TREATMENT OF HIV-ASSOCIATED BURKITT LYMPHOMA

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ABSTRACT

Burkitt lymphoma (BL) is a highly aggressive B-cell malignancy, occurring with increased frequency among patients infected with HIV. For several years, the immunocompromised state of HIV-positive patients was advocated as a sufficient reason to avoid the intensive chemotherapeutic regimens used in HIV-negative BL. However, with the introduction of the highly active antiretroviral therapy (HAART), the subsequent improvement of the immunological state of HIV-positive patients, and the disappointing results of less intensive schedules, investigators began to apply the same chemotherapeutic regimens used as a gold standard in HIV-negative non-Hodgkin lymphoma (NHL), including the use of rituximab. Despite promising results of different schedules in early-phase studies, agreement on the treatment of HIV-positive BL is still lacking, and further trials are needed to define a standard of care. Moreover, new treatment frontiers need to focus on improving the outcome for patients with advanced immunosuppression, unfavourable prognostic features- such as advanced stages and high International Prognostic Index (IPI) scores - and for those with adverse tumour biology.

This paper aims to revise the main epidemiological and physiopathological features of HIV-positive BL, to summarise the most relevant steps in the treatment of affected patients, and to elucidate the role of HAART in allowing HIV-positive patients to be managed with the therapeutic strategies currently used in HIV-negative patients with BL.

Keywords: Burkitt lymphoma, AIDS, HIV, rituximab, chemoimmunotherapy, myc.

INTRODUCTION

Burkitt lymphoma (BL) is an aggressive B-cell non-Hodgkin lymphoma (NHL) with a high cellular turnover and a cell-doubling time of 24–48 hours. The World Health Organization's (WHO) classification of haematological malignancies describes three clinical and epidemiologic variants of BL: endemic, sporadic and HIV-associated BL (HIV-BL).[1] BL accounts for up to 20% of lymphoproliferative malignancies diagnosed in HIV-positive subjects. In Western countries, symptoms related to BL are often the first clinical clues of AIDS onset.[2] The untamed replication kinetics of cancer cells translates into the clinical presentation of the lymphoma, with an extensive extranodal involvement, and high mortality rate when treated with conventional chemotherapy regimens used in patients with diffuse large B-cell lymphoma (DLBCL). For this reason, several chemotherapeutic regimens for patients with HIV-BL have been developed in the last few years. These combinations often include the anti-CD20 monoclonal antibody rituximab, resulting in combinations with excellent efficacy, but important limitations in feasibility and tolerability.

This paper is focused on the different chemotherapeutic regimens used to treat HIV-BL, the impact of the introduction of the highly active antiretroviral therapy (HAART), the role of rituximab and other important drugs, and the rapport between toxicity and efficacy of each chemoimmunotherapy

regimen. Evidence from different trials concerning the introduction of the HAART and the use of rituximab in the chemotherapeutic regimens, which still lack unanimous consent, will be presented as well.

EPIDEMIOLOGY AND RISK FACTORS

HAART, widely used in clinical practice from 1996, has dramatically changed the natural history of HIV infection and AIDS development and has significantly improved the outcomes of HIV-positive patients in terms of host immune response, reduction in opportunistic infections, and incidence of HIV-related NHL (HIV-NHL). Before HAART, the incidence of NHL in HIV-positive patients was 60-200 times higher than in HIV-negative patients;[3] the incidence of HIV-NHL decreased from 13.6 per 100,000 person-years before 1996 to only 1.8 per 100,000 person-years between 2002 and 2006.[4] Nevertheless, the incidence HIV-BL has not been affected by HAART with progressive rates increasing.[5]

The risk of development of BL in HIV-positive patients is 15-fold higher than HIV-negative ones.[6] The mean age of onset is 38 years old, and males are more likely to be affected. Conversely to the incidence of other HIV-NHL, which increases with age, the incidence of HIV-BL shows three different age-related peaks: infancy, adulthood and old age. This trimodal trend has been reported also in the HIV-negative population,[7] and underlies the possibility that age itself, instead of age-related level of immunosuppression, could play a role in the development of HIV-BL. A different relative risk for the development of HIV-BL as related to the way of HIV transmission, has failed to be demonstrated.

PATHOGENESIS

BL development is strongly related to the overexpression of *c-myc* oncogene. The gene encoding for MYC, a cell-cycle regulator, is located on the long arm of chromosome 8. There are three types of balanced translocation, common to all the clinical variants of BL, involving the *c-myc* locus: the t(8;14)(q24;q32), which involves immunoglobulin heavy chain (IGH) genes located in 14q32 and is detected in 70-80% of BL patients; the t(2;8)(p12;q24), which involves IG kappa-light chain locus in the 2p12, and is detected in 15% of BL; and the t(8;22)(q24;q11), which involves IG lambda-light chain genes in the 22q11 and is detected in 5% of BL patients. In all cases, MYC locus is downstream to IG gene enhancers, causing gene overexpression.[8] Expression of MYC in normal B-lymphocytes induces cell apoptosis by a p53-dependent pathway. In malignant B-cells, apoptosis is prevented by mutations in TP53 tumour suppressor gene. Moreover, p53-independent pathways, such as overexpression in B-cell lymphoma 2 (Bcl-2), due to down-regulation of Bim protein, inhibits apoptosis.[9] However, in HIV-positive patients who are not diagnosed with HIV-BL translocation in *c-myc* locus are frequent, which suggests that this mechanism alone is not enough to induce neoplastic proliferation of B-lymphocytes. The translocation seems to be enhanced when the enzyme activation-induced cytidine deaminase (AID) is over-expressed. AID is involved in the IGH class switch.[7] Enzyme induction is favoured by chronic antigenic stimulation of B-lymphocytes, or by signalling, which enhances enzyme over-expression itself.

