)	
				11.1 (1996–2001)	
				32.4 (2002-2007)	
USA	1984–2007	6949	HIV/AIDS	7.3	Seaberg [16]
Switzerland	1985–2006	9429	HIV/AIDS	9.2 (1985–1996)	Franceschi [4]
				21 (1997–2001)	
				28.1 (2002–206)	
USA	1996–2008	20,775	HIV	18.7	Silverberg [17]
Italy	1999–2009	5090	HIV	12.3	Calabresi [18]
France	1997–2009	84,504	HIV	33.5 (1997–2000)	Hleyhel [5]
				21.6 (2001–2004)	
				26.5 (2005–2009)	
USA	1996–2010	448,258	HIV/AIDS	7.7	Hernández-Ramirez [6]

HAART highly active antiretroviral therapy, *RR* standardized rate ratio

data from the United States and South Africa no longer indicate differences in the median age of HIV-positive and HIV-negative individuals with HL [21–23]. In high-prevalence areas such as South Africa, 29% of HL cases were reported to be attributed to HIV [23], while in the United States 4% of HL cases occurred in the setting of HIV [24]. Highest incidence rates are observed among African Americans with 17% of HL cases being HIV-related [24].

19.2.1 CD4 T-Cell Counts and Risk of HIV-HL

Median CD4 cell counts at HL diagnosis is roughly between 150 and 260 cells/μL [7–9, 11, 25–28]. However, data on the relationship of CD4 cell counts and the risk of HIV-HL are somewhat inconsistent. The risk of HIV-HL is highest with CD4 counts between 50 and 100 cells/μL [29–31]. In contrast, the US HIV/AIDS Cancer Match Study found that the incidence of HL decreased in persons with AIDS and falling CD4 cell counts [11]. This finding is in line with data from the German HIV-lymphoma cohort study showing that HL has become as common as non-Hodgkin lymphoma in patients with sustained viral suppression and limited immune deficiency defined as HIV RNA < 50 copies/mL for more than 12 months and CD4 cell counts of >200/μL [32]. However, an analysis of 16 European cohorts suggested that the risk of HL declined more recently and CD4 counts have increased with an adjusted hazard ratio of 0.27 for patients with more than 350 cells as compared to less than 50 cells/μL [30].

The first 6–12 months after initiating cART is the period with the highest risk of HIV-HL diagnosis [27, 31, 33, 34]. There is also some evidence of a higher risk within 12 months after cART initiation [35]. The increased risk within 6 months after initiating cART may, at least in part, be explained by the occurrence of an immune reconstitution inflammatory syndrome (IRIS) [35]. In one cohort, unmasking lymphoma IRIS, defined as lymphoma within 6 months after ART accompanied by a ≥0.5 $\log_{10}$ copies/mL HIV RNA reduction, was observed in 15% of HL cases [36].

Case-control studies showed a marked decline of CD4 cells by 100–168 cells/μL over 12 months prior to HL diagnosis [37, 38].

There is conflicting data on the relationship of HIV RNA and the risk of HIV-HL. While in the European Cohere database, HIV-1 viral replication was not associated with the risk of HIV-HL [30], a more recent study among HIV-infected veterans found that decreased HIV viral load was associated with lower risk of HL [39].

19.3 Pathology

There are differences in the pathology between HIV-HL and HL in the general population. First, the pathology is characterized by a high incidence of unfavorable histological subtypes such as mixed cellularity and lymphocyte depleted [7, 40]. Although a higher proportion of classical HL not otherwise specified (NOS) has been diagnosed in recent years [23, 24, 27], the MC predominance has not changed over the last decades [7–9, 11].

Second, HIV-HL exhibits special features related to the cellular background with the presence of fibrohistiocytoid stromal cell proliferation and the high number of neoplastic cells. These features may pose relevant difficulties in diagnosing and classifying the disease (Fig. 19.1). This finding contrasts with the rather low population of neoplastic cells usually found in HIV-unrelated HL [41]. Compared to HL in the HIV-negative setting, nodal CD4+ T-cells are decreased lacking CD4+ rosetting around HRS [42, 43].

