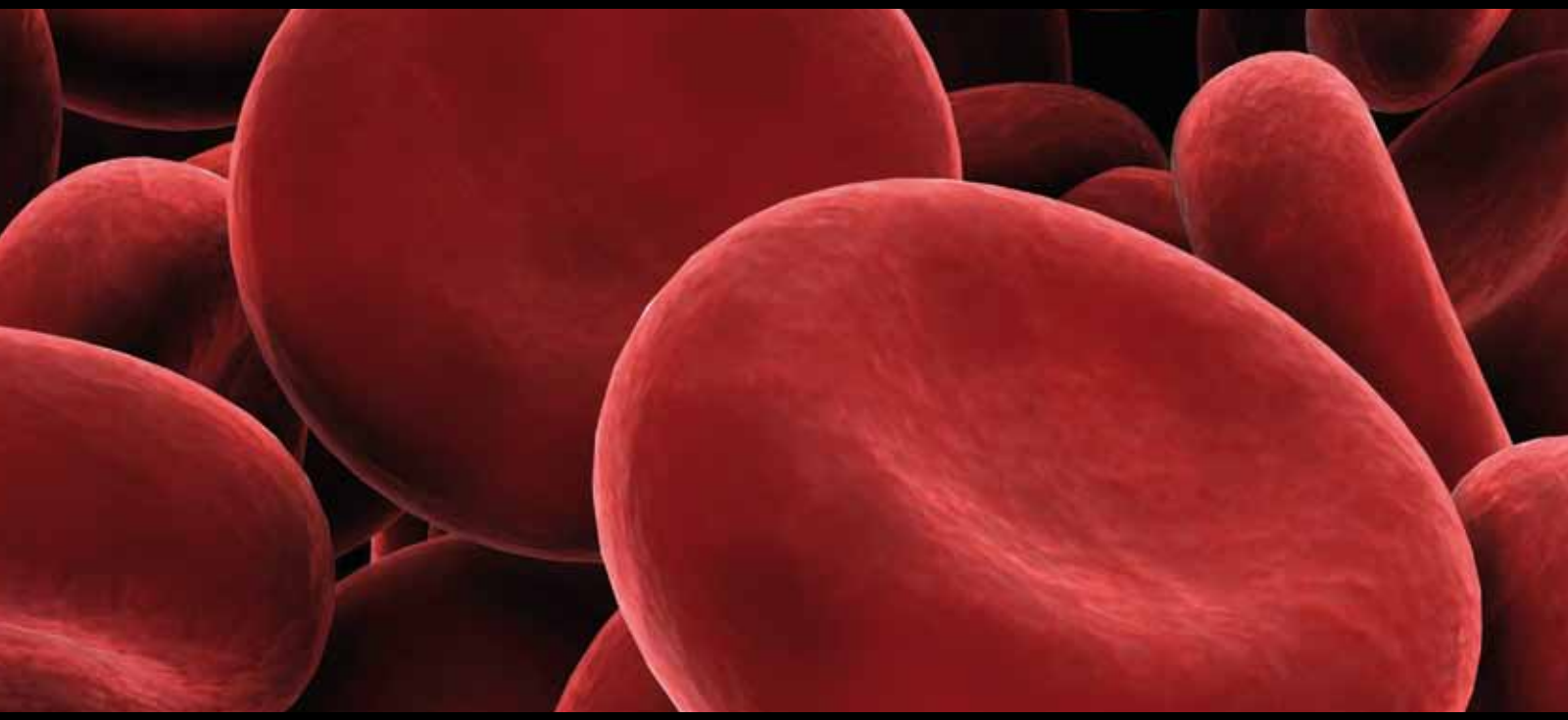
Advances in Hematology

Unanswered Questions in HIV Hematology

Guest Editors: Heather A. Leitch, Jeremy S. Abramson, Matthew C. Cheung, and Lisa K. Hicks



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Editorial Board

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Editorial

Unanswered Questions in HIV Hematology

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Hematological abnormalities are common manifestations of HIV infection that are regularly encountered in the clinical setting. Although initially recognized with the first descriptions of HIV infection over 30 years ago, our understanding of the epidemiology, natural history, and treatment of these blood disorders continues to evolve. Aggressive lymphomas such as diffuse large B-cell lymphoma and primary CNS lymphoma have decreased since the introduction of combination antiretroviral therapy (cART), though these and other HIV-associated malignancies continue to a have a major impact on the morbidity and mortality of persons with HIV. Other blood disorders frequently associated with HIV include cytopenias, particularly anemia and thrombocytopenia. In this special issue, studies investigating hematologic diseases associated with HIV infection are discussed. The diagnosis, treatment, and prognosis of Hodgkin lymphoma (HL) in the era of cART are reviewed by Jacobson and Abramson. Unlike non-Hodgkin lymphomas (NHL), the incidence of HL in HIV-infected patients has not decreased in the cART era. However, the introduction of cART has allowed the delivery of full doses of chemotherapy with significantly improved outcomes. Despite these advances, patients with HIV-associated HL remain at risk of treatment-related toxicity, and interactions between antiretroviral and chemotherapeutic agents necessitate careful attention to supportive care.

Two papers focus on HIV-associated Burkitt lymphoma (BL). Though the outcome of HIV-NHL has improved substantially in the cART era, the outcome of HIV-BL with standard chemotherapy remains poor. J. A. Rodrigo et al. describe the combined experience in four Canadian centers treating patients with HIV-BL with the CODOX-M/IVAC regimen with or without rituximab in the modern era. In this study, intensive chemotherapy with CODOX-M/IVAC ± R yielded acceptable toxicity and favorable survival rates. A. M. Petrich et al. review the larger picture in the treatment of HIV-BL in the paper entitled "*paradigms and controversies in the treatment of HIV-related Burkitt lymphoma*." In this paper, available data on the treatment of patients with HIV-BL with current BL-directed chemotherapy regimens are discussed in detail, including Hyper-CVAD, dose-adjusted EPOCH, the PETHEMA regimen, and CODOX-M/IVAC. Areas of uncertainty in the treatment of these patients include the addition of rituximab to chemotherapy regimens, the optimal approach to patients with relapsed or refractory BL and the role of stem cell transplantation, the appropriate approach to older patients and patients with central nervous system involvement, and the role of antiretroviral therapy and supportive care.

An intriguing and pressing challenge in the management of patients with both malignant and nonmalignant hematologic disorders in HIV infection is the optimal approach to be taken in the developing world. This topic is addressed by M. Ulrickson et al. in the paper "*Epidemiology, diagnosis, and treatment of HIV-associated NHL in resource-limited settings.*" The epidemiology of NHL in Africa is compared to that of the US, and discrepancies in survival highlighted by cancer registries are discussed. Challenges in managing patients with NHL in resource-limited settings include diagnostic challenges due to limited access to a full battery of immunohistochemical tests and limited molecular testing.

Treatment challenges include limited access to antiretroviral regimens, prophylactic agents, IV infusion centers, and a higher incidence of major infectious complications including tuberculosis and hepatitis B. Response assessments are further limited by a lack of ready access to cross-sectional imaging in some regions. Despite these challenges, progress has been made in developing tolerable and effective treatment regimens appropriate to these circumstances, and these important advances are reviewed.

A common nonmalignant complication of HIV infection is immune thrombocytopenia (ITP). The characteristics of HIV-associated ITP were documented prior to the cART era, and the optimal treatment beyond cART is unknown. For this reason, K. L. S. Ambler et al. present a retrospective cohort study reviewing individuals with severe HIV-associated ITP diagnosed in the cART era. Their series is the largest such report of severe HIV-ITP in the post-cART era. The major finding from this study was that, although the various treatments were well tolerated and most patients achieved a safe platelet count, nearly all patients (87%) required retreatment for recurrence of severe ITP. This highlights that new approaches to the treatment of ITP in this population are needed.

The intent of this special issue was to initiate interest in and further inquiry into the many hematologic complications faced by persons living with HIV. In addition to the topics discussed in this issue, areas for future exploration include the approach to management of patients with less common lymphoproliferative disorders such as indolent NHL, paraproteinemias, and Castleman disease, as well as non-malignant causes of cytopenias and their management.

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Research Article

Clinical Features, Treatment, and Outcome of HIV-Associated Immune Thrombocytopenia in the HAART Era

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The characteristics of HIV-associated ITP were documented prior to the HAART era, and the optimal treatment beyond HAART is unknown. We performed a review of patients with HIV-associated ITP and at least one platelet count $< 20 \times 10^9$/L since January 1996. Of 5290 patients in the BC Centre for Excellence in HIV/AIDS database, 31 (0.6%) had an ITP diagnosis and platelet count $< 20 \times 10^9$/L. Initial ITP treatment included IVIG, $n = 12$; steroids, $n = 10$; anti-RhD, $n = 8$; HAART, $n = 3$. Sixteen patients achieved response and nine patients achieved complete response according to the International Working Group criteria. Median time to response was 14 days. Platelet response was not significantly associated with treatment received, but complete response was lower in patients with a history of injection drug use. Complications of ITP treatment occurred in two patients and there were four unrelated deaths. At a median followup of 48 months, 22 patients (71%) required secondary ITP treatment. This is to our knowledge the largest series of severe HIV-associated ITP reported in the HAART era. Although most patients achieved a safe platelet count with primary ITP treatment, nearly all required retreatment for ITP recurrence. New approaches to the treatment of severe ITP in this population are needed.

1. Introduction

An association between immune thrombocytopenia (ITP) and the acquired immune deficiency syndrome (AIDS) was first recognized in 1982 [1]. Prior to the advent of highly active antiretroviral therapy (HAART), the incidence of HIV-associated thrombocytopenia was estimated at 10–30%, and thrombocytopenia was the initial manifestation of HIV in approximately 10% of cases [2, 3]. The incidence varied according to the definition of thrombocytopenia and the characteristics of the baseline population; for example, it was more common in HIV-infected intravenous drug users (IDUs) compared to HIV-infected men who have sex with men [2]. Although thrombocytopenia may occur at any time during the course of HIV infection, the incidence generally correlates with the degree of immunosuppression and is more prevalent in individuals with clinical AIDS [4–6].

In the initial reports of HIV-associated ITP, thrombocytopenia generally responded well to treatment with corticosteroids or splenectomy [7–9]. Subsequent studies showed improved platelet counts with antiretroviral therapy, in particular HAART [10, 11], and this is now the initial treatment of choice for patients with HIV-associated ITP [12]. Since the era of widespread use of HAART, there have been no published studies describing the incidence or clinical features of HIV-associated ITP [3]. Further, there are minimal data on the safety of various treatment regimens in HIV-positive patients, and the optimal treatment approach to HIV-associated ITP beyond HAART is unknown [3, 13]. The objectives of this study were to determine the frequency of severe HIV-associated ITP in the HAART era and to

describe the clinical features, treatment, and outcomes of patients diagnosed with severe HIV-associated ITP in the HAART era.

2. Methods

We searched the BC Centre for Excellence in HIV/AIDS (CFE) database to identify patients with HIV who had at least one platelet count $<100 \times 10^9$/L since January 1996; the year HAART use was widely adopted in British Columbia. For this paper, we chose to focus on patients with severe HIV-associated ITP. Although the International Working Group (IWG) definition of severe ITP includes only patients with clinically relevant bleeding [14], since it would be impossible to identify this group of patients retrospectively from our database, we defined severe thrombocytopenia as at least one platelet count $<20 \times 10^9$/L. We chose this approach because, at our institution, these patients are routinely referred to hematology and generally require treatment, whereas patients with HIV-associated ITP and higher platelet counts are usually managed by their primary care physician or HIV specialist. We reviewed all charts from patients with a platelet count $<20 \times 10^9$/L. For the analysis, we included only patients with a diagnosis of HIV-associated ITP made by a hematologist. Patients were excluded if they had pancytopenia, were taking medications that cause thrombocytopenia, had another documented cause of thrombocytopenia, or did not have documentation of assessment by a hematologist. Coinfection with hepatitis B or C was defined as serologic evidence of hepatitis B or C infection prior to or at the time of ITP diagnosis. Chronic liver disease was defined as radiologic or laboratory evidence of chronic liver dysfunction prior to the time of ITP diagnosis.

The IWG criteria were used to assess response, with complete response (CR) defined as a platelet count $\geq 100 \times 10^9$/L, response (R) defined as a platelet count $\geq 30 \times 10^9$/L and at least a two-fold increase from baseline count and absence of bleeding, no response (NR) defined as failure to achieve a platelet count $\geq 30 \times 10^9$/L or less than a two-fold increase from baseline, or ongoing bleeding, and loss of response defined as recurrent platelet count $<30 \times 10^9$/L or <two-fold greater than baseline or bleeding [14]. Descriptive statistics were used to summarize the data. Response rates were compared using the Fischer's exact test, using SPSS for Windows, version 18.0.

3. Results

Of 5290 patients in the CFE database since 1996, 1357 (26%) had at least one platelet count $<100 \times 10^9$/L, 417 (8%) had at least one platelet count $<50 \times 10^9$/L, 151 (3%) had at least one platelet count $\leq 20 \times 10^9$/L, and 31 patients (0.6%) were diagnosed with HIV-associated ITP and had a platelet count $\leq 20 \times 10^9$/L, see Figure 1.