As in other lymphomas, relative risk increases with high HIV viral load and with the duration of exposure to such elevated viral load.[10,11] These features suggest a pathogenic role of HIV in BL, even though molecular mechanisms of the potential oncogenic effect of HIV have never been demonstrated.[12] Putative mechanisms regard the effect of elevated viral loads inducing a chronic antigenic stimulus for B-cells and cytokines production that may enhance the activity of the AID, promoting *c-myc* translocation and survival signalling to mutated B-lymphocytes.[10] Moreover, one of the HIV envelope proteins, the CD40 ligand, is able to activate AID itself,[13] and Trans-Activator of Transcription (TAT) protein is able to promote B-lymphocytes cell cycle with two different mechanisms. On one hand, TAT enhances the activation of cellular genes, such as IL-6 and IL-10; on the other, TAT inhibits Rb2/p130 protein, a tumour suppressor gene involved in halting cell cycle from G0/G1.[14,15]

Risk for the development of HIV-BL increases with CD4-positive cell count: the majority of patients have ≥250/μL CD4, while the risk lowers when CD4 are <50/μL, with only 15% of cases in patients showing CD4 <100/μL. This is in contrast with other HIV-NHL where the relative risk increases with lowering of CD4.[16] An adequate number of functional CD4 cells seems to be necessary for HIV-BL development and, paradoxically, a competent immune system may have a causative role.[17] CD4+ lymphocytes may be involved in survival signalling to B-lymphocytes of germinal centres, carrying *c-myc* translocation, and in preventing cell death. On the contrary, low CD4 counts may fail to protect aberrant B-lymphocytes, promoting the initiation

Table 1. Diagnosis and staging of HIV-BL.

DIAGNOSIS		
HISTOLOGY	The cells seem to be molded and the cytoplasm is deeply basophilic with squared-off cytoplasmic margins. A 'starry sky' appearance is due to scattered tangible body-laden macrophages that contain apoptotic tumour cells.[79] There are three histologic variants, all of them having very high mitotic rates, with a Ki67 proliferation index close to 100%, and with a high cellular turnover suggested by increased apoptosis.	
	BL with plasmacytoid differentiation	- Most common in HIV-BL - It is associated with EBV in 50% to 70% of cases - It is characterised by medium-sized cells with abundant basophilic cytoplasm and eccentric nuclei
	BL classic	- Accounts for 30% of HIV-BL and it resembles endemic BL - It is associated with EBV in 30% of cases - It is characterised by intermediate-size cells containing coarse chromatin and prominent basophilic nucleoli
	Atypical BL	- It is characterised by cells with greater nuclear pleomorphism and fewer but more prominent nuclei
IMMUNOPHENOTYPE	- Mature B-cell with germinal centre cell differentiation and expression of surface immunoglobulins (sIgs) with light chain restriction - Positive for: CD19, CD20, CD22, CD79a, CD10, Bcl-6 - Negative for: CD5, CD23, terminal deoxynucleotidyl transferase (TdT) - Bcl-2: usually negative; however, Bcl-2 can be expressed in 10% to 20% of cases[80]	
CYTOGENETICS	Karyotypic analysis of neoplastic cells are aimed to identify *c-myc* translocation, by fluorescence in situ hybridisation. Three patterns can be observed.	
	Balanced translocation involving c-myc locus (80-95%)	- *C-myc* translocations are not exclusive of BL, but may be found in other types of NHL, such as in 10-15% of cases of DLBCL, and identifies worse prognosis
	Normal karyotype (10%)	- Molecular mechanisms leading to MYC deregulation are still under investigation[81]
	Complex karyotype (rare)	- Worse prognostic factor[82]
STAGING	- For adult patients Cotswold-modified An Arbor Staging system is used[83] - For paediatric patients St Jude/Murphy Staging system is used (stage IV defined by CNS or bone-marrow involvement)[84]	
PHYSICAL EXAMINATION	- Evaluation of performance status are mandatory	
BLOOD CHEMISTRY	- Full blood count (CD4 count), complete biochemical profile, serum lactate dehydrogenase and uric acid (to assess tumour turnover), viral infections assessment (EBV, HIV viral load, hepatitis B/C viruses)	
INSTRUMENTAL EXAMS	- ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT),[85,86] enhanced total body CT scan - Bone marrow aspirate and biopsy (including flow cytometry and cytogenetic evaluations) - Cerebrospinal fluid sampling by lumbar puncture, with cytologic examination, flow cytometry, physico-chemical examination - Brain MRI (if CNS involvement is suspected or confirmed) - Echocardiography - Some exams should be indicated in the case of clinical or biochemical suspicion of organ involvement, for instance endoscopic studies	

of cell death programs. Moreover, with a lower CD4 number, fewer B-lymphocytes are activated and *c-myc* translocation rate lowers.[7]

Epstein-Barr virus (EBV) was detected in <40% of cases of HIV-BL and in ~100% of cases of endemic BL.[18] This peculiarity seems to lessen the causative role of this virus in this malignancy. One possible explanation is that neoplastic changes occur in highly proliferating B-lymphocytes in the germinal centre in EBV-negative BL, while in EBV-positive cases, they involve memory B-cells, whose survival is promoted by viral infection itself.[19] EBV is able to promote lymphocytes oncogenic transformation, not only with a chronic antigenic stimulation and the consequent cytokines deregulation, but also by means of specific protein production. Epstein-Barr nuclear antigen 1 (EBNA-1) protein allows EBV latent persistence in B-cells genome, increases genetic instability of B-lymphocytes, and could enhance those mutations involved in the selection of the neoplastic clone.[20] Moreover, production of latent membrane protein 1 (LMP-1) promotes both proliferative signalling, via the activation of NF-kB pathway, and anti-apoptotic stimulation via BCL-2 overexpression in B-cells carrying *c-myc* translocation.[21]