Third, a high frequency of EBV association has been shown in HL (80–100%) tissues from HIV-HL [7, 44]. This contrasts to HIV-negative HL in which the EBV genome is observed in 20–50% only according to histological subtype and age at diagnosis. The EBV genome in HIV-HL has been reported to be episomal and clonal, even when detected in multiple independent lesions (Fig. 19.2). The elevated frequency of EBV association with HIV-HL indicates that

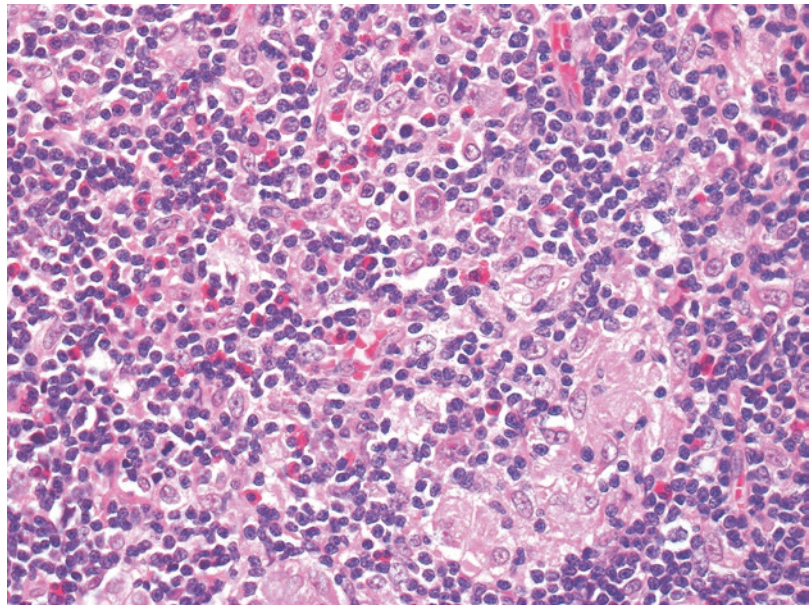

Fig. 19.1 Hodgkin and Reed-Sternberg (H/RS) cells with prominent central nucleoli in a case of HIV-HL (H&E, original magnification ×400)

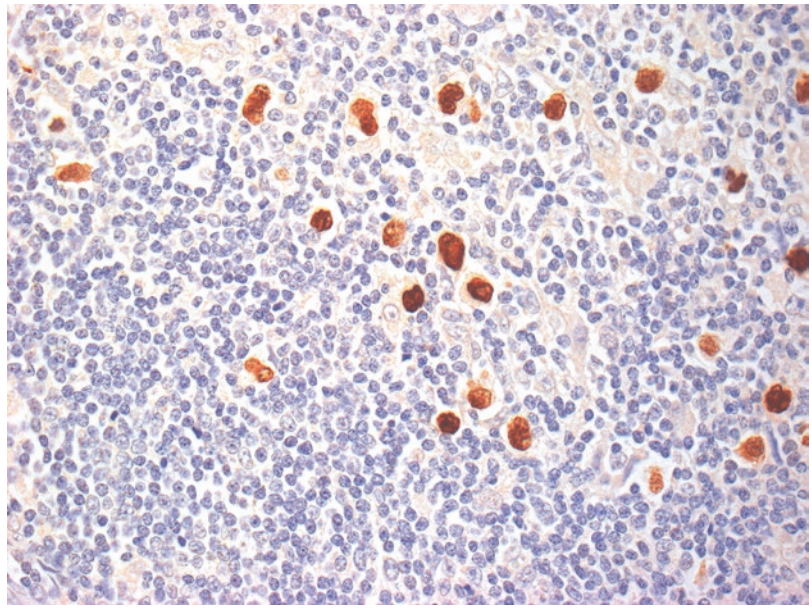

Fig. 19.2 In situ hybridization for EBV-encoded RNA (EBER) in H/RS cells of HIV-HL. The EBER signal is located to the nucleus. (original magnification ×400)

EBV probably represents a relevant factor involved in the pathogenesis of HIV-HL [45]. An etiologic role of EBV in the pathogenesis of HIV-HL is further supported by data showing that latent membrane protein 1 (LMP1) is expressed in the vast majority of HIV-HL cases [44, 45]. LMP1 and LMP2 are important for NF-KB and B-cell receptor signaling as well as for B-cell proliferation [44]. In addition, EBV infection induces an increase in T-regulatory cells and associated immunosuppressive cytokines (IL10) that may inhibit an immune response against EBV+ cells [46].

Finally, RS cells of classical HL of HIV-negative patients represent transformed B-cells originating from pre-apoptotic germinal center

(GC) B-cells [46]. Most HIV-related HL cases express LMP1 and display the BCL6−/CD138+/MUM1 IRF4+ (for multiple myeloma-1 interferon regulatory factor-4) phenotype, thus reflecting post-GC B-cells [47, 48]. The possible contribution of LMP1 to the loss of BCL6 expression seems plausible given that LMP1 can downregulate many B-cell-specific genes [49]. Loss of B-cell identity occurs during the normal differentiation of a GC B-cell into plasma cell or memory B-cell.