3.1. Clinical Characteristics. The clinical characteristics of the 31 patients diagnosed with severe HIV-associated ITP are shown in Table 1. The median age at ITP diagnosis was 37 (range 27–66) years. The median platelet count was 10×10^9/L (range 2–19 $\times 10^9$/L), median hemoglobin was 129 (34–165) g/L, and median neutrophil count was 2.5 (1.0–17.0) $\times 10^9$/L. Seventeen patients (55%) presented with clinical bleeding and four (13%) required packed red blood cell transfusion. Comorbidities included chronic liver disease in five patients, chronic renal failure in two, seizure disorder in two, and chronic obstructive pulmonary disease, Crohn's disease, type 2 diabetes mellitus, peripheral vascular disease, phenylketonuria, prostate cancer, psychiatric disorder, and pulmonary hypertension each in one patient. Twelve patients had hepatitis C and four patients had hepatitis B coinfection. Treatment for the coinfections was not documented. Six patients had a bone marrow aspirate and biopsy and all showed increased megakaryocyte numbers, consistent with a diagnosis of ITP. Of 29 patients with a CD4 count documented at the time of severe ITP diagnosis, the median CD4 was 290 (20–600) cells/μL. Four patients had an HIV viral load documented at the time of severe ITP diagnosis, and it was >100 000 copies/mL in two patients, 92730 and 90 copies/mL in each of the other patients. Ten patients were receiving HAART at the time of severe ITP diagnosis. Of these, three had a CD4 < 200 cells/μL, suggesting suboptimal therapy or adherence to therapy.

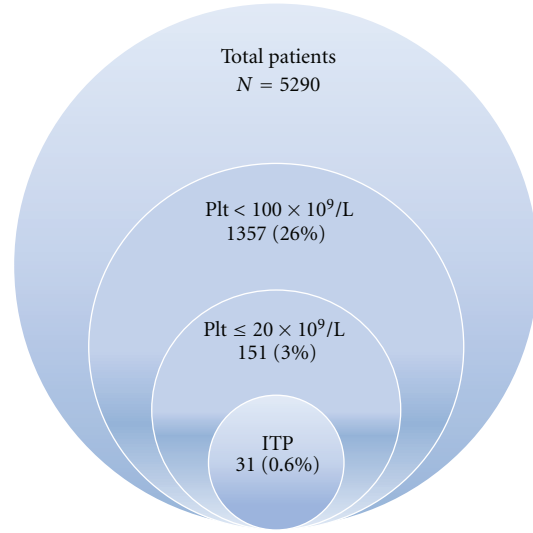

Figure 1: Incidence of thrombocytopenia in HIV-infected individuals in the HAART era.

3.2. Primary ITP Treatment. Treatments received at the first episode of a platelet count $<20 \times 10^9$/L are listed in Table 2. Thirteen patients received HAART as part of their primary ITP treatment, including the ten patients who were receiving HAART prior to the diagnosis of ITP. Of the 18 patients who did not receive HAART with primary ITP therapy, 12 had a CD4 count >200 cells/μL and 13 had IDU as their risk factor for HIV, including the six patients with a CD4 count <200 cells/μL.

Overall, 25 patients achieved a CR or R according to the IWG criteria (see Figure 2). The median platelet response

Table 1: Clinical characteristics of 31 patients with HIV-associated ITP diagnosed since 1996.

Characteristic	*N*
Age at ITP presentation (years)	
≤40	12
>40	19
Gender	
Male	25
Female	5
Transgender (MF)	1
Platelet count ($\times 10^9$/L)	
≤10	15
>10	16
Hemoglobin at ITP diagnosis (g/L)	
<90	4
>90	24
Clinical bleeding	17
Site of bleeding	
Epistaxis	14
Menorrhagia	3
Gingival bleed	2
Gastrointestinal bleed	1
Hemoptysis	1
HIV risk factor ($N = 26$)	
Sexual	10
IDU	16
CD4 at ITP diagnosis (cells/μL, $N = 29$)	
<200	8
≥200	21
Prior AIDS[1]	5
Coinfections	
Hepatitis B	4
Hepatitis C	12
Receiving HAART[2] at ITP diagnosis	
No	20
Yes	10
Comorbidities	15

[1]Mycobacterium avian complex, $n = 2$; *Pneumocystis jirovecii* pneumonia, $n = 2$; anal condylomata, $n = 1$.
[2]HAART was 1 nucleoside analog (NA), 1 protease inhibitor, and either a 2nd NA or a nonnucleoside reverse transcription inhibitor.

within 30 days was 58 (5–322) $\times 10^9$/L and the median time to R was 14 (1–3192) days.

3.3. Secondary ITP Treatment. At a median followup of 48 (0.2–138.5) months, 22 patients (71%) had a loss of response and required secondary ITP treatment for a recurrent platelet count <20 $\times 10^9$/L. The median platelet count at recurrent ITP diagnosis was 10 (5–20) $\times 10^9$/L. The median time to loss of response was 39 (8–858) days. Of 13 patients that received HAART with their primary treatment, seven had recurrent ITP. Six of seven patients who did not relapse received HAART with their primary treatment, three received HAART as treatment for ITP, and three were on HAART prior to ITP diagnosis.

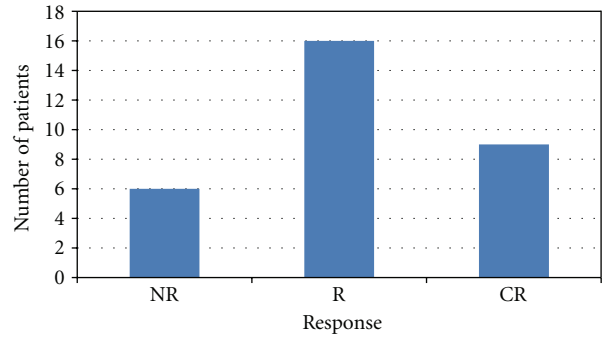

Figure 2: Maximum platelet response.

Secondary treatment included IVIG in nine patients, anti-RhD in six patients, steroids in four patients, splenectomy in three patients, and initiation of HAART in one patient. The median platelet response within 30 days of the initiation of secondary ITP treatment was 42 (21–198) $\times 10^9$/L ($n = 19$). Eleven patients achieved R and eight patients achieved CR to secondary treatment. The median time to response was seven (2–280) days. All three patients who underwent splenectomy achieved a normal platelet count which was sustained at followup of 14, 58, and 123 months.

3.4. Predictors of ITP Response. The probability of response to primary ITP treatment did not appear to be significantly influenced by the choice of treatment or by the number of treatments received; however, firm conclusions regarding this are limited by small patient numbers. When considering patient characteristics, patients with a history of IDU were less likely to achieve a CR ($P = 0.04$, $N = 30$). We did not find a significant difference in any patient characteristics between patients who achieved R compared to those who did not, likely because the number of patients with NR was so small. Loss of response did not appear to be associated with any particular patient or treatment characteristic.

3.5. Complications of Treatment. Complications of treatment were psychiatric effects of steroids in one patient and postsplenectomy fever and hematoma in one patient. There were no opportunistic infections; however, seven patients received prophylaxis for *Pneumocystis jirovecii* pneumonia (PCP), including five patients who received septra, and two patients who received dapsone.

3.6. Survival and Causes of Death. There were four deaths and causes were variceal bleed in two patients, Evan's syndrome and hepatic failure in one patient, and advanced HIV in one patient. Both patients who died of variceal bleeding had a platelet count >50 $\times 10^9$/L at most recent followup, a history of IDU, hepatitis C coinfection, and hepatic cirrhosis. The patient who died of Evan's syndrome had sexual contact as his risk factor for HIV and no history of hepatitis C or chronic liver disease. He was receiving HAART prior to death and the most recent CD4 was 260 cells/μL. His

Table 2: Treatment regimens for HIV-associated ITP and responses achieved.

Treatment	Dose	*N*	Bleeding (%)	R + CR (%)	CR (%)	Median time to R in days (range)	Relapse (%)
IVIG	1 g/kg/day × 2 days	7	6 (86)	5 (71)	4 (57)	4 (3–9)	6 (86)
Anti-D	2.4–4 mg	7	2 (29)	6 (86)	0 (0)	14 (1–61)	4 (57)
Prednisone	50–85 mg daily	4	2 (50)	4 (100)	1 (25)	4.5 (3–13)	3 (75)
HAART alone	*See footnote	4	1 (25)	3 (75)	1 (25)	267 (1–1379)	3 (75)
IVIG + Prednisone	1 g/kg/day × 2 days 50–70 mg	5	4 (80)	5 (100)	3 (60)	11 (3–16)	3 (60)
Anti-D + Prednisone	1.3 mg 40 mg daily	1	1 (100)	1 (100)	0 (0)	22	1 (100)
HAART + Other therapy	**See footnote	9	5 (56)	8 (89)	5 (56)	13.5 (3–22)	4 (44)
None		3	0 (0)	2 (67)	2 (67)	696 (26–3192)	2 (67)

*HAART was 1 nucleoside analog (NA), 1 protease inhibitor, and either a 2nd NA or a nonnucleoside reverse transcription inhibitor.
**Other therapy was IVIG, prednisone, or anti-D in the doses listed above. Patients in this group were also included in the groups above with patients who received the respective therapies without HAART.

platelet count on the day of death was 8×10^9/L. The patient who died of advanced HIV had a history of coinfection with hepatitis C, PCP, TB, and pulmonary hypertension. The most recent platelet count was 23×10^9/L nine days before her death.

4. Discussion

In this study, although the incidence of thrombocytopenia in HIV-infected individuals was high (26%), the incidence of severe HIV-associated thrombocytopenia was only 0.6%. These results are similar to those of studies performed in the era prior to the widespread use of HAART, in which the incidence of platelet count less than 150×10^9/L was 10–30% in HIV-infected individuals, and the incidence of a platelet count less than 50×10^9/L was 1.5–9% [2, 4, 15]. Approximately two-thirds of patients in our study had a CD4 count over 200 cells/μL. Although this seems contrary to previous studies that showed an increased incidence and severity of thrombocytopenia with lower CD4 counts [4–6], in our study, the higher number of patients with CD4 count greater than 200 cells/μL is most likely a reflection of the composition of the baseline population in the HAART era. Importantly, our study shows that control of HIV infection alone is not sufficient to prevent ITP in all patients.

In our population in the HAART era, more patients with severe thrombocytopenia had a history of IDU than sexual contact as their HIV risk factor, consistent with findings in the pre-HAART era [2, 8, 15]. We also found that patients with a history of IDU had inferior platelet response. Potential reasons for this association include higher rates of coinfection with hepatitis C in the IDU population, lower rates of compliance with HAART and other treatments, direct toxicity from the injection drugs, or from contaminating substances mixed in the drugs. In our study the type of drugs and the potential for contaminating substances were not documented, but we did find a high incidence of coinfection with hepatitis C virus, which is consistent with the findings from prior studies [2, 16].

Nearly all patients in this study achieved a safe platelet count with primary ITP treatment. The rates of response to steroids, IVIG, and anti-D were similar to those previously reported and we were unable to show a significant difference in response according to treatment received. In a study of injection drug users with HIV-associated ITP in the pre-HAART era, Landonio showed response rates of 65% and 80% to IVIG and anti-D [8]. Walsh found that 16 of 17 men who have sex with men with ITP in the pre-HAART era responded to prednisone [7].

Although there were few treatment complications in our study, most patients (71%) required secondary treatment for loss of response, including seven of 13 patients receiving HAART with initial ITP therapy. This is consistent with findings from the study by Landonio, in which only four of 17 patients treated with IVIG had sustained remissions, and all patients treated with steroids had recurrent ITP after discontinuation of initial therapy [8]. In a randomized cross-over study of nine patients with severe HIV-associated ITP, Scaradavou found the median duration of response was

19 days following treatment with IVIG and 41 days following anti-RhD [17].

As with primary treatment for ITP, most patients in our study who received secondary treatment for recurrent thrombocytopenia achieved a platelet count $>30 \times 10^9$/L. Although splenectomy appeared to be safe and effective in the three patients who underwent this treatment, given the lifelong increased risk of severe infections, we have reservations about using this therapy in patients with HIV, particularly those with hepatitis C coinfection. In a series of 68 patients who underwent splenectomy for HIV-associated ITP in the pre-HAART era, 82% had sustained platelet counts $>50 \times 10^9$/L and there was no significant difference in progression to AIDS or survival compared to patients without splenectomy. However, two patients died of fulminant septic shock and two others presented with *Streptococcus pneumoniae* meningitis [18].

This is to our knowledge the largest series of patients with severe HIV-related ITP reported since the availability of HAART, and one strength of the study is the substantial length of followup, a median of four years. The main limitation of our study is its retrospective nature. Because of this, small patient numbers, and many variables in this patient population, we cannot make definitive conclusions about the efficacy of one treatment compared to another. In addition, since the study was conducted at a single institution, the results may not apply to other populations. Furthermore, since we chose only to include patients with severe HIV-associated ITP who were referred to hematology, there is selection bias and the findings are not necessarily applicable to patients with mild or moderate thrombocytopenia. Finally, none of the patients in our study were treated with rituximab or thrombopoietin receptor agonists; therefore, we cannot comment on the safety or efficacy of these newer agents in the treatment of HIV-associated ITP.

5. Conclusions

HIV-associated ITP remains an important clinical problem in the era of the widespread use of HAART. Although most patients respond to primary ITP treatment and there are few treatment-related complications, nearly all patients require retreatment for recurrent ITP. Inferior response to treatment was associated with a history of IDU. New approaches to the treatment of HIV-associated ITP in this patient population are needed.

Conflict of Interests

The authors have no relevant conflict of interests to disclose.

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Review Article

Paradigms and Controversies in the Treatment of HIV-Related Burkitt Lymphoma

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Burkitt lymphoma (BL) is a very aggressive subtype of non-Hodgkin's lymphoma that occurs with higher frequency in patients with HIV/AIDS. Patients with HIV-related BL (HIV-BL) are usually treated with high-intensity, multi-agent chemotherapy regimens. The addition of the monoclonal antibody Rituximab to chemotherapy has also been studied in this setting. The potential risks and benefits of commonly used regimens are reviewed herein, along with a discussion of controversial issues in the practical management of HIV-BL, including concurrent anti-retroviral therapy, treatment of relapsed and/or refractory disease, and the role of stem cell transplantation.

1. Introduction

Burkitt lymphoma (BL) is a very aggressive subtype of non-Hodgkin lymphoma (NHL) usually associated with translocation of the MYC oncogene. The World Health Organization (WHO) classification recognizes three clinical variants of BL: sporadic, endemic, and immunodeficiency related [1]. The last of these is particularly common in patients with human immunodeficiency virus (HIV), in whom the lifetime incidence of BL has been estimated at 10–20% [2], and wherein it constitutes an acquired immunodeficiency-syndrome- (AIDS-) defining illness.