CLINICAL PRESENTATION, DIAGNOSIS, STAGING

HIV-BL is a highly aggressive disease, usually presenting with systemic symptoms, advanced stage disease, as well as extensive extranodal involvement. With respect to sporadic BL, HIV-BL shows more common bone marrow infiltration (46% versus 20%), bulky disease (54% versus 13%), less common abdominal lesions (46% versus 91%), rarer leukaemic dissemination, and more frequent meningeal involvement (38% versus 14%), the latter being asymptomatic in 25% of cases.[22]

In the absence of pathognomonic features, diagnosis is formulated on the basis of histologic, immunophenotypic and cytogenetic investigations on the excision biopsy of an involved organ, preferring a lymph node (Table 1). Once the diagnosis is obtained, following the WHO criteria,[1] staging must be performed (Table 1).

TREATMENT

General Background

BL is a highly chemosensitive malignancy, achieving high response rates with available chemotherapy combinations. However, patients who reach complete remission (CR) must be closely monitored, as most relapses occur within the first year[23] and are uncommon after 2 years.[24] While some studies had demonstrated the prognostic role of the International Prognostic Index (IPI), and CD4 cell count and complex karyotype,[25] a therapeutic decision is not usually based on these variables. Most patients are managed with intensified chemoimmunotherapy combinations independently of IPI risk and extension of disease. Only Central Nervous System (CNS) involvement can change therapeutic choice in HIV-BL. Patients with HIV-BL should be managed with modern chemotherapy (see below) in cancer centres with appropriate expertise. This is an important issue considering that failure to achieve complete remission (CR) after first-line chemotherapy is a definitively negative prognostic event.[25] Importantly, the management of these patients is complex, mostly due to the high rates or co-morbidity, co-infections and treatment-related events, as well as the necessity to prevent complications and to manage symptoms. Prevention and treatment of tumour lysis syndrome with alkaline infusions and allopurinole/rasburicase administration, and appropriate G-CSF use are strongly encouraged. While actively treated patients must undergo antifungal prophylaxis with fluconazole, antiviral prophylaxis with acyclovir and prophylaxis for *Pneumocystis jiroveci* with trimethoprim-sulfamethoxazole. During CT, nadir antibiotic prophylaxis with a quinolone is appropriated.

Due to the high frequency of CNS involvement, both at presentation and relapse, the use of intravenous drugs able to penetrate the blood brain barrier and to achieve therapeutic concentrations in the CNS, as well as drug delivery by intrathecal route, are required.

HAART is a relevant component of the treatment of HIV-NHL, and BL is no exception. Before 1996, no standardised treatment was available for HIV-BL, since all HIV-NHL types were managed with the same strategy. Low-dose and less-intensive combinations led to a poor outcome in patients with HIV-BL; CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) regimen was associated with a CR rate of 30-50% and a median survival of 6-9 months,[26,27] and 58% and 18 months, respectively, with the CDE infusion combination.[28] Near 60% of deaths were due to AIDS-related events and not to lymphoma. As a consequence, less intensive approaches have been proposed (m-BACOD), with a median survival

Table 2. Schedule of Hyper-CVAD, PETHEMA-LAL3/07-GMALL regimen (± Rituximab), CODOX-M/IVAC standard e/o modified, DA-EPOCH (± Rituximab).

Cyclophosphamide (CTX), vincristine (VCN), doxorubicin (DOXO), dexamethasone (DEX), methotrexate (MTX), cytarabine (Ara-C), Prednisone (PDN), ifosfamide (IFO), teniposide (VM26), rituximab (R), vindesine (VND), etoposide (VP16), therapy intra-thecal (TIT), intravenous (i.v.), continuous infusion (civ.), orally (o.), days (d), hours (h), patients (pts), chemotherapy (CT), absolute neutrophil count (ANC).

a) Ara-C to 1 g/m^2 if pts>60 y.
b) MTX 0.5 g/m^2 if pts>50 y.
c) Two additional doses of rituximab were administered 3 and 6 weeks after the last C cycle.
d) Depending on centre.
e) Maximum dose 750 mg/m^2.
f) VP16 reduce by 25% if ANC nadir<500/μL or platelets<25,000/μL (both for at least 3 d) If this occurs during a cycle in which no CTX was given or creatinine clearance<40 mL/min.
g) DOXO reduce by 25% if ANC nadir<500/μL or platelets<25,000/μL (both for at least 3 d) if this occurs during a cycle in which no CTX was given or direct bilirubin>2.5 mg/dl.
h) VCN reduce to 0.3 mg/m^2/day if constipation or unable to walk on heels; reduce to 25% if direct bilirubin>2.5 mg/dl or creatinine clearance<40 mL/min; discontinue if difficulty ambulating.
i) R discontinue if skin/mucositis attributed to R.