19.4 Clinical Presentation and Prognostic Factors

Approximately 65–80% of patients present with advanced stages or B-symptoms. Compared to HL in the general population, the bone marrow is more frequently involved and can be the only involved site of disease [23].

There is only limited evidence on the role of PET scans in the diagnosis of HIV-lymphoma. As ^{18}FDG can mark benign reactive nodes as seen in HIV infection, findings should be interpreted with caution. False-positive results may occur in ART-naive viremic patients and those with high HIV viral loads or low CD4 counts [50–55].

The routine diagnostic workup should include not only CD4 T-cell counts and HIV RNA but also hepatitis B and hepatitis C virus serology.

19.4.1 Prognostic Factors

Before the introduction of cART, results of chemotherapy and outcomes of patients with HIV-HL were not satisfactory [56–58]. This was mainly due to the poor tolerance of standard chemotherapy with high rates of opportunistic infections and toxic deaths. However, several cohort studies have shown that complete remission (CR) and overall survival (OS) rates were significantly higher in patients on cART as compared to those treated in the pre-cART era [59–63]. Factors independently associated with improved OS included response to cART, higher CD4 T-cell counts at HL diagnosis, and achievement of CR [61–63]. A large retrospective analysis of 596 HIV-HL patients from six European countries that included patients treated in the pre- and post-cART era found two parameters independently associated with OS: CD4 counts <200 cells/μL (HR 1.63) and IPS > 2 (HR 2.33) [64]. A multi-institutional retrospective study of 229 advanced HIV-HL patients who had received ABVD plus cART also showed CD4 cell counts <200/μL to be an independent adverse prognostic factor for PFS and OS [28].

Given the somewhat inconsistent data on the predictive power of the International Prognostic Score (IPS) in HIV-HL [7, 9, 25, 28, 65], treatment decisions should not be based on IPS.

An analysis from the National Cancer Database showed that among patients with HIV-HL who received chemotherapy, HIV status was not significantly associated with higher mortality in classical histological subtypes, while prognosis remained poor for those patients with undetermined histology, suggesting a more aggressive biology or other high-risk characteristics in this subgroup [66].

19.5 Management

19.5.1 Primary Chemotherapy

ABVD is the most common treatment for HIV-HL [28, 67–72]. In retrospective studies, ABVD (mainly 5–6 cycles) with concomitant cART resulted in CR rates of 74–89% and 5-year OS rates of 76–81% (Table 19.2). In comparative studies, no significant differences in the 5-year event-free survival (EFS) and OS were observed between HIV-positive and HIV-negative patients [8, 9, 72].

The use of the Stanford V regimen and concomitant cART resulted in CR rates of 81% and a 3-year OS rate of 51% in a prospective trial performed in the early cART era [25]. Although this represented a clear advantage compared to the pre-cART era, it was still below what is being reported in the general population.

Table 19.2 Results from retrospective studies on ABVD in HIV-HL in the cART-era

N	Recruitment period	Stage III/IV (%)	CD4 counts[a]	No cycles	CR rate (%)	OS	Toxic deaths	Comment	Reference
62	1996–2005	100	129/μl	6: 68% 8: 15% <6: 17%	87	76% (5-year) 65% (14-year)	5% ($n = 3$)	Concurrent cART in al pts	Xicoy [67] Xicoy [68]
93	1997–2010	80	185/μl	6	74	81% (5-year)	1% ($n = 1$)	Concurrent cART in 92/93 pts; no impact of HIV-status on OS	Montoto [8]
229	NR–2010	100	180/μl	5 (median, range 3-8)	83	78% (5-year)	NR	Concurrent cART in all pts	Castillo [28]
68	2008–2014	76	387/μl	3–4 (stage I/II)[b]	NR	94% (2-year)	NR	Concurrent cART in 67/68 pts; no impact of HIV-status on OS	Besson [9]
21	1995–2013	NR	182/μl	6–8	89	73% (10-year)	10% ($n = 2$)[c]	Concurrent cART in all pts; no impact of HIV-status on OS	Sorigué [72]

CR complete remission, *OS* overall survival, *NR* not reported
[a]Median, at HL diagnosis
[b]ABVD given to 65/68 pts, no. of cycles for stage III/IV not reported
[c]Death in induction

