HIV-Associated Malignant Lymphoma

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Summary

Acquired immune deficiency syndrome (AIDS)-related lymphomas (ARL) still represent a relevant field of clinical research. For most histological subtypes of ARL, no optimal initial therapy has been clearly defined so far. Rituximab plus chemotherapy is feasible and effective and should be offered to all patients with CD20-positive ARL regardless of their CD4 cell count. Combination antiretroviral therapy (cART) should be given concomitantly with chemotherapy, bearing in mind potential drug-drug interactions. Appropriate treatment of ARL is determined by a number of factors such as lymphoma stage, performance status, comorbidities, histological subtype, and immunosuppression. Treatment should principally be the same as in human immunodeficiency virus (HIV)-negative lymphoma patients. In HIV-related Hodgkin's lymphoma, high cure rates have been achieved with stage-adapted treatment approaches, albeit with worse outcomes compared to immunocompetent patients.

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Introduction

People living with human immunodeficiency virus (HIV) have an increased relative risk of developing non-Hodgkin's lymphoma (NHL) [1, 2]. The 2 most frequent subtypes are diffuse large B-cell

lymphoma (DLBCL) and Burkitt lymphoma/leukemia (BL). Both are acquired immune deficiency syndrome (AIDS)-defining illnesses, while Hodgkin's lymphoma (HL) is one of the most common non-AIDS-defining malignancies. As the life expectancy of HIV-positive individuals has increased in the cART era, malignancies have become an important cause of morbidity and mortality. Recent experience indicates that NHL is the most frequent event among all AIDS-related deaths [3].

Overall, patients with ARL can be treated successfully with standard chemotherapy regimens and concomitant cART without outstandingly high rates of toxicity [4]. The exact and accurate determination of disease stage and histological subtype, the performance status, and the recording of comorbidities are essential in finding an individual treatment approach.

Diagnosis and Staging

Whenever possible, diagnosis should be based on tissue biopsy and not on fine needle aspiration in order to correctly determine the specific lymphoma subtype. The World Health Organization (WHO) has classified ARL into 3 groups: lymphoma occurring in immunocompetent and HIV-positive patients; lymphoma occurring more specifically in HIV-positive patients; and lymphoma occurring in other immunodeficiency states (table 1).

Pretreatment evaluation (table 2) and staging should be performed according to the general recommendations for patients with malignant lymphomas [5, 6].

At the time of diagnosis, patients with ARL more often present with an advanced stage, B symptoms, extranodal involvement, and involvement of unusual sites (e.g., soft tissue, body cavity) compared to HIV-negative patients [7, 8].

Table 1. WHO classification of lymphoid malignancies associated with human immunodeficiency virus (HIV) infection [58]

Lymphoma also occurring in immunocompetent patients
Diffuse large B cell lymphomas
Centroblastic
Immunoblastic (including primary CNS lymphoma)
Burkitt and Burkitt-like lymphomas
Extranodal MALT lymphoma (rare)
Peripheral T cell lymphoma (rare)
Classical Hodgkin's lymphoma
Lymphoma occurring more specifically in HIV-positive patients
Primary effusion lymphoma
Plasmablastic lymphoma of the oral cavity
Lymphoma occurring in other immunodeficiency states
Polymorphic B cell lymphoma (PTLD-like) (rare)

CNS = Central nervous system; MALT = marginal zone lymphoma of mucosa-associated lymphoid tissue; PTLD = posttransplant lymphoproliferative disorder.

Table 2. Pretreatment evaluation/baseline investigations

Medical history
Physical examination
Blood count with differential, chemistries with electrolytes, liver and renal function, lactate dehydrogenase, urate, phosphate, C-reactive protein, immunoglobulins, serum protein electrophoresis, CD4 count, viral load, hepatitis B and C screening, pregnancy test in women
Computed tomography scan of the neck, chest, abdomen, and pelvis with contrast, ideally combined with positron emission tomography scan
Unilateral bone marrow biopsy
Electrocardiogram, echocardiography
Magnetic resonance imaging of the brain and spine if indicated
Cerebrospinal fluid examination if indicated
Upper and lower endoscopy if indicated

Chemotherapy and cART

The optimal initial therapy for ARL has not been clearly defined yet. The appropriate treatment regimen is determined by stage, performance status, comorbidities, and histological subtype, similar to HIV-negative lymphoma patients.

Current guidelines suggest that antiretroviral therapy should be initiated as soon as possible, irrespective of the CD4 cell count [9]. Delayed introduction of cART has been shown to significantly increase the risk of developing ARL [10]. Furthermore, a significant improvement in complete remission (CR) rates and survival for all patients with ARL receiving cART has been demonstrated [11].

There should be no restrictions for the prompt use of cART. The use of integrase inhibitors bears advantages concerning drug-drug interactions and confers a faster decline of the viremia. By contrast, CYP3A4 inhibitors such as ritonavir and cobicistat-containing regimens should be avoided wherever possible to prevent severe adverse effects [12, 13].