HYPER-CVAD REGIMEN[49]

- **8 courses** of alternating intensive CT every 3 weeks
- **TIT:** 12 mg of MTX d 2 and 100 mg of Ara-C d 7 every cycle
- **HAART** during CT is recommended

Odd-numbered Courses (1-3-5-7)				Even-numbered Courses (2-4-6-8)			
CTX	300 mg/m^2	i.v. twice	d 1-3	**MTX**	1000 mg/m^2	i.v. over 24 h	d 1
VCN	2 mg	i.v.	d 4, 11				
DOXO	50 mg/m^2	i.v.	d 4	**Ara-C**[a]	3000 mg/m^2	i.v. twice	d 2-3
DEX	40 mg/d	i.v. or o.	d 1-4 and d 11-14				

PETHEMA REGIMEN[53]

- **8 courses** of alternating intensive CT every 3 weeks
- **Pre-phase** (to prevent lysis syndrome) **CTX** 200 mg/m^2 i.v. and **PDN** 60 mg/m^2 i.v. d 1-5
- **TIT:** MTX 12 mg, Ara-C 30 mg, hydrocortisone 20 mg d 1 and 5 of each cycle
- **HAART** during CT is recommended

Odd-numbered A-cycles (induction and 2-4-6)				Even-numbered B-cycles (1-3-5-7)			
VCN	2 mg	i.v.	d 1	**VCN**	2 mg	1.v.	d 1
MTX[b]	3000 mg/m^2	i.v. over 24 h	d 1	**MTX**	3000 mg/m^2	i.v. over 24 h	d 1
IFO	800 mg/m^2	i.v.	d 1-5	**CTX**	200 mg/m^2	i.v.	d 1-5
DEX	10 mg/d	i.v. or o.	d 1-5	**DEX**	10 mg/d	i.v. or o.	d 1-5
VM26	100 mg/m^2	i.v.	d 4-5	**DOXO**	25 mg/m^2	i.v.	d 4-5
Ara-C	150 mg/m^2	i.v. twice	d 4-5				

PETHEMA REGIMEN + R[54]

- **6 courses** of alternating intensive CT every 4 weeks
- **Pre-phase** (to prevent lysis syndrome) **CTX** 200 mg/m^2 i.v. and **PDN** 60 mg/m^2 i.v. d 1-5
- **TIT:** MTX 15 mg, Ara-C 40 mg, DEX 20 mg d 2 and 6 of each A e B cycles
- **HAART** during CT is recommended

A-cycles (1-4)				B-cycles (2-5)				C-cycles (3-6)[c]			
R	375 mg/m^2	i.v.	d 1	**R**	375 mg/m^2	i.v.	d 1	**R**	375 mg/m^2	i.v.	d 1
VCN	2 mg	i.v.	d 2	**VCN**	2 mg	i.v.	d 2	**VDN**	3 mg/m^2 (max. 5 mg)	i.v.	d 2

MTX	1500 mg/m²	i.v. over 24 h	d 2	**MTX**	1500 mg/m²	i.v. over 24 h	d 2	**MTX**	1500 mg/m²	i.v. over 24 h	d 2
IFO	800 mg/m²	i.v.	d 2-6	**CTX**	200 mg/m²	i.v.	d 2-6	**DEX**	10 mg/d	i.v.	d 2-6
VM26	100 mg/m²	i.v.	d 5-6	**DEX**	10 mg/d	i.v.	d 2-6	**VP16**	250 mg/m²	i.v.	d 5-6
Ara-C	150 mg/m²	i.v. twice	d 5-6	**DOXO**	25 mg/m²	i.v.	d 4-5	**Ara-C**	2000 mg/m²	i.v. twice	d 6

CODOX-M/IVAC REGIMEN[55]

- **low risk pts** received 3 cycles of CODOX-M
- **high risk pts** received alternating cycles of CODOX-M, IVAC, CODOX-M, IVAC
- **HAART** during CT is recommended

CODOX-M				IVAC			
CTX	800 mg/m²	i.v.	d 1	**IFO**	1500 mg/m²	i.v.	d 1-5
CTX	200 mg/m²	i.v.	d 2-5	**VP16**	60 mg/m²	i.v.	d 1-5
DOXO	40 mg/m²	i.v.	d 1	**Ara-C**	2000 mg/m²	i.v. twice	d 1-2
VCN	1.5 mg/m²	i.v.	d 1, 8, 15				
MTX	6720 mg/m²	i.v. over 24 h	d 10				
TIT Ara-C 70 mg d 1, 3 MTX 12 mg d 15				**TIT** MTX 12 mg d 5			

CODOX-M/IVAC REGIMEN Modified

Noy et al.[56]	**R** 375 mg/m² d 1, **CTX** 800 mg/m² twice d 1-2, **VCN** 2 mg cap, **MTX** 3000 mg/m²
Montoto et al.[58]	**VCN** 1.5 mg/m² (cap 2 mg), **MTX** 3000 mg/m² **for pts>65 y** MTX decreased to 1000 mg/m², IFO decreased to 1000 mg/m², Ara-C decreased to 1000 mg/m²
Barnes et al.[60]	**R** 375 mg/m² d 1, **CTX** 800 mg/m² twice d 1-2, **DOXO** 50 mg/m², **VCN** 2 mg cap, **MTX** 3000 mg/m², **TIT** Ara-C 50 mg
Rodrigo et al.[57]	**CTX** 800 mg/m² twice d1-2, **DOXO** 50 mg/m², **VCN** 2 mg cap, **R** 375 mg/m² d 8 (of CODOX-M) and d 4 (of IVAC), **MTX** 3000 mg/m² or standard[(d)], **TIT** Ara-C 50 mg (during CODOX-M) and MTX 12 mg (twice during IVAC) or standard[(d)]

DA-EPOCH REGIMEN[65]

- **6 courses** every 3 weeks
- **TIT** total 8 MTX 12 mg d 1,5 of cycles 3 through 6