19.5.1.1 Stage-Adapted Approach

A stage-adapted treatment approach was investigated in another prospective trial [7]. Patients with early favorable HL received 2–4 cycles of ABVD followed by involved-field radiation, patients with early unfavorable disease were treated with 4 cycles of BEACOPP baseline or 4 cycles of ABVD, and patients with advanced HIV-HL received 6–8 cycles of BEACOPP baseline. In patients with advanced HIV infection, BEACOPP was replaced by ABVD; 94% received concurrent cART while on protocol therapy. The CR rate for patients with early favorable, early unfavorable, and advanced-stage HL was 96%, 100%, and 86%, respectively (Table 19.3). The 2-year OS of the entire study population was 90.7% with no significant difference between early favorable (95.7%), early unfavorable (100%), and advanced HL (86.8%). Treatment-related mortality in patients with advanced disease was 7% with three of four toxic deaths having occurred after the seventh cycle of BEACOPP. Thus, if the BEACOPP regimen is chosen, the number of cycles should be limited to six. In HIV-negative patients with HL, 6 cycles of the more intensified BEACOPP-escalated regimen proved superior to 8 cycles [73]. An overview of prospective clinical studies in HIV-HL in the cART era is given in Table 19.3 [7, 25, 74–76, 78].

Taken together, a stage-adapted treatment approach in HIV-HL is feasible and effective. Two cycles of ABVD followed by involved-field (IF) radiation therapy (RT) can be regarded as standard treatment for early favorable HL. 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 also be preferred in early-stage HIV-HL [77]. While the use of 4 cycles of ABVD followed by 30-Gy IF-RT

Table 19.3 Results from prospective studies on HIV-HL in the cART-era

Regimen	*N*	Recruitment period	Stage III/IV (%)	No cycles (median)	CR rate (%)	OS	Toxic deaths	Comment	Reference
Stanford V	59	1997–2001	71	Planned treatment in 69%[a]	81	51% (3-year)	2% (1/59)	2 deaths of OI 5-yr OS 54%	Spina [25, 78]
BEACOPP	12	1993–2002	92	6	100	75% (3-year)	17% (2/12)	cART in 4/12 pts	Hartmann [74]
VEBEP	73	2001–2008	70	NR	67	66% (3-year)	6% (4/73)	Results not yet fully published	Spina [75]
BEACOPP or ABVD	71	2004–2010	100	7	86	87% (2-year)	6% (4/71)	Fatal neutropenic sepsis in 3 of 4 pts beyond cycle 7	Hentrich [7]
ABVD or BEACOPP	14	2004–2010	Early unfavorable	4	100	100% (2-year)	0	1 relapse	
ABVD	23	2004–2010	Early favorable	2	96	96% (2-year)	4% (1/23)	1 fatal neutropenic sepsis after cycle 1	
ABVD	12	2010–2012	100	6 (PET2-) 2 (PET2+) + 6× BEACOPP	75	100% (2-year)	0	2-year PFS 83% with response-adapted treatment	Danilov [76]

VEBEP vinblastine, epirubicine, bleomycin, etoposide, prednisone; *NR* not reported
[a]12-week chemotherapy without dose reduction or delay in administration

may be considered standard of care for patients with early-stage unfavorable HL, six cycles of ABVD or BEACOPP baseline may be applied to patients with advanced-stage HIV-HL [69, 79].

19.5.1.2 PET-Adapted Approach

Although the predictive value of positive interim PET scans may be hampered by false-positive results in patients with HIV, data from a retrospective cohort study indicate a high negative predictive value of a ^{18}FDG-PET scan performed after 2–3 cycles of ABVD (PET2 or PET3) [80].

A response-adapted therapy based on early interim ^{18}FDG-PET was investigated in a US Intergroup Trial that included both HIV-positive and HIV-negative patients with HL [76]. Patients with stage III/IV classical HL who had CD4 cell counts ≥150/μL at registration or ≥250/μL at any time within 8 months prior to HL diagnosis received 2 cycles of ABVD followed by interim FDG-PET. Patients with a negative PET2 (Deauville ≤3) subsequently received four additional cycles of ABVD, while PET2-positive patients received 6 cycles of BEACOPP baseline. Ten of twelve (83%) HIV-HL patients who completed 2 cycles of ABVD achieved a negative PET2 status and two remained PET-positive with Deauville scores of four and five. With a median follow-up of 39 months, three patients developed progressive disease (all PET2-negative) resulting in an estimated PFS of 83% at 2 years.