Prophylaxis against Opportunistic Infections

Cotrimoxazole prophylaxis against *pneumocystis jiroveci* pneumonia and toxoplasmosis should be administered during immunosuppressive treatment with chemotherapy or biological agents such as rituximab regardless of the CD4 cell count [9].

Diffuse Large B-Cell Lymphoma

DLBCL is the most common subtype of HIV-related lymphomas. It accounts for approximately 45% of all ARL [14].

R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, oral prednisone) is the most frequently used chemotherapy regimen for the treatment of HIV-related DLBCL. The only randomized phase III trial comparing CHOP versus R-CHOP conducted in the cART era showed an increased death rate from infectious complications, especially in patients with a CD4 count below 50 cells/ μ l and in those who received rituximab maintenance therapy which is not standard treatment for aggressive lymphomas [15]. However, a number of subsequent prospective clinical studies along with a pooled analysis of 1,546 patients demonstrated that the addition of rituximab to the CHOP regimen was beneficial and did not lead to a higher rate of death from infectious complications [16–19].

CR rates for R-CHOP immunochemotherapy range between 58 and 77% [15–17]. In the German AIDS-Related Lymphoma Cohort Study, the 2-year overall survival (OS) was reported to be 63% [14].

Dose-adjusted (DA) R-EPOCH (rituximab, etoposide, vincristine, oral prednisone, and bolus dose-escalated cyclophosphamide) with continuous infusion over 96-h showed high CR rates of 71 and 91%, respectively, in 2 phase II trials treating HIV-related DLBCL patients [20, 21]. However, a randomized prospective trial in HIV-negative DLBCL showed DA-R-EPOCH and R-CHOP to be equally effective [22]. Nevertheless, R-EPOCH seems to be a reasonable alternative to R-CHOP.

A central nervous system (CNS)-directed diagnostic work up may be performed according to the CNS International Prognostic Index (CNS-IPI) established for HIV-negative DLBCL [23]. As there is no conclusive data on CNS prophylaxis in HIV-related DLBCL, intrathecal or intravenous methotrexate should be given to prevent secondary CNS manifestation following the same criteria as in HIV-negative patients.

In summary, HIV-positive patients with DLBCL should be treated with rituximab-containing chemotherapy. Special care must be taken in patients with a CD4 count below 50 cells/ μ l, and these patients need appropriate antimicrobial prophylaxis, granulocyte-colony stimulating factor support, and prompt treatment of opportunistic infections. 6–8 cycles of R-CHOP are standard of care [24]. In Germany, a prospective trial evaluating the role of R-CHOEP in DLBCL is in preparation.

Burkitt Lymphoma/Leukemia

Patients with BL respond poorly to moderate chemotherapy regimens like CHOP [25]. In addition, up to 30% of BL patients (regardless of HIV status) will develop CNS involvement [26]. HIV-negative patients with BL are mostly treated with dose-intensive combination chemotherapy containing rituximab and CNS prophylaxis. In Germany, the vast majority of BL patients receive the B-cell acute lymphoblastic leukemia (B-ALL)/NHL protocol of the German Multicenter Study Group for the Treatment of Adult Acute Lymphoblastic Leukemia (GMALL). This regimen is also feasible and effective in HIV-positive BL patients, resulting in a CR rate of 80% and a 4-year OS of 72% [21]. However, toxicity is high with 11% of deaths upon induction reported in 2 cohorts involving a total of 81 patients [27].

Other dose-intensive regimens like CODOX-M/IVAC (cyclophosphamide, doxorubicin, vincristine, methotrexate, etoposide, ifosfamide, cytarabine) or HyperCVAD/HD-MTX (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone followed by high-dose methotrexate) in combination with rituximab show similar results with CR rates between 63 and 93% [28–30].

Alternatively, R-EPOCH may be considered for HIV-positive patients with BL, but so far there is only very limited (although promising) data with this approach in the setting of HIV [20] and further studies are required before recommendations regarding its use in this entity can be made. Therefore, patients with HIV-related BL should be treated with intensive regimens such as the B-ALL/NHL 2002 protocol (including CNS prophylaxis and rituximab), provided the patient's performance status allows for such intensive treatment.

Plasmablastic Lymphoma

Plasmablastic lymphoma (PBL) has been estimated to account for less than 3–12% of all HIV-related lymphomas [14, 31] featuring a lack of CD20 expression and generally high expression of CD138, a well-differentiated plasma cell marker [32]. Due to its very aggressive clinical course and the disappointing outcome with CHOP or CHOP-like regimens, more intensive chemotherapy protocols have been suggested such as the B-ALL/NHL protocol, CODOX-M/IVAC, or consolidation with high-dose (HD) chemotherapy and subsequent autologous stem cell transplantation (SCT). However, the results did not show superior outcomes [33–35], while early clinical stage and complete response to chemotherapy were associated with a better outcome [34]. Bortezomib alone or in combination with chemotherapy has been used with some efficacy in HIV-related PBL [36]. The best approach to therapy still remains unclear.