Oral therapy d 1-5	**PDN** 60 mg/m²/d
Infused agents (civ. of 96 h) d 1-4	**VP16**[f] 50 mg/m²/d, **DOXO**[g] 10 mg/m²/d, **VCN**[h] 0.4 mg/m²/d
Bolus agents d 5	
CTX First cycle	After cycle 1 (DA-CTX[e])
if CD4cells≥100/µL CTX 375 mg/m²	if nadir ANC>500/µL or platelets>25,000/µL CTX ↑187 mg above previous cycle
If CD4cells<100/µL CTX 187 mg/m²	if nadir ANC<500/µL or platelets<25,000/µL CTX ↓187 mg above previous cycle

DA-EPOCH-R REGIMEN[47]

Same schedule DA-EPOCH with additional R 375[i] mg/m²

Arm A: before each EPOCH cycle	**Arm B:** weekly times 6 weeks after EPOCH completed

of 8 months, and ~10% of patients alive at 2 years.[29-31] The introduction of HAART has contributed to significant improvement of host immune response, reduced the risk of opportunistic infection,[32-35] and allowed HIV-positive patients to be treated with the same strategies used in HIV-negative patients,[36] often with similar results.[37] The risks and benefits of continuing HAART during chemotherapy have been variably interpreted. Some physicians are concerned by the uncontrolled HIV replication that may worsen immune function, whereas others are concerned by the risk of adverse effects of HAART on efficacy. Pharmacokinetic analyses have showed a 1.5-fold reduction in cyclophosphamide clearance in patients treated with CHOP plus HAART, while no changes in doxorubicin clearance.[38] CD4 increase during chemotherapy has raised the concern that HAART protects T-cells from chemotherapy. In HIV-BL patients treated with DA-EPOCH and SC-EPOCH-RR, HAART has been suspended for ~7 weeks in most cases,[39,40] without a relevant increase of infections, and with only a transient increase of HIV viral loads and decrease of CD4 cells. There is some concern over the use of protease inhibitors (PIs) during chemotherapy as these drugs induce cytochrome P450 isoenzymes 3A (CYP 3A) inhibition. However, data from clinical trials suggest similar clinical outcome when protease inhibitor-containing regimen are compared with non-PI-based regimen, but possibly at the expense of greater myelotoxicity.[41] Available evidence seems to suggest that HAART interruption during short-term chemotherapy is irrelevant from a clinical point of view, while longer treatments should request continued HAART assumption.

The Role of Rituximab

The advent of rituximab, a monoclonal antibody against the B-cell antigen CD20, has significantly improved outcomes in several B-cell lymphomas, including BL.[42] The intense expression of CD20 in tumour cells provides a strong rationale for the use of this antibody in Burkitt-oriented chemotherapies. However, the application of rituximab to HIV-BL is controversial, mostly due to its potential risk of additional immunosuppression and increased incidence of major infectious events, which was shown in a large randomised clinical trial.[43] Subsequent studies have not confirmed this excessive infectious risk,[44] and some groups have introduced rituximab to their prior protocols to treat HIV-NHL patients, with a high CR rate and without increased toxicities.[45,46] A recent trial from the Aids Malignancy Consortium (AMC) confirmed a good tolerance of the rituximab-chemotherapy combination, with or without HAART, though increased infectious deaths in patients with a CD4 count <50 cells/mL remained problematic.[47]

CHOP and Rituximab-CHOP Regimens

Among the first-generation schedule, CHOP and CHOP-like regimen were extensively studied in national cooperative-group trials and have been considered the standard approach for patients with aggressive NHL in the HIV setting. Full dose CHOP combined with HAART has been associated with 48% CRR, and a 5-year EFS of 40%.[38,32] As expected, dose reduction of CHOP drugs have been associated with better tolerability, while efficacy remained unchanged.[32] In HAART era, the wide use of rituximab-CHOP (R-CHOP) regimen has been associated with remarkably improved results in HIV-positive patients with DLBCL, while survival figures in BL have remained largely disappointing. In fact, median time to progression (TTP) was 22 weeks and 157 weeks for HIV-BL and other NHL, respectively,[43] and survival data were not statistically different among patients with HIV-BL and patients with other lymphoma categories, especially DLBCL. The response rate for DLBCL was 81% and the response rate for HIV-BL was 73%.[48]

Intensified Regimens

Hyper-CVAD was one of the first regimens assessed in HIV-BL[49] (Table 2); this combination was assessed in a series of HIV-associated aggressive lymphomas, with only six cases of HIV-BL. HAART has been assumted by 64% of patients, with no evidence of increased toxicity.[50] Overall, tolerability and efficacy in HIV-BL are similar to those obtained in HIV-negative patients.[50,51] There are no data on addiction of rituximab to this schedule in HIV-BL. This combination has been associated with infectious events in 85% of cases, severe myelosuppression, neurotoxicity, a 15% treatment-related mortality (TRM), and only 23% of patients completed the planned treatment (eight courses) (Tables 3).

A multidrug combination derived from the German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia GM-ALL B-ALL 05/93 protocol (Table 2) has been assessed in HIV-BL patients by PETHEMA Group.[52,53] More recently, this complex regimen was combined with rituximab and assessed in a prospective trial.[54] The addition of rituximab has been associated with improved tolerability and efficacy, but improvements should

Table 3. Feasibility, tolerability and toxicity of more commonly used chemotherapy regimens.

Patients (pts), number (N.°), days (d), chemotherapy (CT), treatment-related mortality (TRM), not reported (NR), rituximab (R).

a) Only 6 pts had HIV-BL.
b) Treatment termination due to reasons different from progression disease.
c) 14 pts with HIV-BL (other with L3ALL).
d) 16 pts with HIV-BL (other with L3ALL).
e) Toxicity expressed in number of courses.
f) 4 pts not received rituximab.
g) 7 pts with HIV-BL.
h) 8 pts with HIV-BL.
i) 16 pts with HIV-BL.
l) 11 pts with HIV-BL.
m) 10 pts with HIV-BL.