In a study from South Africa that included 57 patients with HIV-HL, only 59.6% had a negative ^{18}FDG-PET (Deauville score 1–3) performed 8 weeks following completion of chemotherapy with ABVD. However, residual FDG avidity at sites of disease involvement identified during primary staging was not histologically confirmed and data on PFS and OS were not provided in this study [81]. The role of interim PET in HIV-HL should be further investigated in well-designed clinical trials.

19.5.1.3 Brentuximab Vedotin with Chemotherapy

Brentuximab vedotin (BV), an antibody-drug conjugate of the antimitotic agent monomethyl auristatin E targeting CD30, in combination with doxorubicin, vinblastine, and dacarbazine (AVD-BV) had superior efficacy to ABVD in the treatment of HIV-negative patients with advanced-stage HL [82]. In the setting of HIV, the combination of BV plus AVD is currently being investigated in AMC-085, a study by the AIDS Malignancy Consortium (NCT 01771107). Preliminary data on six patients showed grade 3 non-hematological toxicity in three patients and negative PET/CT scans in six of six patients following 6 cycles of therapy [83]. Thus, AVD-BV also seems feasible and effective in HIV-HL. The phase II portion of AMC-085 (51 subjects) is actively accruing in both the United States and France.

19.5.1.4 Combination Antiretroviral Therapy (cART)

Chemotherapy and concomitant cART have been shown to be feasible and effective during chemotherapy for HIV-HL. Furthermore, there is evidence that increased viremia during the 6 months after lymphoma diagnosis is associated with an increased risk of death between 6 months and 5 years after diagnosis [84]. Thus, cART should either be continued or initiated in parallel to chemotherapy according to current guidelines for the use of ART [69, 79, 85]. However, the potential of interactions between cytotoxics and antiretrovirals must be considered. Especially strong enzyme inhibitors such as ritonavir-boosted protease inhibitors or cobicistat should be avoided because of an increased risk of toxicity [86–90].

19.5.2 Relapsed and Resistant Disease

Patients with relapsed or refractory HIV-HL should be considered early for high-dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT) [69, 79]. Peripheral blood stem cells can be effectively mobilized [91], and autologous stem cell transplantation (ASCT) has been shown to be a useful treatment in HIV-infected lymphoma patients with chemotherapy-sensitive relapse [92–95]. In a prospective phase II study on 40 patients with chemotherapy-sensitive relapsed/persistent HIV-lymphoma (of which 15 had HL), HDCT plus ASCT resulted in 1-year and 2-year OS probabilities of 87% and 82%, respectively [95]. One-year transplant-related mortality (TRM) was 5.2%. Retrospective studies did not show significant differences in survival between HIV-positive and HIV-negative lymphoma patients undergoing ASCT [93, 94]. Notably, ASCT in HIV-infected individuals does not worsen the initial immune impairment and does not enhance viral replication [96]. However, in a comparative analysis by the EBMT, TRM was 8% in HIV-positive compared to 2% in HIV-negative patients [93]. A more recent analysis of patients with HIV-lymphoma undergoing ASCT also found an increased TRM of 9% [97].

19.5.2.1 Brentuximab Vedotin

Case studies indicate that brentuximab vedotin alone is a valid treatment option in relapsed/refractory HIV-HL [98, 99]. In a patient with relapsed HIV-HL, BV given as bridging therapy prior to planned ASCT resulted not only in disease stabilization but also in a transient loss of detectable HIV-1 RNA [99]. Another case report presented a patient with relapsed HIV-HL who experienced a second complete remission after treatment with BV [98].

19.5.2.2 Checkpoint Inhibitors

Immune checkpoint inhibitors (ICIs) have dramatically improved the survival of patients with certain cancers and demonstrated high efficacy in HIV-negative patients with relapsed/refractory HL [100, 101]. The anti-programmed cell death protein 1 (PD1) agent nivolumab also proved safe and efficacious in a number of case reports on relapsed/refractory HIV-HL. Of five cases published in the literature, three achieved a complete remission and two a partial remission during treatment with nivolumab [102–105]. A review of 73 HIV-infected cancer patients treated with ICIs showed a 9% rate of grade 3 or higher

immune-related events [106]. Patients with HIV did not experience increased side effects, and HIV remained undetectable in 93% of patients (26 of 28) known to have undetectable viral load before treatment. Most patients had received either nivolumab (39.7%) or pembrolizumab (35.6%) [106].

Ongoing prospective clinical trials will further define the role of ICI therapy in patients with HIV-HL.

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