The difference in clinical variants of BL may be explained by variation in stage of B-cell development at which lymphomagenesis occurs and by a potential relationship with Epstein Barr virus (EBV). It has been shown, for instance, that cases of endemic and AIDS-related BL (both of which are generally EBV related) have considerably highermutation rates than those of sporadic BL; EBV-positive BLs also have higher levels of somatic hypermutation of their variable region heavy chain genes, and evidence of antigen selection (whereas EBV-negative BLs generally fail to show this selection)[3]. These data suggest that EBV-negative BL arises from an early centroblast, while EBV-positive BL arises later in development, likely from a memory B cell or late germinal center B cell. Gene expression signatures of the three variants also appear to be distinct, with differences between endemic and sporadic cases of BL in terms of expression of proteins that influence the oncogenic potential of MYC [4], ectopic expression of which is a near-universal phenomenon in BL.

Historically, HIV/AIDS-related BL (HIV-BL) has represented a therapeutic challenge, mainly due to (a) the toxicity involved in treating HIV-positive patients with very intense and immunosuppressive regimens found to be successful in HIV-negative patients with BL, (b) the paucity of data from randomized controlled trials, and (c) the relatively small number of patients with this disease. As we will explore in this paper, several paradigms exist with respect to effective treatment of HIV-BL, though controversies and questions remain. The goal of this paper is to review the data behind several chemotherapeutic regimens and discuss several issues of particular relevance to this population.

2. Chemotherapy Regimens

The evolution of therapy for BL (reviewed by Magrath [5]) dates to at least 20 years before the first cases of HIV were reported, and the multiagent regimens devised during that time have formed the basis for trials in HIV-BL. In the 1970s, it was shown that treatment with short-course, high-intensity, multiagent chemotherapy, built on a backbone of cyclophosphamide, vincristine, and methotrexate, could result in substantial rates of durable remission [6] and that repeated intrathecal (IT) chemotherapy seemed important to the prevention of central nervous system (CNS) relapse [7]. When similar approaches were taken with HIV-positive patients [8, 9], similarly high rates of complete response (CR) were achieved. A trend toward inferior 5-year overall survival (OS) was appreciated in the HIV-positive patients, and was attributed to delayed complications of HIV, such as Kaposi's sarcoma and opportunistic infections. Importantly, treatment-related toxicity and mortality did not seem to be appreciably increased in the HIV-positive population. These data helped pave the way for further investigation of intensive therapy for patients with HIV-BL.

2.1. Hyper-CVAD. In 2002, Cortes et al. [10] reported their experience using Hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, in cycles alternating with methotrexate and cytarabine), along with highly active antiretroviral therapy (HAART) in patients with AIDS-related Burkitt lymphoma ($n = 6$) and leukemia ($n = 7$). Ten patients were over the age of 35, and nine were diagnosed with HIV at time of diagnosis of BL; median CD4+ T-cell (CD4) count was 77/μL. Patients received a median of 6 cycles of therapy, though over 20% of cycles were delayed or reduced due to toxicity, and 35% were complicated by fever or infection. Interestingly, of seven patients who were on HAART or started during the first course, six remained alive in CR at time of publication, whereas all four patients who did not receive HAART died (three of causes related to progression of HIV-BL).

The data for the addition of rituximab to this regimen (R-Hyper-CVAD) for HIV-BL remains somewhat lacking. The same group reported improved outcomes using R-Hyper-CVAD, as compared to historical cohorts treated with Hyper-CVAD without rituximab [11]. However, 45% of the patients included were diagnosed with B-cell acute lymphoblastic leukemia, as opposed to typical BL. When reporting on six HIV-BL patients included in the study, in abstract form at the 2003 meeting of the American Society of Clinical Oncology (ASCO) [12], they noted three deaths in CR due to HIV-related malignancy or infection.

2.2. CODOX-M/IVAC. Using the CODOX-M/IVAC regimen (dose-intense cyclophosphamide, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine) in HIV-negative adults ($n = 20$) with BL, Magrath and colleagues reported 100% 2-year EFS [13], but at the cost of often severe neurotoxicity. In 2003, Wang and colleagues [14] reported their single-institution experience with CODOX-M/IVAC for patients with HIV-BL. When analyzing HIV-BL patients treated with CODOX-M/IVAC ($n = 8$) to those treated with less intense regimens ($n = 6$), they noted similar rates of CR (63% versus 67%, resp.) and 2-year EFS (57% versus 60%, resp.) in spite of disproportionately more high-risk patients in the CODOX-M/IVAC cohort (88% versus 33%). Furthermore, when all HIV-BL patients ($n = 14$) were analyzed (irrespective of treatment regimen) in comparison to HIV-negative patients with BL treated in similar fashion over the same time period ($n = 24$), HIV status affected rates of neither CR (HIV-positive patients, 64%; HIV-negative patients, 63%) nor 2-year EFS (HIV-positive patients, 59%; HIV-negative patients, 62%). The authors concluded that CODOX-M/IVAC (a) may overcome high-risk features in HIV-BL, and (b) did not appear significantly more toxic in patients with HIV-BL as compared to HIV-negative patients with BL.

CODOX-M/IVAC was subsequently modified by Lacasce and colleagues [15] by decreasing the dose of methotrexate, capping the vincristine dose, modifying the dose schedule of cyclophosphamide (to permit for earlier use of growth factor), and increasing the doxorubicin dose, all for the sake of preserving efficacy while reducing risk of neurotoxicity. In so doing, the authors realized a 2-year OS of 71% in HIV-negative patients with BL ($n = 14$), while observing seemingly significantly lower rates of neurotoxicity. This so-called "modified Magrath regimen," constitutes with slight additional modification (including moving high-dose methotrexate from day 10 to day 15 in order to minimize toxicity), constitutes the chemotherapeutic backbone of an ongoing AIDS Malignancy Consortium (AMC) trial (AMC 048), which also adds rituximab to all cycles of therapy. At a median follow-up of nine months, with 34 patients treated, the authors reported no treatment-related mortality (TRM) and one-year OS of 82% [16].

2.3. Dose-Adjusted EPOCH. In spite of the beneficial effects of HAART upon incidence and outcome of ARL, concerns remained over the interaction between cytotoxic chemotherapy and agents included in HAART [17]. With this in mind, the National Institutes of Health (NIH) explored the use of infusional dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-EPOCH) in ARL, with suspension of HAART for the duration of chemotherapy (planned 6 cycles) [18]. DA-EPOCH was chosen because (a) pre-clinical data suggested that sustained concentrations of doxorubicin, vincristine, and etoposide resulted in relatively less tumor resistance [19], and (b) inter-cycle dose adjustment permitted for maintenance of dose intensity while ameliorating toxicity [18]. In this trial, seven of 39 patients (18%) had BL, and those with BL had a significantly higher rate of CNS involvement versus those with diffuse large B-cell lymphoma (DLBCL; 4/7 versus 5/31, resp., $P = 0.04$). Although reporting of the BL subset was otherwise lacking, the trend toward inferior 53-month survival observed for BL, as compared to DLBCL (43% versus 66%, $P = 0.22$), was attributed to the high rate of CNS disease,

as each patient with BL who died during follow-up was known to have CNS involvement prior to therapy.

Success with EPOCH led NIH investigators to evaluate the addition of rituximab to this regimen in HIV-BL. It had been observed that high levels of response and OS could be maintained by giving short-course EPOCH with dose-dense rituximab (SC-EPOCH-RR), with number of courses determined by interim positron emission tomography-computed axial tomography (PET-CT) staging, to patients with HIV-related DLBCL [20]. This so-called "short course" consisted of three cycles of EPOCH-RR, followed by PET-CT, after which those with negative results received one additional cycle, and those with evidence of persistent disease received an additional 2-3 cycles. In HIV-DLBCL, OS of 73% at 53 months of follow-up was achieved [20]. Based on these results, the authors turned their attention to PET-CT-directed DA-EPOCH-R in HIV-BL and reported results as recently as 2009 [21], wherein 8 patients had been treated with 100% CR rate and OS and no TRM. Results updated as of September 29, 2011, indicate that each patient was treated with either three or four total cycles of DA-EPOCH-RR, and all remain in CR [22]. Of note no patients in this trial had CNS involvement, and suspension of HAART was a requirement.

The AMC evaluated the addition of rituximab to DA-EPOCH for patients with newly diagnosed ARL in a randomized phase II trial (AMC 034 [23]), in which patients received either rituximab concurrently with each cycle (Arm A) or weekly for six cycles upon completion of DA-EPOCH (Arm B). DA-EPOCH was administered for two cycles beyond CR for a total of between 4 and 6 cycles. Although most patients had HIV-DLBCL, a significant proportion (27/106; 25%) had HIV-BL. When the response rate was analyzed in all treated patients who had DLBCL, CR occurred in 25 of 35 patients (71%; 95% CI, 54%–85%) in the concurrent arm and 20 of 44 patients in the sequential arm (46%; 95% CI, 30%–61%). For those who had Burkitt-like lymphoma and other highly aggressive subtypes, CR occurred in 10 of 16 patients in the concurrent arm (63%; 95% CI, 35%–85%) and 9 of 11 patients in the sequential arm (82%; 95% CI, 48%–98%). The study was not powered to evaluate differences in patient outcomes between study arms based upon histology (DLBCL versus BL).

At the 2011 ASCO Annual Meeting, Evans et al. [24] reported on their single-institution experience using both R-Hyper-CVAD ($n = 7$) and R-EPOCH ($n = 14$) in HIV-BL. CR was achieved in 43% of patients treated with R-Hyper-CVAD patients, versus 71% in those treated with R-EPOCH. Febrile neutropenia was observed in 86% versus 29% of patients and tumor lysis syndrome (TLS) in 43% versus 14% of patients for those treated with R-Hyper-CVAD and R-EPOCH, respectively. The authors interpreted this data as suggestive of the possibility that R-EPOCH may result in a higher rate of CR and lower rate of infectious complications and TLS, when compared to R-Hyper-CVAD.

2.4. PETHEMA Regimen. The Spanish cooperative group Programa Espanol de Tratamiento en Hematología (PETHEMA) reported in 2008 their outcomes in HIV-BL patients, as treated identically to BL patients without HIV [25]. Their regimen was based upon one devised and reported by the German Multicenter Study Group for the Treatment of Adult Acute Lymphoblastic Leukemia (GMALL) [26] and relied on a short, intense, non-cross-resistant cocktail of cytotoxic agents, along with rituximab (a total of twelve agents are included in the protocol). In the PETHEMA trial, although three HIV-BL patients died of infectious causes, the remaining 16 (84%) achieved CR. This regimen may involve a higher incidence of toxicity, as 18% of HIV-negative patients and 32% of HIV-BL patients (P = NS) were not able to receive the full 6 cycles of planned therapy. Nevertheless, neither the 2-year DFS (93%; 95% CI, 82%–99% in HIV-negative and 87%; 95% CI, 72%–99% in HIV-positive) nor the 2-year OS (82%; 95% CI, 65%–99% in HIV-negative and 73%; 95% CI, 54%–92% in HIV-positive) differed significantly. CNS involvement was rare in this series (3/17 among HIV-negative; 1/19 among HIV-positive), though it was reported by the authors as not impacting outcome.

Expanded results from use of this regimen in 72 HIV-BL patients were reported at the ASH 2010 Annual Meeting [27]. Complete response (CR) was attained in 49 pts (81%), 7 (12%) died in induction, and 4 (7%) were resistant. No relapses were observed after a median follow-up of 2.6 years. In a multivariate analysis, CD4 count <200/mL and involvement of 2 or more extranodal areas predicted for inferior rates of CR, while CD4 count <200/mL and Eastern Cooperative Oncology Group (ECOG) performance status (PS) greater than 2 predicted for inferior OS.

3. Areas of Uncertainty

3.1. Rituximab. The use of rituximab in patients with ARL has garnered controversy since the reporting of AMC 010 [28], in which the risk of infection-related deaths appeared to offset any benefit of the drug in patients with ARL (80% of which had DLBCL histology) treated with a chemotherapy backbone of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). In AMC 034 [23], among eight patients with baseline CD4 counts below 50/μL, three (38%) experienced treatment-related infectious fatalities. A retrospective review of HIV-BL patients treated with aggressive regimens has questioned whether rituximab improves outcomes [29].

However, in AMC 034, which had a relatively larger proportion of patients with HIV-BL as compared to AMC 010, rates of serious infection, and of infection-related death, were modest and not greater than what would be expected with EPOCH alone. The incorporation of rituximab into the PETHEMA regimen corroborates the idea that high cure rates with modest rates of infectious complications can be achieved in patients with HIV-BL [27]. Similarly, the safety data of rituximab plus EPOCH reported in patients with HIV-DLBCL [20], and implicit in the 100% survival preliminarily reported for those with HIV-BL [22], indicates that rituximab can be safely given to patients with ARL,

particularly to those in whom baseline CD4 count is greater than 50/μL. In the HIV-negative population, the addition of rituximab appears to improve outcomes in BL when added to intensive multiagent chemotherapy [30]. Ultimately, in the absence of randomized data in patients with HIV-BL (which is uniformly CD20+), the overwhelming evidence of the safety and efficacy of the addition of rituximab to chemotherapy in both HIV-DLBCL and HIV-BL warrants its ongoing inclusion in protocols for all patients with ARL.