Regimen	Pts N°	Planned CT (days)	TRM (%)	Severe infections	Mycotic infections	Mucositis	Incompleted treatment[b] (%)
Hyper-CVAD[49] (prospective)	13[a]	168	15	85	23	NR	77
PETHEMA-LAL3/97-GMALL[53] (prospective)	19[c]	173	21	37	NR	32	72
PETHEMA-LAL3/97-GMALL+R[54] (prospective)	19[d]	173	16	26[e]	21	27	32
CODOX-M/IVAC[55] (retrospective)	8	84	13	88	NR	75	14
Modified CODOX-M/IVAC + R[56] (prospective)	22	84	0	32	5	9	36
Modified CODOX-M/IVAC(58) (retrospective)	30	84	10	20	NR	43	50
Modified CODOX-M/IVAC + R[60] (retrospective)	14[f]	84	10	20	NR	NR	NR
Modified CODOX-M/IVAC + R[57] (retrospective)	14[f]	84	0	50	NR	43	50
DA-EPOCH[65] (prospective)	39[g]	126	0	13	NR	3	23
DA-EPOCH + R[66] (prospective)	23[h]	126	0	16	NR	NR	NR
DA-EPOCH + R[47] Arm A (prospective)	51[i]	126	9.8	27	NR	2	6
DA-EPOCH + R[47] Arm B (prospective)	55[l]	189	7.3	29	NR	7	5
DA-EPOCH + R[67] (prospective)	29[m]	126	NR	NR	NR	NR	NR
Short-term chemo-immunotherapy[70] (retrospective)	15	90	6.7	35	NR	NR	13.4

not be attributed exclusively to rituximab considering that supportive care was also optimised and HAART was used in all patients. Overall, infection rates were not affected by the addition of rituximab.[53] Importantly, there were no differences in TRM or in CR rates between HIV-negative and HIV-positive patients, showing that this schedule can safely be applied to HIV-positive patients. Results were reported together for patients with BL-HIV or mature B-cell acute lymphoblastic leukaemia (L3ALL), and schedules for these subgroups of patients were similar, but not identical. Since toxicities and outcome were not reported separately, conclusions may be misleading (Tables 3 and 4). This regimen is very long (173 days) and exhibits a high toxicity rate, with a TRM of ~20%. The use of methotrexate in every cycle resulted in increased incidence of mucositis.

CODOX-M/IVAC is the most investigated chemotherapy combination in HIV-BL patients (Table 2). It is currently with different modifications of dosage and schedule according to patient's age, co-morbidity and risk.[55,24] Dose adjustments, mostly of methotrexate and vincristine, were followed by an evident reduction in adverse events, with only grade 1-2 mucositis, neurotoxicity and TRM (Tables 2 and 3), and with a progressive immunological recovery and CD4+ counts.[56-58] CODOX-M/IVAC, combined or not with rituximab, has been assessed in a few, small series of patients with HIV-BL (Table 3 and 4), resulting in a TRM of ~15%, severe infections in ~65% of cases, mycosis infections in ~5%, and mucositis in 75%.[56-60] Improved outcome in recent studies can be explained by a better management of patients and also by a positive patient selection. In fact, the study population had a remarkably better immune status, with high CD4 counts (median: 375/μL), lower HIV viral load (median <50 copies/mL) and more limited stage of disease (only 50% had stage IV).[56-58] Recent studies demonstrated that HAART can be used during CODOX-M/IVAC, without additional toxicities, resulting in an acceptable TRM, similar to those reported in HIV-negative patients. Although the addition of rituximab in recent series improved outcome and prevented relapses, without an increase in infectious events (Table 3), cytopaenias, myelosuppression and nephrotoxicity remain important concerns in HIV-BL patients treated with CODOX-M/IVAC.

Infusion Regimens

Infusion chemotherapy regimens exhibit a high activity in lymphoma patients, even when they were previously exposed to the cytostatics administered as an intravenous bolus, suggesting a schedule-dependent effect in favour of the infusional administration of certain cytotoxic agents in patients with lymphoid neoplasms.[61] This was the rationale for the use of infusional regimens in the treatment of HIV-NHL. CDE regimen, consisting of a 96-hour continuous intravenous infusion of cyclophosphamide (800 mg/m^2), doxorubicin (50 mg/m^2), and etoposide (240 mg/m^2) was the first assessed combination in HIV-BL, which was associated with a CRR of 45%, a 2-year FFS of 36% and 2-year OS of 43%, with significantly better tolerability and efficacy in patients treated in the HAART era.[62] Pooled results of three phase II trials addressing activity and tolerability of rituximab+CDE regimen have showed encouraging results, with a 70% CRR and a 2-year OS of 64%, but with increased risk for life-threatening infection (TRM= 8%).[63] These results were significantly poorer among patients with BL.

Another group has reported encouraging results with a 96-hour infusion regimen of doxorubicin, etoposide, and vincristine used in conjunction with intravenous bolus cyclophosphamide plus oral prednisone (EPOCH regimen) (Table 2). This regimen has been developed on the base of *in vitro* studies showing that tumour cells are relatively less resistant to prolonged low concentration exposure to the natural product–derived agents vincristine, doxorubicin, and etoposide, compared with brief higher concentration exposure.[64] In a first US National Cancer Institute (NCI) trial,[65] EPOCH therapy resulted in a 74% CRR and a 72% survival rate at a median follow-up of 53 months) in 39 patients with HIV-NHL (Table 3 and 4). The dose-adjustment strategy (DA-EPOCH) was implemented to reduce haematopoietic toxicity, and HAART was withheld during the study to avoid an increased risk of haematological toxicity with chemotherapy. HIV-BL patients enrolled were very few, and toxicities and subgroup analyses were not performed. Importantly, all deaths were related to CNS involvement, which was expected since DA-EPOCH does not include drugs that penetrate blood brain barrier, like methotrexate or cytarabine.