Primary Effusion Lymphoma

This very rare entity is associated with a poor prognosis, even in the cART era, with a median OS in the range of 6–10 months [37,

38]. No randomized trials exist. If possible, patients with primary effusion lymphoma (PEL) should be entered into clinical trials with novel treatment approaches like bortezomib [39] or other targeted therapies because of the disappointing results of 'standard' treatment with CHOP or CHOP-like regimens [40].

Treatment of Relapsed or Refractory Systemic HIV-Related NHL

Before the introduction of cART, treatment of patients with relapsed or refractory ARL was disappointing with a median survival of only a few months. However, with the continuous improvement in immune recovery, several clinical trials have shown that intensive salvage regimens followed by HD chemotherapy and autologous SCT are feasible and effective in chemotherapy-sensitive relapsed or refractory ARL [41, 42]. A recent large series by the European Society for Blood and Marrow Transplantation (EBMT) suggested that in the cART/chemoimmunotherapy era, the variables that impact the prognosis of autologous SCT for ARL are related to the characteristics of the lymphoma and pretreatment rather than to HIV characteristics [43].

Platinum-based regimens such as ICE (ifosfamide, carboplatin, etoposide) or DHAP (cisplatin, HD cytarabine, dexamethasone) as used in HIV-negative patients are common second-line regimens, usually combined with rituximab, leading to response rates of about 60% [44].

Allogeneic SCT has been performed in selected cases of relapsed HIV-related lymphoma treated in the cART era [45–47]. Both, reduced intensity conditioning and myeloablative conditioning proved feasible. However, given the limited amount of experience and the lack of long-term efficacy data, no firm conclusions can be drawn. The results of a phase II multicenter trial will provide further insight into the feasibility and safety of allogeneic SCT for HIV-infected patients with chemotherapy-sensitive hematological malignancies (clinicaltrials.gov/ct2/show/NCT01410344).

Brentuximab vedotin has been successfully used in a patient with HIV infection and relapsed anaplastic large cell lymphoma [48].

Primary CNS Lymphoma

Since the introduction of cART, the incidence of HIV-associated primary CNS lymphoma (PCNSL) has decreased significantly. The OS among AIDS-related PCNSL patients has improved over time but remains poor [49], and no prospective trials are available.

In HIV-negative patients with PCNSL, the treatment of choice are protocols containing HD methotrexate and HD cytarabine in combination with rituximab. This approach may now be offered to the majority of HIV-positive patients, in particular those with a well-controlled HIV viral load and good performance status. If treatment is well tolerated and treatment response is documented, consolidation with HD chemotherapy and subsequent autologous SCT may be considered [50, 51].

Table 3. German Hodgkin's Lymphoma Study Group (GHSG) risk factors defining treatment groups in Hodgkin's lymphoma (adapted from [59])

Early stage
CS I–II without risk factors
Early unfavorable stage
CS I, CS IIA with ≥ 1 risk factor; CS IIB with risk factors C/D but no A/B
Advanced stage
CS IIB with risk factors A/B, CS III–IV
Risk factors: large mediastinal mass (A), extranodal disease (B), elevated erythrocyte sedimentation rate (C), ≥ 3 nodal sites (D).
CS = Clinical stage.

Monotherapy with CNS-penetrating agents like HD methotrexate combined with radiotherapy or whole-brain radiotherapy alone are generally well tolerated palliative approaches and can be useful in reducing symptoms [52].

Hodgkin's Lymphoma

As in most ARL, HIV-positive patients with HL showed poor outcomes and treatment was associated with significant toxicity before the introduction of cART [53]. However, current data from prospective and retrospective trials have shown promising results. In the prospective German multicenter study using a stage-adapted treatment approach, CR rates were 96% for early-stage favorable, 100% for early-stage unfavorable, and 86% for advanced-stage HL [54]. 2 comparative studies on ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) in HL showed that HIV infection did not adversely affect progression-free and event-free survival or OS [41,

55]. In 1 of the studies in patients with HIV-related HL, most of them with stage III/IV disease, 4–6 cycles of ABVD led to a CR rate of 74% with a 5-year OS of 81% [56].

Treatment of HIV-positive HL patients should be stage-adapted (table 3). Patients with early favorable disease should receive 2 cycles of ABVD with subsequent 20-Gy involved-field radiotherapy. 4 cycles of ABVD followed by 30-Gy involved-field radiotherapy is the treatment of choice for patients with early unfavorable disease, and patients with advanced stage should receive 6 cycles of BEA-COPP baseline (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisolone) or 6–8 cycles of ABVD [54].

While no data are currently available on the use of PD1 inhibitors in HIV-related HL, brentuximab vedotin proved effective in a patient with relapsed HL [48]. The combination of brentuximab vedotin and AVD (adriamycin, vinblastine, dacarbazine) is currently being investigated in the upfront treatment of advanced-stage HIV-related HL (clinicaltrials.gov/ct2/show/NCT01771107) [57].

In conclusion, there is a large body of evidence that HIV-infected individuals who are treated with standard therapies and cART for DLBCL, BL, and HL now have an outcome similar to that of their uninfected counterparts. However, optimal therapies for entities such as PBL, PEL, or high-risk DLBCL have yet to be defined.

Disclosure Statement

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