3.2. Relapsed/Refractory Disease and Stem Cell Transplant. No prospective data is available regarding the treatment and outcome of relapsed and/or refractory (rel/ref) HIV-BL. The AMC has conducted a retrospective study of patients with ARL treated at member institutions [31] and found that of 12 patients with rel/ref HIV-BL, none received stem cell transplantation (SCT), and only one patient survived beyond one year, only to succumb to malignancy. A French report of 14 patients with ARL treated with autologous SCT (ASCT) included two patients with HIV-BL, both of whom died within a month of transplant due to refractory disease [32]. On the other hand, the City of Hope reported that four of five HIV-BL patients were alive in CR at between 20 and 60 months from time of ASCT [33]. In an ongoing Italian trial of patients with HIV-BL, with a provisional intensification phase that includes ASCT [34], thirteen patients have been treated with 38-day induction consisting of methylprednisolone, cyclophosphamide, vincristine, rituximab, methotrexate, VP-16, and doxorubicin, with IT prophylaxis. Those with <CR after induction were referred for ASCT. They report successful transplantation of three such patients, though specific data regarding EFS and OS in this small population remains unclear. Another small series documenting the feasibility of ASCT in ARL [35] did not specify outcomes for HIV-BL patients. Even in the HIV-negative population, data regarding management is scarce. A retrospective evaluation that included 32 patients with rel/ref BL [36] found that ASCT was associated with 3-year OS of 37% in chemosensitive disease, but only 7% in chemoresistant disease, with most patients in the latter group relapsing and dying within six months.

3.3. Older Patients. Patient's age above 40 years has been recognized as a risk factor for poor outcome in BL since at least 1990 [8]. It also bears noting that, while Magrath et al. [13] achieved a 100% 2-year OS with CODOX/M-IVAC when treating adults with median age of 25, a similar regimen, when applied to patients with median age of 47 [15], yielded a seemingly inferior 2-year OS of 71%. Nonetheless, a recent review of HIV-negative BL suggests that, since the year 2000, a higher proportion of patients above 40 are being included in clinical trials and the gap in their prognosis is narrowing [37]. Although this might suggest that these "older" patients ought to be treated similarly to younger adults, it remains unclear whether this holds true for those with HIV-BL. The reports in patients with HIV-BL that support the use of Hyper-CVAD [10], DA-EPOCH-RR [22], and the PETHEMA regimen [25] have each included patients over 40, though none provided outcome data specific to this subset. The median age of patients enrolled in the ongoing AMC 048 trial, as of last report, was age 40 [38], so this may permit further comparison between HIV-BL patients above and below this age. Consideration of patient age is likely to increase in the future, given the recent documented increase in the number of persons over 40 living with HIV, which now account for over 40% of the HIV-positive population in the United States [39].

3.4. Central Nervous System Involvement. In each of the HIV-BL-specific series discussed above (Table 1), the incidence of reported CNS involvement was low, and no clear conclusions are apparent with regard to the clinical impact of CNS involvement at the time of diagnosis. One controlled trial that predated modern chemotherapy sought to address the role of CSF prophylaxis in BL ($n = 10$ each in control and treatment arms; all patients HIV-negative). In this trial, there was no difference between the arms in terms of subsequent development of CNS disease [40]. However, given the propensity of BL to relapse in with CNS involvement, the poor outcomes seen in such cases [5, 41], and the relatively low risk of added toxicity observed with the addition of CNS prophylaxis, all recent trials/series have employed aggressive CNS-directed prophylaxis with IT chemotherapy.

3.5. Antiretroviral Therapy and Supportive Care. The use of HAART appears to improve response to chemotherapy and clinical outcomes when used in ARL [42] and has been shown as early as 1996 to be safely administered with infusional CDE (cyclophosphamide, doxorubicin, and etoposide) in patients with HIV-related NHL [17]. Although controlled data is lacking as to the appropriate use of HAART in HIV-BL, HAART has been included in patients treated with Hyper-CVAD [10]; the excellent results achieved with the PETHEMA regimen [25], wherein HAART was mandatory, seem to weigh in favor of its use. On the other hand, it bears noting that the NIH has shown that safety and efficacy can be maintained with suspension of HAART in patients with HIV-related NHL, during the administration of aggressive chemotherapy [18]. Use of Zidovudine is avoided in HAART regimens for ARL patients due to the risk of myelosuppression, and deleterious interaction between HAART agents and chemotherapy, such as that between tenofovir and methotrexate, have been documented [43].

HIV patients are prone to development of BL at higher CD4 counts as compared to other AIDS-associated malignancies [44]. However, lower CD4 counts may have contributed to the higher rates of infectious deaths observed both in HIV-BL patients treated with Hyper-CVAD [10] and in ARL patients treated on AMC-010 with R-CHOP [28]. Subsequent trials [20, 21, 23] seem to clearly support the safety and efficacy of aggressive chemotherapy, including rituximab, in patients with CD4 counts greater than 50/μL. Rituximab should be held in patients with very low CD4 counts (<50/uL) due to the increased risk of infections associated with this drug in this subset of patients. Patients on treatment with rituximab with active hepatitis B (HBV)

Table 1: Comparison of trials/series including patients with HIV-BL.

Chemotherapy regimen (reference)	Number of patients	Patient characteristics	ORR (%)	CRR (%)	OS/EFS	Comments
Hyper-CVAD [10]	13	6 with BL, 7 with L3-ALL; 31% with preexisting HIV; median CD4: 77/μL 23% CSF+	100	92	48% OS at 2 years	HAART appeared to improve outcome; CNS ppx: alternating MTX and Ara-C $\times$ 16 total
CODOX-M/IVAC [14]	8	88% with stage IV disease; median CD4: 149/μL 21% CSF+	N/A	63	57% EFS at 2 years	Impact of HAART unclear; CNS ppx: Ara-C (x2) and MTX with each cycle
DA-EPOCH-R [21]	8	56% with stage III or IV; 76% with extranodal disease; CD4 count data N/A; proportion CSF+ N/A	100	100	96% EFS at 35 mo.	HAART use unclear; CNS ppx: MTX $\times$ 6 total
DA-EPOCH-R [23] Concurrent	51*	25% with HIV-BL*; 79% with advanced stage; median CD4: 181–194/μL	88	73	70% OS at 2 years	CRR for HIV-BL: 63% (10/16)
Sequential	55*	CNS ppx and HAART at discretion of treating physician	77	55	67% OS at 2 years	CRR for HIV-BL: 82% (9/11)
PETHEMA [25]	19	58% with stage III or IV; 89% with preexisting HIV; 58% with CD4 count >200/μL 5% CSF+	88	88	77% OS at 2 years	HAART mandatory; CNS ppx: MTX, Ara-C, Dex $\times$ 8

HIV: human immunodeficiency virus; HIV-BL: HIV/AIDS-related Burkitt lymphoma; ORR: overall response rate; CRR: complete response rate; OS: overall survival; EFS: event-free survival; L3-ALL: Burkitt cell acute lymphoblastic lymphoma; HAART: highly active antiretroviral therapy; CSF: cerebrospinal fluid; CNS: central nervous system; MTX: methotrexate; Ara-C: cytarabine; Dex: dexamethasone; N/A: not available. Please refer to text for explanation of chemotherapy regimen abbreviations.

*Most patients treated as part of AMC 034 had HIV/AIDS-related DLBCL (see text for further explanation).

infections should be treated concurrently with lamivudine to prevent hepatitis B reactivation. However, single-agent HBV prophylaxis in the absence of HAART promotes the emergence of resistant strains of HIV, and the use of HAART should therefore be strongly recommended in this population, in accordance with US Department of Health & Human Services Guidelines [45]. Routine supportive care for HIV-BL includes prophylaxis against tumor lysis, CNS disease, and opportunistic infections, especially pneumocystis carinii, fungal infections and mycobacterium avium-intracellulare. The use of granulocyte colony-stimulating factors is also recommended beginning 24–48 hours after treatment until postnadir recovery of white blood cell counts given the myelosuppressive potential of BL chemotherapy regimens.

4. Conclusions

No available randomized data directly compare currently used regimens in BL in either the HIV-positive or HIV-negative populations. Nevertheless, the trials described in this paper suggest that patients with HIV may be treated with similar regimens as their HIV-negative counterparts along with appropriate supportive care. The exception to this are HIV patients with baseline CD4 counts below 50/μL, as these patients have historically been either excluded from receiving rituximab in clinical trials or shown to be at significant risk for treatment-related mortality [23].

It remains important to distinguish HIV-BL from HIV-DLBCL, just as it is essential to distinguish the two histologies in the HIV-negative population. Those with HIV-BL, for instance, have distinct oncogenic mechanisms [4], higher rates of CNS involvement [18], and more aggressive clinical course that warrants more intensive therapy [46], as compared to those with HIV-DLBCL. As a result of these differences, the regimens for HIV-BL tend to carry greater risks of TRM as compared to those used for HIV-DLBCL, but with lower rates of late relapse, resulting in long-term survival rates that tend to approximate 50–80% for either histology [10, 16, 18, 20, 23–25, 34].

With respect to chemotherapy regimens used in untreated HIV-BL, several conclusions seem reasonable: (1) though the number of patients was very small, Hyper-CVAD appears effective, but may carry an increased risk of mortality in patients not receiving HAART or with poor performance status. The addition of rituximab to Hyper-CVAD has not shown significantly improved patient outcomes in HIV-BL. (2) CODOX-M/IVAC is associated with high CR rates but unacceptable neurotoxicity and myelosuppression. Modification of CODOX-M/IVAC by decreasing the dose of methotrexate, capping the vincristine dose, modifying the cyclophosphamide dose schedule, and increasing doxorubicin doses have reduced toxicity while preserving efficacy. The addition of rituximab to the modified CODOX-M/IVAC regimen is under investigation by the AMC. (3) Although the PETHEMA regimen achieved excellent clinical outcomes, the addition of rituximab to this or a similar regimen has not been studied prospectively. In addition, the mandatory use of HAART in this trial demonstrated the feasibility of such an approach. (4) Results for the infusional DA-EPOCH chemotherapy backbone (as reported by both the NIH and

Table 2: Paradigms in the treatment of HIV/AIDS-related Burkitt lymphoma.

(i) Hyper-CVAD appears effective but may carry an increased risk of mortality in patients not receiving HAART or with poor performance status. The addition of rituximab to Hyper-CVAD has not shown significantly improved patient outcomes in HIV-BL.
(ii) CODOX-M/IVAC is associated with high CR rates but unacceptable neurotoxicity and myelosuppression. Modification of CODOX-M/IVAC has reduced toxicity while preserving efficacy. The addition of rituximab to the modified CODOX-M/IVAC regimen is under investigation by the AMC.
(iii) Although the PETHEMA regimen achieved excellent clinical outcomes, the addition of rituximab to this or a similar regimen has not been studied prospectively.
(iv) Results for the infusional R-EPOCH chemotherapy backbone (as reported by both the NIH and AMC) are promising, with high CR rates, and warrant further prospective investigation in larger trials.
(v) Patient screening for CNS involvement, along with appropriate CNS prophylaxis, is recommended and is particularly important with the use of R-EPOCH, as none of the agents in this regimen has significant penetration of the CNS.
(vi) There are insufficient data to support autologous stem cell transplantation as initial therapy for HIV-BL patients, though transplant may benefit a subset of patients with chemosensitive relapsed disease.
(vii) Supportive care for HIV-BL patients is important and includes HAART as well as prophylaxis against tumor lysis syndrome, CNS relapse, and opportunistic infections.

AMC) are promising, with high CR and OS rates, and warrant further prospective investigation in larger trials.

In addition, the following tenets of effective therapy, though lacking the support of randomized data, seem warranted: patient screening for CNS involvement along with appropriate CNS prophylaxis is recommended and is particularly important with DA-EPOCH, as none of the agents in this regimen achieves clinically meaningful CNS penetration. Insufficient data exist to support HDT-ASCT as initial therapy for HIV-BL or as consolidation therapy for those in first CR, though it may benefit a subset of patients with chemosensitive relapsed disease. Supportive care for HIV-BL patients is important and includes HAART, as well as prophylaxis against tumor lysis syndrome, CNS disease, and opportunistic infections. The selection of individual regimens must be made by weighing the risks and benefits for individual patients.

In closing, Table 2 provides in summarized format what we believe are some of the most important principles supported by our review of the existing data for the treatment of HIV-BL.

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Review Article

Epidemiology, Diagnosis, and Treatment of HIV-Associated Non-Hodgkin Lymphoma in Resource-Limited Settings

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Lymphoma was a common complication of HIV infection in the pre-antiretroviral era, and the incidence of HIV-associated lymphoma has dropped dramatically since the introduction of combination antiretroviral therapy (cART) in resource-rich regions. Conversely, lymphoma is an increasingly common complication of HIV infection in resource-limited settings where the prevalence of HIV infection is high. Relatively little is known, however, about the true incidence and optimal treatment regimens for HIV-associated lymphoma in resource-poor regions. We review the epidemiology, diagnosis, and treatment of HIV-associated non-Hodgkin lymphoma in developing nations and highlight areas for further research that may benefit care in both settings. Examples include risk modification and dose modification of chemotherapy based on HIV risk factors, improving our understanding of the current burden of disease through national cancer registries, and developing cost-effective hematopathological diagnostic strategies to optimize care delivery and maximize use of available chemotherapy.

1. Introduction

An association between the acquired immunodeficiency syndrome (AIDS) and lymphoma was first suggested in 1982 after four young men in San Francisco with severe immunodeficiency were diagnosed with a "Burkitt-like lymphoma" [1, 2]. Since that time, HIV has been identified as the causative agent of the underlying immunodeficiency and non-Hodgkin lymphoma (NHL) was designated as an AIDS-defining malignancy [3]. While most of the early descriptions of the emerging immunodeficiency syndrome were reported in patients living in the United States, most of the burden of HIV disease now affects resource-limited nations, with approximately two-thirds of HIV-positive individuals living in sub-Saharan Africa and only 8% within Western nations [4]. The discovery and widespread use of combination antiretroviral therapy (cART) in resource-rich countries has both decreased the incidence of HIV-associated lymphoma and improved its prognosis [5, 6]. While the availability of cART has improved in resource-poor nations due to extraordinary recent efforts, similar changes in the incidence and outcome of HIV-associated lymphomas have not yet been noted. Therefore, increased efforts should be dedicated to improving the diagnosis, supportive care, and treatment of this disorder in these nations.