The addition of rituximab to DA-EPOCH (DA-EPOCH-R) has been associated with promising preliminary results in a prospective trial including 23 patients with BL (8 of them were HIV-positive), half of them advanced stage; at a median follow-up of 27 months, CR and OS rates were 100%, without toxic death.[66] A randomised phase II trial has demonstrated that concurrent rituximab plus infusion of EPOCH is

Table 4. Activity and efficacy of more commonly used chemotherapy regimens.

Rituximab (R), years (y), complete response (CR), 2-year-Progression Free Survival (2-y-PFS), 2-year-Overall-Survival (2-y-OS), Disease Free Survival (DFS), not reported (NR).

a) Percentuale relativa a pts in statio III e IV.
b) This is 1-year-OS.
c) This is 3-years-EFS.
d) This is 3-years-OS.
e) Dati generali riguardanti l' intera popolazione (80 pts) non solo i 14 HIV-BL.
f) This is 3-years-PFS.
g) Median HIV viral load log_{10}.
h) PFS and OS at 53 months.

Regimen	Median age y (range)	Stage IV (%)	Median CD4/μL	Median viral load copies/mL	Median follow-up (months)	CR (%)	2-y-PFS (%)	2-y-OS (%)
Hyper-CVAD[49] (prospective)	43 (32-55)	31	77	32,000	29	92	DFS:52	48
PETHEMA-LAL3/97-GMALL[53] (prospective)	41 (23-65)	57[a]	420	400,000	31	68	DFS:71	46
CODOX-M/IVAC[55] (retrospective)	41 (19-61)	88	149	6,357	34	63	EFS:60	NR
PETHEMA-LAL3/97-GMALL+R[54] (prospective)	39 (29-54)	42[a]	NR	NR	22	84	DFS:87	73
Modified CODOX-M/IVAC + R[56] (prospective)	40 (19-55)	NR	290	15,600	17	NR	NR	85.7[b]
Modified CODOX-M/IVAC[58] (retrospective)	38 (28-69)	70[a]	171	96,000	22	70	75[c]	52[d]
Modified CODOX-M/IVAC + R[60] (retrospective)	46 (17-78)	73[e]	237	22,604	NR	93	68[f]	68[d]
Modified CODOX-M/IVAC + R[57] (retrospective)	46 (32-56)	50	375	<50	12	86	ND	83
DA-EPOCH[65] (prospective)	40 (31-57)	67[a]	198	4.4[g]	53	74	73[h]	60[h]
DA-EPOCH + R[66] (prospective)	31 (18-66)	52	NR	NR	27	100	100	100
DA-EPOCH + R[47] Arm A (prospective)	44	84[a]	181	NR	30	63	66	70
DA-EPOCH + R[47] Arm B (prospective)	43	75[a]	194	NR	30	82	63	67
DA-EPOCH + R[67] (prospective)	35 (16-88)	59[a]	NR	NR	57	NR	NR	100
Short-term chemo-immunotherapy[70] (retrospective)	42 (27-63)	87[a]	248	23.640	25	80	73	73

Table 5. Short-term chemoimmunotherapy proposed by GICAT (Gruppo Italiano Cooperativo AIDS e Tumori).

Cyclophosphamide (CTX), methotrexate (MTX), cytarabine (ara-C), vincristine (VCN), doxorubicin (DOXO), rituximab (R), etoposide (VP16), metylprednisolone (MP), intravenous (i.v.), therapy intra-thecal (TIT), carmustine (BCNU), melphalan (M), autologous stem cell transplant (ASCT).

REGIMEN: Short-term chemoimmunotherapy[70]	
Schedule	**Therapeutic programme**
Induction -2; -1 **MP** 0.5 - 1 mg/Kg/d i.v. 0 **MP** 0.5 - 1 mg/Kg/d i.v. **CTX** 500 mg/m^2 over 1 h infusion **VCR** 2 mg total dose i.v. bolus 1 **MP** 0.5 - 1 mg/kg/d i.v. **CTX** 500 mg/m^2 over 1-h infusion 2 **R** 375 mg/m^2 5 **MTX** 12 mg + **Ara-C** 50 mg + steroids, i.t. 7 **MTX** 3 g/m^2 i.v. over 6 h+ leucovorin rescue 14 **R** 375 mg/m2 15 **VP16** 250 mg/m^2 every 12 h 19 **MTX** 12 mg + Ara-C 50 mg + steroids, i.t. 21 **MTX** 3 g/m^2 i.v. over 6 h + leucovorin rescue 29 **R** 375 mg/m^2 **DOXO** 50 mg/m^2 i.v. bolus 33 **MTX** 12 mg + Ara-C 50 mg + steroids, i.t. 36 **R** 375 mg/m^2 **VCN** 2 mg total dose i.v. bolus **Consolidation** 50–51 **Ara-C** 2 g/m^2 in a 3-h infusion, twice a day (every 12 h) 52 **R** 375 mg/m^2 60 **R** 375 mg/m^2	**After induction:** If CR, high dose Ara-C and R based consolidation phase If PR, high dose Ara-C and R based consolidation phase followed by BEAM (BCNU, vp16, Ara-C, M) plus ASCT If SD/PD intensification phase, followed by BEAM plus ASCT **At the end of CT** If initial bulky disease or residual PET-positive single lesion were administered 36 Gy involved field irradiation

associated with improved outcome with respect to sequential administration of rituximab and EPOCH in 106 patients with HIV-NHL.[47] This trial included only 27 HIV-BL patients, but activity in these patients was encouraging with both combinations, with a CRR of 63% in concurrent arm and 82% in sequential arm. Recently, the efficacy of DA-EPOCH-R was assessed in patients with *myc*-related aggressive-B-cell lymphomas; preliminary results of 29 patients with BL (10 HIV-positive) showed a 100% OS at a median follow-up of 57 months[67] (Table 3 and 4).