2. History and Epidemiology

The incidence of the three AIDS-defining NHLs, diffuse large B-cell lymphoma (DLBCL), primary CNS lymphoma, and Burkitt lymphoma (BL), increased steadily in the United States between 1981 and 1990, at which time the incidence rate leveled off and began declining with the widespread availability of cART in 1996 [7]. Over 25,000 Americans with HIV have been diagnosed with NHL since the beginning of the HIV pandemic [8].

In Africa, the AIDS epidemic was first reported by Clumeck et al. and Van De Perre et al. in 1984 when they

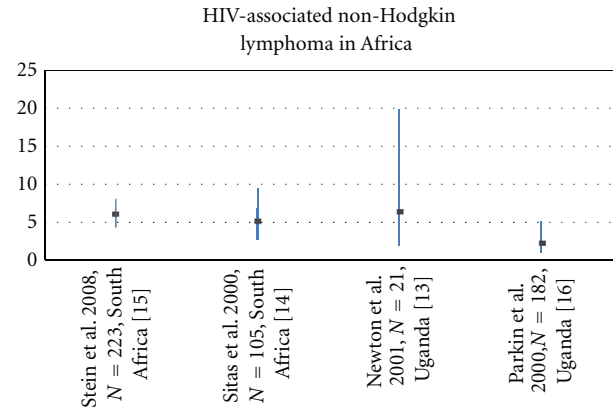

Figure 1: Odds Ratios (ORs) with 95% Confidence Intervals (CIs) for the association between NHL and HIV infection in sub-Saharan Africa.

described a group of Africans cared for in Belgium with profound immunosuppression and a series of patients in Kigali, Rwanda with infectious complications or generalized Kaposi sarcoma, respectively [9, 10]. Nearly equal numbers of men and women were reported in these articles, in contrast to the predominately male epidemiology described early in the United States HIV experience. The incidence of NHL in sub-Saharan Africa did not increase as markedly early in the HIV epidemic when compared to the increase seen in the US HIV population. This has been attributed to the higher rate of infectious complications that were seen in HIV-infected patients in resource-limited nations, which prevented the subsequent development of malignancies [11]. This decreased incidence may also simply reflect underreporting, attributable to more limited pathology services in combination with differences in the epidemiology of adenopathy in sub-Saharan Africa. Since the most common empiric clinical diagnosis of persistent lymphadenopathy is tuberculosis and not lymphoma, many cases may have gone unnoticed without biopsy confirmation [12]. By the mid-1990s, an increase in lymphoma risk associated with HIV was noted and at present most studies report a 5-6-fold increased risk for development of NHL in HIV-infected individuals living in Africa as seen in Figure 1 [13–16].

On average, patients in Africa present with HIV-associated complications at a higher CD4 count compared to those in resource-rich nations. With current supportive care, the burden of HIV-associated NHL is currently estimated at about 15,000 per year in the equatorial belt of Africa alone [17, 18]. The true incidence is believed to be higher, due to continued limitations in diagnosis and presentation to medical care, though the HIV-associated risk for NHL still does not seem to be as high as in resource-rich nations in the pre-cART era. Data from the International Agency for Research on Cancer shows that the incidence of NHL in most countries of Africa exceeds that of the USA by 2–5-fold. Although cancer registry data in Africa do not routinely capture the HIV status of new cancer cases, Figure 2 clearly illustrates that the incidence of NHL is highest in African countries with a high prevalence of HIV infection, though part of this trend may reflect improved diagnosis associated with HIV clinics.

The Kampala Cancer Registry is one of the oldest continually operating cancer registries in Africa and one of two which are WHO-certified. This registry was created in 1954 and enables an estimation of the impact of HIV infection on rates of malignancy in the area and serves as a tool for ongoing research [19]. The incidence of NHL in Kampala has increased 6.7% annually in men and 11% annually in women since the beginning of the HIV pandemic [20]. Linking HIV and cancer registries in Uganda showed that the incidence of NHL was 6.7-fold higher among HIV-infected persons in Uganda compared with those who are HIV negative, lending credence to the hypothesis that the increase in NHL incidence in sub-Saharan Africa is in part fueled by the HIV pandemic.

Comprehensive data on survival after a diagnosis of NHL in HIV-positive persons are lacking in both resource-rich and resource-poor regions. However, two recent studies highlight the discrepancies in survival between patients in these two settings. In the USA, 47% of HIV-positive persons diagnosed with non-CNS NHL were alive 2 years after their diagnosis [21], which was nearly identical to the survival among HIV-positive Ugandans who received cART [22]. Of note, however, is the fact that 100% of HIV-positive Ugandans with NHL who failed to receive cART died within one year of NHL diagnosis, highlighting the importance of the comanagement of HIV and cancer.

Increasing the number of such registries and the quality of data collected will contribute significantly to improving our understanding of the epidemiology of lymphoma in Africa. Collecting information on HIV-associated malignancies at clinics that distribute antiretrovirals is one potential way to increase the available data.

3. Diagnosis

A necessary complement to expanded cancer registry data in resource-poor nations is continued improvement in diagnostic accuracy, especially of hematological neoplasms. The accurate diagnosis of lymphomas can be challenging, even for pathologists in developed nations without hematopathological specialization. Diagnostic modifications were made in 20% of a series of submitted lymphoma cases in the United Kingdom after central review. After evaluation of associated clinical data in each of the cases, the authors concluded that clinical management likely would have differed in about half of the cases with diagnostic discrepancies [23]. Similarly, the diagnosis of lymphoma in developing nations is challenging and significant modifications in final diagnosis have been reported after hematopathology review. A retrospective analysis of 207 NHL cases in Kenya resulted in the histologic reclassification of 41% of the cases [24]. An additional study by Parkins and authors reviewed 150 cases of suspected lymphoproliferative disorders from two teaching hospitals in Ghana at the time of diagnosis. After this review, modifications were made to the diagnoses of 44% of patients, and alterations in the subsequent clinical management in 31% of the 150 patients as a result. Some of the final

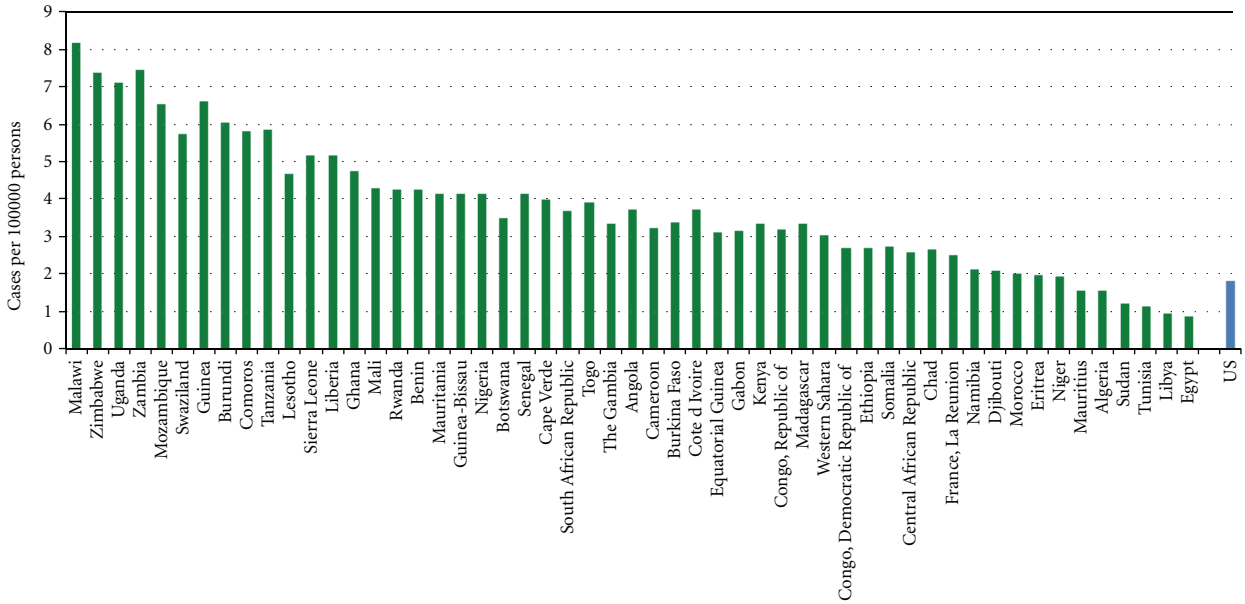

Figure 2: Incidence of non-Hodgkin lymphoma in Africa compared to the United States. Data courtesy of GLOBOCAN 2008.

diagnoses in this group included nasopharyngeal carcinoma and tuberculosis, with marked differences in management resulting [25]. The rates of significant diagnostic changes do vary between studies, however. In a prospective trial of combination chemotherapy in HIV-associated lymphoma in East Africa, pathological review led to changes in diagnosis in only 6% of the 32 patients with tissue samples available. Additionally, when the outcomes of patients with pathological confirmation were compared to those that did not undergo pathological review, no differences in outcome were noted [26].

As optimal therapies become more varied for each lymphoma subtype, it is likely that the clinical significance of diagnostic accuracy will increase. An initial attempt to improve this diagnostic accuracy in a cost-effective manner was recently reported by Naresh and colleagues through a description of a diagnostic algorithm for Burkitt lymphoma. They described a three-tiered method for diagnosis that involved increasing numbers of immunohistochemical tests in each tier if the diagnosis remained unclear. They were able to confirm a diagnosis of BL versus DLBCL in 82% of the cases using the first phase of studies (CD10, bcl2, and morphology) and in 92% of cases with the addition of testing for Ki-67, CD38, and CD44 [27]. This type of data can be used to guide developing health systems in prioritizing the diagnostic procedures that are most cost-effective.

The benefit of immunohistochemistry, not routinely available in resource-limited regions at present, extends beyond its assistance in confirming a diagnosis in this age of increasing numbers of targeted therapies. Discovering immunophenotypic differences of lymphomas in varying patient populations may promote discovery of novel targeted agents as well as further evaluation of current agents in clinical trials, even at the present time. For example, Tumwine and authors described the immunohistochemical features of 119 cases of lymphoma in Kampala, Uganda. 37% of the Burkitt lymphoma cases were CD30 positive [28], twice the rate of 18% noted in a similar series from the United Kingdom [29]. With the recent development of an antibody-chemotherapy conjugate that targets CD30, such a finding could impact treatment outcomes in this population [30].

4. Chemotherapy in the Pre-cART Era

At the present time, standard therapy for HIV-associated lymphoma in Africa does not include targeted therapy, such as rituximab, as current medication costs are prohibitive. Therefore, treatment is delivered with standard cytotoxic agents alone. Because of the similarities between the current patient population in resource-limited nations and patients in resource-rich nations in the pre-cART era, a historical review of chemotherapy for HIV-associated lymphomas is helpful for identifying potential areas of further study.

Initially, the treatment of AIDS-associated lymphoma in the United States achieved complete response (CR) rates of 53% with combination chemotherapy usually involving CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), though these responses were tempered by a rate of relapse of 54%. Additionally, significant infectious complications were noted in 42% of the cohort, which contributed to a mortality rate of 85% during a three-year study by Ziegler and colleagues reported in 1984 [31].

The next generation of chemotherapy trials in AIDS-related lymphoma studied more aggressive chemotherapy combinations in recognition of the fact that such cases typically presented at a more advanced stage, had a higher grade at presentation, an increased risk of relapse, and an increased frequency of extranodal disease compared with non-AIDS-related lymphomas. For example, Gill and authors compared

M-BACOD (high-dose methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone) with an even more intensive regimen using high-dose cytarabine and high-dose methotrexate in combination with other agents. Rates of complete remission were 54% and 33% in the two groups, respectively, and the overall survival was 11 months in the M-BACOD group compared to 6 months in the cytarabine/methotrexate arm. This trend towards shorter survival was attributed to a higher rate of opportunistic infections in the cytarabine/methotrexate arm, with more than 75% developing this complication [32]. Similarly, Kaplan and colleagues found a high-dose regimen, COMET-A (cyclophosphamide, vincristine, methotrexate, etoposide, and high-dose cytarabine), was associated with decreased overall survival when compared to standard therapy such as CHOP in patients with HIV-associated lymphoma. Outcomes in both of these studies were best predicted by pretreatment CD4 count, performance status and presence of extranodal disease [33]. Since infectious complications overwhelmed any potential advantage to these aggressive regimens, less-intensive chemotherapy regimens were studied next.

A 1997 study by the AIDS Clinical Trials Group (ACTG 142) therefore compared lower-dose m-BACOD to standard dose m-BACOD with GM-CSF support. The lower-dose regimen was associated with decreased hematological toxicity and similar rates of response. CR rate in the low-dose arm was 39%, compared to 52% in the standard-dose arm while median overall survival was 35 weeks compared to 31 weeks, respectively. Neither of these differences was statistically significant [34]. The survival impact of regimen-related toxicity in the treatment of HIV-associated lymphomas in the pre-cART era was further clarified by a trial conducted by Mounier and colleagues where the selection of chemotherapy was adjusted based on clinical risk factors present at diagnosis. Subjects treated between 1993 and 1999 were stratified based on ECOG performance status of 2–4, a prior clinical diagnosis of AIDS, and a CD4 count less than 100 cells/μL. Patients with none of these risk factors received one of two aggressive chemotherapy regimens and no differences in overall survival were noted between 4 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and 3 cycles of ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisolone). Patients with one risk factor received either standard-dose or low-dose CHOP, again without any difference in overall survival. The third group, with either 2 or 3 risk factors, received either 4 cycles of low-dose CHOP or 12 cycles of vincristine and prednisolone. There were no differences in overall survival between regimens in any of the risk groups, though lymphoma-specific outcomes were improved in the more aggressive arms of each subset. It should be noted that after 1996 most patients were started on cART, and this subset composed about one-third of the entire study cohort. While cART did decrease the number of patients with 2-3 risk factors and improve overall survival, it did not lead to any significant differences between chemotherapy regimens in risk-stratified patients [35]. Therefore, a decrease in regimen intensity and dose adjustment by hematological parameters for high-risk patients should be considered when treating lymphoma in patients not on cART.

The balance of minimizing myelotoxicity and infectious risk while optimizing lymphoma therapy has an even narrower therapeutic window in resource-limited nations due to the decreased availability of supportive care measures such as broad-spectrum antibiotics and the high rates of baseline cytopenias. Concurrent use of other supportive medications may be a major contributor to the high rates of cytopenias in African patients with HIV infection. For example, in a study of 498 patients started on antiretroviral therapy in Cote d'Ivoire, the observed 24% rate of grade 3-4 neutropenia was ascribed to the combined administration of trimethoprim/sulfamethoxazole and zidovudine (AZT). While the neutropenia usually resolved with discontinuation of the TMP/SMX, the omission of this prophylactic therapy increased the risk of infectious complications, a risk that would likely increase further in the setting of cytotoxic chemotherapy [36]. This infectious risk was demonstrated clinically in an early trial of chemotherapy for HIV-associated Burkitt lymphoma in Africa. This cohort of BL patients older than 16 years old, treated between 1993 and 1996, experienced a treatment-related mortality rate of 46% with a median overall survival of 15 weeks [37].

5. Chemotherapy in the cART Era

After the discovery and widespread use of cART in resource-rich countries, overall survival in HIV-associated lymphoma improved, in one study from an average of 6 months to 20 months [6], and more aggressive treatment regimens were once again considered. With the additional immunological support enabled with cART, the next major trial of chemotherapy in HIV-associated lymphoma compared CHOP to rituximab-CHOP combination therapy and was reported by Kaplan and authors as part of the AIDS Malignancy Consortium trial 010. This study found a trend towards increased efficacy (CR rate of 58% versus 47%) in the rituximab plus chemotherapy arm, however, also noted a significantly increased risk of treatment-related death in the combination arm of 14% compared to 2%. This increased risk of death was attributed to increased infectious complications during the treatment course and, on additional analysis, seemed to predominate in patients with CD4 counts <50 cells/μL. This finding supports the importance of risk stratification by CD4 count, even in patients on cART at the start of chemotherapy [38].

For a time, this report led to decreased use of rituximab therapy in patients with HIV-associated lymphoma. However, additional data was recently provided by Dunleavy and colleagues [39] and Sparano and colleagues [40] in a pair of articles published in 2010. In these studies, rituximab therapy was used to treat HIV-positive patients with DLBCL and NHL, respectively. There were no treatment-associated infectious deaths noted in the study by Dunleavy, supporting the safety of rituximab in this setting. Additionally, this study demonstrated other methods aimed at decreasing the duration of associated immunosuppression and myelotoxicity with chemotherapy regimens. The authors

utilized a decreased number of cycles of infusional EPOCH in combination with "dose-dense" rituximab (given on days 1 and 5). The EPOCH was dose adjusted based on hematological parameters per protocol prior to each cycle of therapy, thereby regulating the average neutrophil nadir. Second, the study utilized interim FDG-PET scans to guide the number of chemotherapy cycles, with one cycle given after the first negative PET-CT. By using this strategy, about 80% of the patients received only three cycles of therapy with the highest number of received cycles being 5, delivered in 12% of the subjects. The CR rate was 91% with 5-year PFS and OS of 84% and 68%, respectively. Of the 10 deaths on study, half were due to lymphoma and 5 occurred while subjects remained in remission. 3 of these deaths were due to opportunistic infection and 1 developed a secondary Burkitt lymphoma. The immediate application of this treatment regimen in resource-limited settings is prevented for multiple reasons. First, a lack of hospital beds and hospital staff relative to the large numbers of patients in need of treatment prevents delivery of five days of infusional EPOCH. Second, while this regimen is dose adjusted for hematological parameters, it is delivered with G-CSF support, a therapy that is not available in most resource-poor settings. Third, PET scans, and even CT scans, are not available in routine clinical practice at the present time to rationally select patients that may safely receive fewer cycles of chemotherapy.

Even with these limitations, however, several principles can be incorporated to improve care in resource-poor settings. Dose adjustment has been investigated in trials of chemotherapy in sub-Saharan Africa with some success. One such study, and the first prospective trial investigating chemotherapy for HIV-associated lymphomas in Africa, was performed by Mwanda and colleagues, reported in 2009 [26]. This study utilized a dose-modified oral chemotherapy regimen based on a United States trial that was completed before the availability of antiretroviral therapy [41]. The dose-modified regimen included lomustine (50 mg/m^2 day 1, cycle 1 only), etoposide (100 mg/m^2 days 1–3), cyclophosphamide (100 mg/m^2 days 22–26), and procarbazine (100 mg/m^2 days 22–26). As the initial regimen required G-CSF support, doses were decreased in the protocol to prevent this requirement. Additional modifications during therapy were also outlined, in a manner similar to the infusional EPOCH regimen. These adjustments led to a 50% dose reduction in all medications for an absolute WBC count less than 3,000 cells/μL or a platelet count under 100,000 cells/μL. For WBC count less than 1,500 cells/μL or platelets under 50,000 cells/μL doses were held until counts improved. If counts did not improve within three weeks, subjects were removed from the protocol—though this did not occur in any subjects on protocol. Median CD4 count in the 49-patient cohort was 198 cells/μL, 37% of patients were on antiretroviral therapy, and most had a history of previous opportunistic infection. 65% of the patients completed the two cycles determined by the protocol and a 6% treatment-related mortality was noted during the study, a significant improvement from previous studies. The reported CR rate was 58% with 78% having an objective response, numbers that are comparable to pre-cART studies in resource-rich nations. Median overall survival was 12 months, though a large variance was noted in patients on cART compared to no retroviral therapy with a median overall survival in the latter group of about 6 months.

This study serves as an example that prospective chemotherapy trials can be completed in resource-limited settings. It also identifies additional benefits from such studies, which may aid the management of HIV-associated lymphoma in resource-rich nations. First, this study by Mwanda and colleagues in East Africa is notable for its inclusion of female participants. In contrast to the >85% male composition of many of the other major trials in the field [6, 35, 39, 40] this cohort was composed of 60% women. Second, the chemotherapy regimen was composed of some medications that are known to cross the blood-brain barrier (lomustine, procarbazine) and without additional intrathecal therapy the rate of CNS relapse (6%) was similar compared to other trials performed prior to widespread availability of cART. Further investigation of the use of CNS-active agents in HIV-associated lymphoma therapy may be warranted, especially in situations where delivery of intrathecal therapy is difficult.

6. Supportive Care

Since platelet transfusions are currently not routinely available in most resource-limited nations [42], conditions exist to study chemotherapy regimens that decrease the need for transfusion and to evaluate adjunctive therapies that may decrease bleeding complications in the setting of thrombocytopenia such as aminocaproic acid [43]. This could improve our understanding of the optimal management of patients in resource-rich nations that have an objection to receiving blood products.

Another aspect of the regimen used by Mwanda that may warrant further study is the avoidance of corticosteroids, even though they are known to be active lympholytics. The rationale for not including corticosteroids in the study regimen is avoidance of potential exacerbation of concurrent Kaposi sarcoma (KS) and HHV-8 infection, an important consideration as the prevalence of KS is highest in East Africa [44]. Similarly, increased immunosuppression due to corticosteroid administration could be associated with increased toxicity in patients with HIV due to other infectious comorbidities. The increased risk of reactivation or infection with *M. tuberculosis* is a consideration when balancing the risks and benefits of corticosteroids in high prevalence regions [45]. Hepatitis B virus (HBV) is another infection that has been shown to reactivate more commonly when corticosteroids are included in chemotherapy regimens for lymphoma [46] and is well known to reactivate during rituximab therapy if viral prophylaxis is not administered in previously exposed patients [47]. There is a 13% rate of detectable serum hepatitis B DNA in patients admitted to Mulago Hospital in Uganda, [48] which could enable further clarification of the magnitude of risk associated with HBV reactivation compared with the treatment benefit of corticosteroids. These results could improve clinical decision-making concerning the ideal chemotherapy regimen to use in the setting of concurrent HIV and HBV infection.

7. Conclusions

While a large portion of the improvements in treatment of HIV-associated lymphomas in resource-limited nations will occur as a result of earlier diagnosis, increased access to cART, and optimal treatment of concurrent infectious disease, significant opportunities to improve the hematological management of such cases also exist. Some of these advances may also benefit patients with HIV-associated lymphoma in resource-rich nations. Examples include improved risk modification and dose modification of chemotherapy, improved diagnostic capabilities with eventual implementation of targeted therapies based on the immunophenotypic profile, and an increased understanding of optimal supportive care for patients with infectious comorbidities.

The cost of cancer care is often raised as a barrier to increasing access in resource-limited settings. On the contrary, however, it is the cost of inaction that is estimated to be much more significant. The Global Task Force on Expanded Access to Cancer Care and Control estimated that the world could have saved $131 billion in 2010 by investing in cancer treatment and prevention to limit the associated disability-adjusted life years [49]. Similarly, the 2011 World Economic Forum report identified noncommunicable diseases as a global economic threat, framing health care as an investment instead of simply expenditure [50]. This perspective, in combination with the fact that "cancer now kills more people each year in (low and middle-income countries) than AIDS, tuberculosis, and malaria combined" [51] highlights the ethical and financial imperative to improve the care of lymphoma globally and serves as a call to action for the hematology community.

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Review Article

HIV-Associated Hodgkin's Lymphoma: Prognosis and Therapy in the Era of cART

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Patients with human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) are at increased risk for developing Hodgkin's lymphoma (HL), a risk that has not decreased despite the success of combination antiretroviral therapy (cART) in the modern era. HIV-associated HL (HIV-HL) differs from HL in non-HIV-infected patients in that it is nearly always associated with Epstein-Barr virus (EBV) and more often presents with high-risk features of advanced disease, systemic "B" symptoms, and extranodal involvement. Before the introduction of cART, patients with HIV-HL had lower response rates and worse outcomes than non-HIV-infected HL patients treated with conventional chemotherapy. The introduction of cART, however, has allowed for the delivery of full-dose and dose-intensive chemotherapy regimens with improved outcomes that approach those seen in non-HIV infected patients. Despite these significant advances, HIV-HL patients remain at increased risk for treatment-related toxicities and drug-drug interactions which require careful attention and supportive care to insure the safe administration of therapy. This paper will address the modern diagnosis, risk stratification, and therapy of HIV-associated HL.

1. Introduction

Since the introduction of combination antiretroviral therapy (cART) in 1996, patients with human immunodeficiency virus (HIV) infection are living longer, with improved immune function and a reduced risk of developing acquired immune deficiency syndrome (AIDS) [1, 2]. In concert with improved viral control, there has been a substantial change in the landscape of malignancies occurring in the setting of HIV. AIDS-defining cancers such as Kaposi's sarcoma (KS) and non-Hodgkin's lymphomas (NHL) have declined significantly, though the change in NHL incidence has not applied evenly across disease subtypes. Diffuse large B-cell lymphoma, primary CNS lymphoma, plasmablastic lymphoma, and primary effusion lymphoma have all declined, while Burkitt lymphoma has remained stable. Over the same time period, non-AIDS-defining malignancies, including numerous solid tumors and Hodgkin's lymphoma (HL), have remained stable or have increased in incidence [3, 4]. The growth of an aging population with HIV has contributed to this rise, but the risk of many of these cancers remains significantly increased above that observed in the general population, suggesting an effect of ongoing virus-mediated immune suppression and stimulation on cancer risk despite the salutary effects of antiretroviral therapy [3–8].

There will be approximately 8800 new cases of HL diagnosed this year in the United States and 1300 deaths [9]. HL outside of HIV is a disease characterized by a bimodal age distribution with an initial peak at age 20–30 and a second peak at age 50–65 [10], while the median age of HL presentation in HIV is in the 30s [11]. The incidence of this disease in HIV-positive patients is 5–10 times higher than in the general population, and may be increasing since the introduction of cART [3–8, 12, 13]. Histologically, the malignant Hodgkin Reed-Sternberg (HRS) cells comprise less than 1% of the tumor cellularity, with the majority made up of surrounding polyclonal lymphocytes, eosinophils, neutrophils, macrophages, plasma cells, fibroblasts, and collagen. The HRS cell interacts with its microenvironment via cell-cell contact and elaboration of growth factors and cytokines,

which results in a surrounding cellular milieu that protects it from host immune attack. The surrounding environmental cells likewise support the HRS cells via cell-cell signaling and cytokine production which provides the necessary signals that promote proliferation and survival of the HRS cell itself. Severe immunosuppression, as in advanced HIV/AIDS, may disrupt this productive relationship with the host microenvironment, resulting in a decreased incidence of HL in the setting of profound immunosuppression. This may explain why the incidence of HL in HIV peaks at a modestly decreased CD4 count (150–199 cells/μL), and disease risk is associated with cART, but it is rarely seen at severely depressed CD4 counts [4, 14, 15]. While the introduction of cART has not resulted in a decreased incidence of this disease, it has resulted in significantly improved outcomes following treatment, resulting largely from decreased treatment-related morbidity and mortality, the ability to treat with full-dose chemotherapy regimens, and an increasing incidence of lower-risk disease. As such, patients with HIV-HL now enjoy similar response rates and progression-free and overall survivals to their stage- and risk-matched non-HIV infected counterparts.