Short-Term Chemoimmunotherapy

A dose-dense, short-term chemotherapy programme including seven active drugs and intrathecal drug delivery has showed excellent activity and safety profiles in HIV-negative patients with BL in the pre-rituximab era.[68] This regimen, proposed by the Gruppo Italiano Cooperativo AIDS e Tumori (GICAT), has been modified to be used with maintained efficacy and improved tolerability in HIV-BL. In particular, six doses of rituximab have been added and methotrexate dose has been reduced from 150 and 250 mg/Kg to 3 g/m^2, mostly to avoid mucositis, which constitutes an important route of access for infectious agents, and one of the main causes of death in these patients.[69] Treatment consists of a 36-day induction phase including sequential doses of fractionated cyclophosphamide, high doses of methotrexate and cytarabine, doxorubicin, vincristine, and etoposide, rituximab and intrathecal prophylaxis/treatment (Table 7). Subsequent treatment is tailored according to the objective response to induction phase: patients in CR are referred to high-dose cytarabine-based consolidation phase (Table 7); patients in partial response are referred to consolidation followed by BEAM plus autologous stem cell transplant; patients with stable or progressive disease are referred to intensification phase, followed by BEAM+ASCT. At the end of chemoimmunotherapy, patients with initial bulky disease or with a residual PET-positive

single lesion are evaluated for 36-Gy involved-field irradiation.

This modified chemoimmunotherapy regimen in 15 consecutive HIV-BL, with excellent safety profile and efficacy.[70] This intensive, short-term chemoimmunotherapy regimen is fast, safe, cost-effective, and active in HIV-BL, especially in patients responsive to HAART and with adequate CD4+ cell counts. It showed tolerability and efficacy similar to those reported with the original regimen in HIV-negative patients with BL,[68] and its activity and efficacy are similar to those attained with more demanding and resource consuming regimen in HIV-BL, with an apparently better tolerability profile (Tables 2 and 3). In fact, this program was delivered in a shorter period (median 90 days; range 52-143), without cases of mucositis, opportunistic infections and interruption due to toxicity, with manageable haematological toxicity, only mild infectious and a single toxic death. Autologous peripheral blood stem cell (APBSC) collection was successful in 9 out of 11 patients (median: $14 \cdot 10^6$ CD34+ cells/kg). There was a single case of G4 non-haematological toxicity (transient diarrhoea). Patients with Hepatitis B virus (HBV) or Hepatitis C virus (HCV) positivity completed the planned treatment (ASCT in three), and experienced only transient G3 increase of transaminase serum level, without significant chemotherapy delay. CRR at the end of the whole treatment was 80%; at a median follow-up of 25 months (range 9-33), 11 patients remained disease-free, with a 2-year PFS and OS of 73%. CD4+ cell count ≥200 cells/μL is a favourable prognostic factor.[70] These encouraging results will be confirmed in an ongoing multicentre prospective phase II trial called the CARMEN trial (ClinicalTrials.gov Identifier: NCT01516593).

Salvage Therapy and Role of Stem Cell Transplant

Standard salvage treatment for patients with relapsed or refractory HIV-BL remains to be defined as there are no studies focused on this issue, and recommendations are based on retrospective studies of HIV-associated lymphomas that include a few HIV-BL patients.[71-74] The first choice concerns the type of treatment, based upon patients' clinical conditions: supportive care, palliative chemotherapy or high-dose chemotherapy (HDC) plus autologous stem cell transplantation (ASCT).[75] The latter is considered the best curative option for HIV-negative patients with relapsed disease.[76] In the absence of significant differences, in terms of OS and PFS between HIV negative and HIV positive patients, this schedule is considered to be feasible even in HIV-related lymphomas.[72] In most patients, data is based on the outcome after HDC/ASCT of the entire HIV-positive population, not exclusively on HIV-BL.[71-74] In other case series, HDC/ASCT led to very poor outcome in HIV-BL, sometimes due to inefficiency of induction chemotherapy,[75] or to early deaths after ASCT.[77] Ferreri et al. demonstrated a very promising outcome with BEAM + ASCT after induction therapy in patients who achieved CR, resulting in 5 CR beyond the 6 CR obtained with induction therapy alone.[70] There are no data on allo-SCT in relapsed HIV BL.[78]

CONCLUSIONS

The introduction of HAART allowed the treatment of HIV-BL patients with the same intensive schedules proved to be curative in HIV-negative BL. Since there are no randomised trials comparing different first-line schedules (Table 4), gold standard regimen for HIV-BL is still debated. Available literature is mostly constituted by small retrospective and prospective studies considering patients with different lymphoma categories, other than HIV-BL. Thus, analysis and comparison of outcomes and toxicities is very difficult, potentially leading to unreliable conclusions. Adding rituximab on various schedules demonstrated good efficacy and tolerability compared to chemotherapy alone. The use of improved supportive therapy and antimicrobial prophylaxis significantly reduced adverse events, improving outcome. New de-escalated regimens could produce the same positive results obtained by more intensive and resource consuming combinations, with a lower risk of severe toxicity.[70] These innovative regimens should be assessed in prospective trials aimed also to identify prognostic markers to establish a risk-tailored overall strategy.

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