2. Epidemiology and Pathology

The epidemiologic and pathologic pattern of HIV-associated HL is distinct from that observed in HIV-negative patients. There is an increased risk of developing HL in HIV-infected patients compared to the general population, and this risk remains increased since the advent of cART [3–8, 12, 13]. In a prospective cohort of 11,112 HIV-positive patients, the incidence of HL was nearly 14 times higher than that of the general population, with variation based on the era of diagnosis; standardized incidence was 4.5 times higher than the general population in the pre-cART era (1983–1985) compared to 32 times higher in the cART era (2002–2007) [4]. These observations were replicated in the Swiss HIV Cohort Study of 9429 HIV-infected patients, where HL standardized incidence was 9 times increased in the pre-cART era, compared with 21 times increased in the early cART era and 28 times increased in the late cART era [7]. This is consistent with multivariate analysis revealing that cART and specifically nonnucleoside reverse transcriptase inhibitors are associated with an increased risk of developing HIV-HL [4]. In addition, the pattern of histologic subtypes of HL seen in HIV-infected patients differs from the general population, with a greater proportion of mixed cellularity (MC) and lymphocyte depletion (LD) observed in the former [16, 17]. MC and LD subtypes of classical HL are correlated with more advanced immune compromise, while nodular sclerosis (NS) histology increases with higher CD4 counts and use of cART [15].

Viral oncogenesis appears to play a greater role in HIV-HL than HL in the general population. Epstein-Barr virus (EBV) can be detected in approximately one-third of cases of non-HIV-associated HL, compared to nearly all cases of HIV-HL [11, 15]. HRS cells in HIV-HL express the EBV-transforming protein latent membrane protein 1 (LMP-1), and the EBV genomes from multiple disease sites in the same HIV-HL patient are episomal and clonal, suggesting that EBV is directly involved in lymphomagenesis [18–21].

3. Clinical Presentation and Prognostic Factors

HIV-HL in the modern era presents at a median age in the mid 30s after a median time from HIV diagnosis of approximately 7 1/2 years. Approximately one quarter of patients will have a prior AIDS diagnosis at the time their cancer is diagnosed, and the majority of patients will be diagnosed while receiving cART. The median CD4 count at HL diagnosis is approximately 240 cells/μL. The most common histology is MC in approximately half of patients, followed by NS in one quarter and LD in approximately 10%. Representative pathologic images are shown in Figure 1. The majority of patients present with advanced-stage disease (Ann Arbor stage III-IV), though the incidence of early-stage disease appears to be increasing in the cART era. The majority of patients still present with systemic "B" symptoms, and extranodal involvement remains common [11, 17, 22–24].

Prior to the availability of cART, prognosis of HIV-HL was poor with very few patients cured of their disease. A number of adverse prognostic factors were identified, including MC subtype, extranodal involvement, presence of systemic "B" symptoms, and a high International Prognostic Score (IPS) [11, 25]. The development of cART has significantly changed the natural history and risk stratification of HIV-HL. The Spanish GESIDA group compared 83 patients with HIV-HL treated with cART to 21 patients with HIV-HL not treated with cART and found similarly high-risk clinical characteristics in the two groups at baseline but with significantly better outcome in patients receiving cART, including a higher complete remission (CR) rate (91% versus 70%) and longer median OS longer (not reached versus 39 months) [26]. A CD4 count >100/μL and use of cART were independently associated with a favorable outcome. Other studies have documented the importance of cART on prognosis with improved responses to chemotherapy and survival in the cART era [27, 28]. Importantly, it appears that responding to cART is significant as patients who fail to respond to cART have similarly poor outcomes as patients in the pre-cART era [28].

4. Initial Staging and Evaluation

Regardless of an underlying HIV diagnosis, all patients with newly diagnosed HL require a careful medical history including questions regarding systemic "B" symptoms, and a physical exam with attention paid to both nodal and extranodal sites. Laboratory evaluation should include a complete blood count with differential, erythrocyte sedimentation rate, and chemistry tests including a complete metabolic panel with liver function tests and albumin. Baseline HIV parameters including CD4 count and viral load should be tested, along with hepatitis B and C serologies given risk of coinfection. Patients with any HIV-associated malignancy may present with concurrent opportunistic infections or other

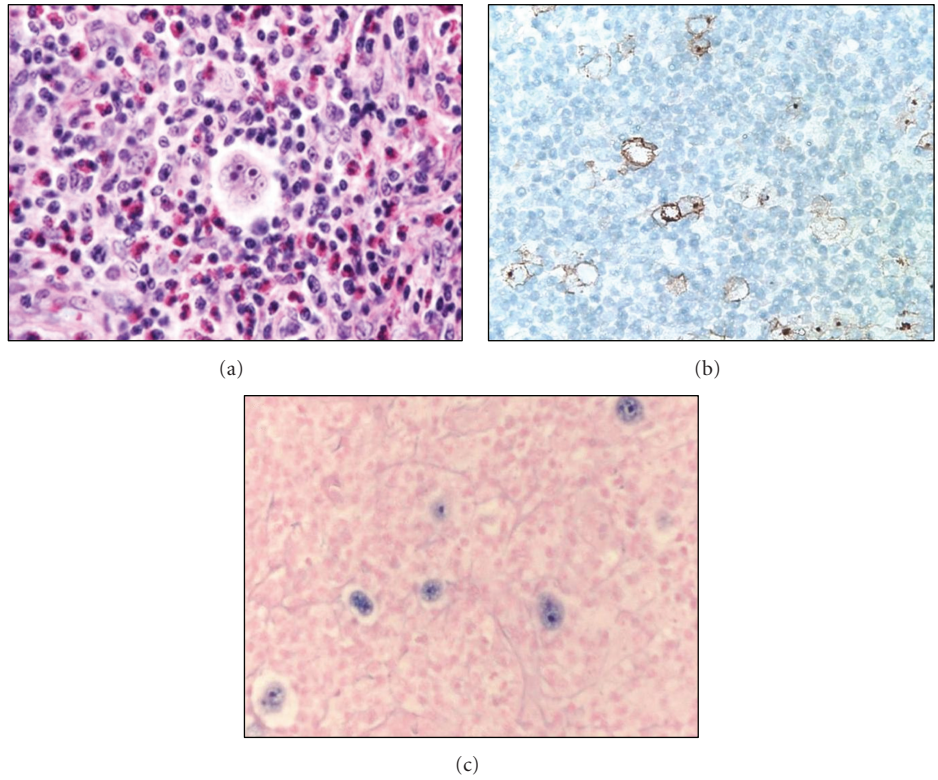

Figure 1: Representative images of mixed cellularity HIV-associated classical Hodgkin's lymphoma. (a) High-power H and E image shows a prominent Hodgkin Reed Sternberg (HRS) cell surrounded by a mixed population of lymphocytes, eosinophils, granulocytes, and histiocytes. (b) Low-power view of CD30 immunohistochemistry highlights the rare large HRS cells, as does in-situ hybridization for EBER (c), reflecting the Epstein-Barr virus (EBV) infection of HRS cells.

HIV-associated malignancies, so any findings not readily ascribed to the HL should be evaluated further as clinically indicated.

Initial radiographic staging is increasingly with Positron Emission Tomography/Computed Tomography (PET/CT) scans, which are associated with a higher sensitivity, specificity, and positive and negative predictive value than traditional CT scans in the initial staging of HL [29]. They may also be useful in evaluating for bone marrow involvement, which is often patchy in HL, though false positives do occur [30]. The value of PET/CT scans for staging specifically in patients with HIV-associated HL has not been studied and is less clear than that in the non-HIV-infected patients due to a higher rate of false positives owing to the competing infectious, inflammatory, and/or malignant processes that may produce PET-avid lesions in immunosuppressed patients. PET certainly adds to the sensitivity in detecting extranodal sites of disease, which are present in the majority of patients with HIV-HL and may be missed on conventional CT scanning. Bone marrow aspiration and biopsy should generally be performed at diagnosis and repeated following therapy for confirmation of CR only if positive at presentation. Patients with HIV/AIDS are at increased risk for cardiovascular and pulmonary disease of multiple etiologies, and these organs may also be injured by chemotherapy; as a result, all patients should have a pre-treatment assessment of cardiac function (echocardiogram or multigated acquisition scan) and pulmonary function tests, given the risks associated with doxorubicin and bleomycin, respectively.

5. Initial Treatment

The most commonly used initial systemic therapy for HL worldwide is the combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). When ABVD was given to patients with HIV-HL in the pre-cART era, the objective response rate was a disappointing 62% with a median OS of only 1.5 years [31]. Even though the majority of these patients had high-risk features at diagnosis including stage IV disease, bone marrow involvement, and "B" symptoms, these results are markedly inferior to outcomes expected in high-risk patients with HL not associated with HIV. Despite all patients receiving granulocyte-colony-stimulating factor (G-CSF), over half of these patients experienced significant neutropenia requiring treatment delays, and the incidence of opportunistic infections, despite prophylactic antimicrobials, was 29%, with the same percentage of patients experiencing fatal infections during the study period. A slightly higher response rate but shorter OS was observed when epirubicin, bleomycin, and vinblastine were given to HIV-HL patients before the introduction of cART, but most of the responders were patients with a better performance status and without a history of opportunistic

Table 1: Prospective studies of combination chemotherapy for HIV-HL in the cART era.

Regimen	*N*	Initial CD4 Count/μL,	Advanced stage	Extranodal disease	"B" symptoms	Response rate	Overall survival
EBV [32]	17	184	88%	77%	82%	82%	48% (36 m)
EBVP [33]	35	219	83%	84%	89%	91%	32% (36 m)
ABVD [34]	62	129	100%	N/R	89%	87%	76% (60 m)
Stanford V [35]	59	238	71%	47%	75%	89%	51% (36 m)
BEACOPP [36]	12	205	92%	42%	83%	100%	75% (36 m)
VEBEP [37]	71	248	70%	NR	NR	79%	69% (48 m)

EBV: epirubicin, bleomycin, vinblastine; EBVP: epirubicin, bleomycin, vinblastine, prednisone; ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; VEBEP: vinorelbine, epirubicin, bleomycin, cyclophosphamide, prednisone; NR: not reported.

infections [32]. Decreased response rates, due to dose reductions and delays, higher risk disease, and increased treatment-related morbidity and mortality all contribute to the inferior outcomes during this era.

The introduction of cART and its associated improved control of HIV infection, immune status, and performance status have allowed for administration of full-dose-intensive regimens with improved outcomes (Table 1). In the early cART era, the treatment of 35 patients with advanced high-risk HIV-HL with EBV plus prednisone (EBVP) and either zidovudine or dideoxyinosine resulted in an overall response rate of 91%, but still with a disappointing median overall survival of 16 months and a 3-year OS and DFS of 32% and 53%, respectively [33], highlighting an ongoing high rate of nonrelapse mortality. The delivery of chemotherapy with cART proved feasible, however, and demonstrated an increased ability to cure HL in a subset of these very high-risk patients.

As cART has evolved, treatment results in HIV-HL have further improved. A prospective phase 2 study of the Stanford V regimen with cART in 59 patients with HIV-HL found that less than one-third of patients required a dose reduction or delay [35]. These patients had better risk disease than those reported previously, with a greater proportion of patients with a good performance status and early-stage disease, and fewer patients with extranodal involvement and "B" symptoms. The median pre-treatment CD4 count was 238 cells/μL. Eighty-one percent of patients achieved a CR, with a 5-year OS and DFS of 59% and 68%, respectively. An IPS <2 was associated with improved freedom from progression. The more intensive regimen of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) similarly resulted in a high rate of CR in all 12 HIV-HL patients in a small report [36]. Two-thirds of these patients had a good performance status and the median CD4 count was 205/μL, but there was a greater proportion of advanced-stage disease, "B" symptoms, and extranodal involvement than that in the European Intergroup study of Stanford V. After 4 years, there had only been one relapse, but the incidence of severe neutropenia was 75%, and two patients died from opportunistic infections.

ABVD was reexamined in conjunction with cART in a cohort of 62 high-risk HIV-HL patients, 87% of whom achieved a CR, with an encouraging 5-year OS and event-free survival (EFS) of 76% and 71%, respectively [34]. An immunologic response to cART was associated with improved outcome. Finally, GICAT explored the use of epirubicin, bleomycin, vinorelbine, cyclophosphamide, and prednisone (VEBEP) in 71 patients with HIV-HL, many of whom had advanced-stage and high-risk disease by IPS [37]. The CR rate was 67%, with 69% of patients alive and 86% of patients disease-free at 2 years.

As noted earlier, the introduction of cART has resulted in an increased number of HIV-HL patients presenting with earlier-stage disease. The optimum therapy for early-stage HL is controversial and an area of active investigation. Combined modality therapy with chemotherapy and radiation has been the standard of care, but late complications of radiotherapy including secondary malignancies and heart and lung disease have prompted consideration of chemotherapy alone in selected patients. Randomized trials in nonbulky limited-stage disease have identified no survival benefit favoring inclusion of radiotherapy, and retrospective analyses of chemotherapy alone show encouraging results, so avoiding radiotherapy is an option for limited stage patients without presenting bulk, with the caveat that HIV-HL patients have not been included in these studies [45–47]. Although this has not been studied in patients with early-stage HIV-HL, it is reasonable to approach the treatment of early stage HIV-HL similarly to that of HL patients without concomitant HIV infection, with appropriate attention to supportive care.

These data demonstrate that HIV-HL patients treated with concurrent cART in the modern era achieve similarly encouraging results as those seen in the general population when disease risk factors are matched. The improved outcomes in patients with HIV-HL demonstrate the importance of improved immunologic status and performance status, and the ability to treat on schedule and at full dose intensity in the modern era.

6. Relapsed and Refractory Disease

Despite improved outcomes with initial therapy, a number of HIV-HL patients still relapse, for whom prognosis is poor. High-dose chemotherapy with autologous stem cell transplantation (HDC-ASCT) remains the standard of care in HIV-negative patients with relapsed HL based on improved PFS and EFS compared to traditional salvage chemotherapy [48, 49]. In the cART era, HDC-ASCT has been shown to be

Table 2: Studies of high-dose chemotherapy with autologous stem cell transplantation in relapsed HIV-associated lymphomas.

Study	*N*	%HL	cART	Complete response	Disease-free survival	Overall survival	Treatment-related mortality
Gabarre et al. [38]	14	43%	Yes	71%	29% (26 m)	36% (32 m)	0%
Krishnan et al. [39]	20	10%	Yes	90%	85% (32 m)	85% (32 m)	5%
Serrano et al. [40]	14	21%	Yes	73%	65% (30 m)	65% (30 m)	0%
Spitzer et al. [41]	20	25%	Yes	53%	49% (6 m)	74% (6 m)	5%
Balsalobre et al. [42]	68	26%	Yes	NR	56% (32 m)	61% (32 m)	4%
Re et al. [43]	50 (27*)	38%	Yes	48% (89%*)	49% (44 m) (74% (44 m)*)	50% (44 m) (75% (44 m)*)	0%
Díez-Martín et al. [44]	53	34%	Yes	NR	61% (30 m)	62% (30 m)	NR

NR: not reported.
*Indicates results for only patients who received high-dose chemotherapy followed by autologous stem cell transplantation.

a feasible and successful strategy in relapsed or refractory HIV-HL as well, but with significant potential toxicity [38–44, 50] (Table 2). A prospective study of HDC-ASCT as salvage therapy for AIDS-related lymphomas included 50 patients, 24 of whom actually received the planned HDC-ASCT [50]. The median OS for the entire cohort was only 7 months, but the median OS for patients undergoing transplantation had not been reached at 44 months, demonstrating that a favorable outcome can be achieved in selected cases of relapsed HIV-HL. These findings are supported by a retrospective analysis of HDC-ASCT in relapsed HIV-associated lymphoma patients (one-third of whom had HL), where PFS and OS were similar to an HIV-negative cohort matched for disease risk factors [44]. The incidence of grade 3 and 4 toxicities following HDC-ASCT for HIV-HL is approximately 30–40%, including upper and lower gastrointestinal toxicity, hepatotoxicity, and neutropenic infections [38–44, 50]. In addition, the rate of viral reactivation and infections with cytomegalovirus, herpes zoster virus, and/or varicella zoster virus is 10–25%, and 5–7% for fungal infections; these are similar to that observed following HDC-ASCT in non-HIV patients [38–44, 50, 51]. The rate of transplant-related mortality is also comparable to that seen following autologous transplantation in patients not infected with HIV and ranges from 0 to 5% across available studies [38–44, 50]. For appropriately selected patients, HDC-ASCT is feasible and effective salvage therapy for relapsed or refractory HIV-HL, but this should only be performed at transplant centers experienced in the administration of high-dose chemotherapy to HIV-infected individuals.

The data exploring the use of allogeneic stem cell transplant are retrospective or based on case reports. The Center for International Blood and Marrow Transplantation Research reported the experience of 27 HIV-associated lymphoma patients treated with allogeneic transplantation from 1986 to 2003 [52]. Two-year OS was only 22% in this group, although survival was improved in the post- compared with pre-cART era. Given the limited experience and high-risks of this approach, allogeneic stem cell transplantation should be considered experimental and optimally performed in the setting of a clinical trial.

For patients who are not candidates for, or who have relapsed after, HDC-ASCT, traditional chemotherapy agents remain available as monotherapy or in combination. While these therapies may induce remissions, this is without significant opportunity for cure and is associated with ongoing chemotherapy toxicities and immune suppression. Novel agents are now becoming available for relapsed/refractory HL, though they have not been studied to date in the HIV-HL population. Brentuximab vedotin (SGN-35) is a monoclonal antibody against CD30 that is bound to the microtubule toxin monomethyl auristatin E (MMAE) and has recently been FDA approved for the treatment of Hodgkin lymphoma that has relapsed after HDC-ASCT, or in patients ineligible for ASCT. In non-HIV-infected HL patients, all of whom had failed prior HDC-ASCT, the overall response rate was a remarkable 75% with 34% of patients achieving a CR, many of which appeared durable [53]. This novel targeted therapy emerges as an appealing chemotherapy-sparing treatment option for relapsed HIV-HL patients who have relapsed after, or are not candidates for, high-dose chemotherapy. Additional novel agents are currently under investigation and appear promising in HL, including mTOR inhibitors and histone deacetylase inhibitors, among others.

7. Restaging and Follow-Up

Following completion of therapy, restaging with PET/CT scans in non-HIV-infected HL patients is better at differentiating between viable and necrotic/fibrotic tumor than traditional CT scans and has a higher positive and negative predictive value [54]. In addition, an interim PET/CT response after 2-3 cycles of chemotherapy carries significant prognostic value in this disease, although patients who convert to PET negative at the end of therapy have been shown to do similarly well to those who are PET negative mid-therapy [55–58]. There is no evidence to date, however, that interim PET/CT results can be used to alter treatment plans, and this is being evaluated in a number of ongoing clinical trials. PET/CT for lymphoma restaging should also be interpreted with some caution in the setting of HIV, as they appear to be less specific for persistent disease than in non-HIV-infected patients [59]. Positive PET scans should,

therefore, prompt tissue sampling to confirm persistent or recurrent disease prior to altering therapy for presumed treatment failure. At present, surveillance PET/CT scans should not be performed in routine follow-up after patients achieve a CR, where CT scans alone remain sufficient.

8. Toxicity and Supportive Care

While the use of cART in combination with full-dose chemotherapy has resulted in improved clinical outcomes, HIV-positive HL patients remain at significantly increased risk for treatment-related complications, including infections and drug toxicity. Drug interactions between antiretroviral medications and chemotherapy may lead to increased levels and toxicity of some agents, while others may become subtherapeutic [60]. Numerous antiretroviral drugs, particularly the nonnucleoside reverse transcriptase inhibitors, serve as inducers of the cytochrome P450 (CYP450) system, while others, especially the protease inhibitors, inhibit CYP450. Manipulation of the CYP450 system affects the metabolism of both antiretroviral drugs and chemotherapy agents. Multiple chemotherapies, including doxorubicin, dacarbazine, vinblastine, and etoposide, are metabolized by the CYP450 system, and as such their levels may be increased or decreased in the setting of CYP450 inhibition or induction, respectively. This may lead to enhanced myelosuppression, as well as increased risk of neuropathy related to increased vinblastine levels. Stavudine and didanosine are likewise associated with neurotoxicity and should be avoided when treating with a vinca alkaloid or other neurotoxic chemotherapies (taxanes and platinums). There is evidence that use of chemotherapy and zidovudine, with its affect on myelopoiesis, and/or protease inhibitors, with their potent inhibition of CYP3A, results in greater myelotoxicity and prolonged neutropenia; avoidance of these drugs should be considered, if possible [61]. The routine, prophylactic use of G-CSF and *Pneumocystis jiroveci* prophylaxis (regardless of the CD4 count prior to treatment) is recommended for all patients to minimize the extent of myelosuppression and the risk of infection in these immunosuppressed patients. Additionally, providers should pay careful attention to pulmonary symptoms during treatment, as the effect of HIV disease and associated opportunistic infections of the lungs may potentiate the pulmonary toxicity of bleomycin. Caution should also be taken in dosing of hepatically cleared chemotherapy agents such as vinca alkaloids and doxorubicin based on bilirubin levels. Certain protease inhibitors, most notably atazanavir and indinavir, cause an indirect hyperbilirubinemia due to inhibition of UGT1A1 in the liver, but this does not affect drug clearance. An indirect hyperbilirubinemia with a normal direct bilirubin and absence of other findings of hepatotoxicity should, therefore, not prompt dose reductions of chemotherapy drugs. These risks notwithstanding cART can clearly be administered safely in combination with chemotherapy, even with dose-intensive regimens, with acceptable toxicity profiles [32–37, 62, 63]. Careful attention, however, must be paid to potential drug-drug interactions and toxicities. Given the increased risk of toxicities due to drug-drug interactions but the clear benefit of administering combination chemotherapy concurrently with cART, these patients should ideally be cared for by oncologists experienced in the care of HIV-associated malignancies, and their care requires close collaboration of a multidisciplinary care team including oncologists and infectious disease specialists.

9. Conclusions

Although the incidence of HIV-HL has not declined in the decades since the introduction of cART, the prognosis has significantly improved and is now analogous to their risk- and stage-matched HIV-negative counterparts when treated with full-dose chemotherapy and concurrent cART. The lack of randomized trials in this disease makes it difficult to identify an optimum regimen for the upfront treatment of these patients, but ABVD appears to be efficacious and well tolerated, even in high-risk patients. Further study is needed to compare treatment regimens and to validate the use of PET/CT scans in the staging, interim restaging, and post-treatment evaluation of HIV-HL. In addition, the promising experience of novel therapies like brentuximab vedotin and others will ideally be tested specifically in HIV-infected patients. Finally, evaluation of long-term and late-treatment-related toxicity is needed in patients with HIV-HL due to the increasing success of our therapies and the encouragingly long survivals of these patients in the modern era.

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Clinical Study

HIV-Associated Burkitt Lymphoma: Good Efficacy and Tolerance of Intensive Chemotherapy Including CODOX-M/IVAC with or without Rituximab in the HAART Era

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Background. The outcome of HIV-associated non-Hodgkin lymphoma (NHL) has improved substantially in the highly active antiretroviral therapy (HAART) era. However, HIV-Burkitt lymphoma (BL), which accounts for up to 20% of HIV-NHL, has poor outcome with standard chemotherapy. *Patients and Methods*. We retrospectively reviewed HIV-BL treated in the HAART era with the Magrath regimen (CODOX-M/IVAC±R) at four Canadian centres. *Results*. Fourteen patients with HIV-BL received at least one CODOX-M/IVAC±R treatment. Median age at BL diagnosis was 45.5 years, CD4 count 375 cells/mL and HIV viral load (VL) <50 copies/mL. Patients received PCP prophylaxis and G-CSF, 13 received HAART with chemotherapy and 10 rituximab. There were 63 episodes of toxicity, none fatal, including: bacterial infection, $n = 20$; grade 3-4 hematologic toxicity, $n = 14$; febrile neutropenia, $n = 7$; oral thrush; and ifosfamide neurological toxicity, $n = 1$ each. At a median followup of 11.7 months, 12 (86%) patients are alive and in remission. All 10 patients who received HAART, chemotherapy, and rituximab are alive. CD4 counts and HIV VL 6 months following BL therapy completion ($n = 5$ patients) were >250 cells/mL and undetectable, respectively, in 4. *Conclusion*. Intensive chemotherapy with CODOX-M/IVAC±R yielded acceptable toxicity and good survival rates in patients with HIV-associated Burkitt lymphoma receiving HAART.

1. Introduction

Burkitt lymphoma (BL) is a highly aggressive B-cell non-Hodgkin Lymphoma (NHL) associated with chromosomal translocations resulting in upregulation of the proto-oncogene C-MYC, which drives progression through the cell cycle [1]. It has an estimated incidence of 1200 patients per year in the United States [2]. Immunodeficiency associated BL is more commonly seen with human immunodeficiency virus (HIV) infection than other forms of immunodeficiency [3] though its incidence is lowest in patients with a CD4 count <50 cells/mL [4]. NHL accounts for approximately one third of AIDS-related malignancies and the frequency of BL is 2.4–20% of HIV-associated NHL [5].

Several trials comparing the outcomes of patients with HIV-NHL have demonstrated improved outcomes in the HAART era [6–12]. Since the availability of rituximab (R), a monoclonal antibody directed against the B cell antigen CD20, outcomes have improved in HIV-negative B-cell lymphoma [13, 14]. In patients with BL or B-cell ALL treated with the intensive hyper-CVAD regimen; the addition of rituximab was identified in multivariate analysis as a favourable prognostic factor [15]. However, trials assessing the impact

of rituximab in HIV-related NHL have shown mixed results [16–18]. An AIDS Malignancy Consortium (AMC) trial of CHOP versus CHOP-R for HIV-NHL showed a 14% rate of infectious deaths in the CHOP-R arm versus 2% with CHOP, offsetting an improvement in lymphoma control with CHOP-R [17]. However, in this study, HAART use was not uniform and most infectious deaths occurred in patients with a CD4 count <50 cells/mL. Conversely, a single institution review of patients treated with CHOP-like chemotherapy with or without rituximab for HIV-related diffuse large B-cell lymphoma (DLBCL) reported that CHOP-R was feasible in patients receiving HAART and yielded an overall survival (OS) of 86% at 30 months. This was superior to outcomes in patients receiving chemotherapy with HAART but no rituximab ($P < 0.03$), and the only toxic deaths seen with rituximab were in patients not receiving HAART [16]. A third study showed a 2-year OS rate of 75% in patients receiving rituximab with chemotherapy for HIV-associated NHL [19]. Finally, a recent trial from the AMC confirmed good tolerance of immunochemotherapy with or without HAART, though increased infectious deaths in patients with a CD4 count <50 cells/mL remained problematic [20].

In HIV-negative patients with BL, the most successful treatments are intensive multiagent chemotherapy protocols given over a short period to circumvent the development of drug resistance [19, 21–23]. Prior to the HAART era, HIV patients tolerated standard chemotherapy regimens poorly [24] and intensive chemotherapy was generally not feasible. However, a recent study of HIV-BL showed poor outcomes with standard chemotherapy, underscoring the need for intensification of therapy appropriate to the lymphoma [25]. Since the advent of HAART, intensification of chemotherapy in HIV-infected patients has been possible [26–28].

In 1996, Magrath et al. reported the use of the chemotherapy regimen CODOX-M/IVAC, which yielded a two-year event free survival of 85–92% in patients with BL [29]. In this study, we reviewed the outcomes of patients with HIV-associated BL who received intensive chemotherapy with the Magrath regimen and HAART, with or without rituximab.

2. Patients and Methods

Patients treated with the Magrath regimen were identified from the database of the hematology practices [30]. Patients from two centers in Toronto, Ontario and two centers in Vancouver, British Columbia (BC) were included. All patients had biopsy proven BL and were HIV positive at lymphoma diagnosis.

Clinical characteristics and details of therapy were abstracted by chart review. Patient demographics, details of HIV infection and treatment, BL stage, toxicity of therapy, lymphoma response to therapy, and survival were recorded. Patients underwent standard diagnostic and staging investigations for lymphoma including: history and physical examination; excisional or core needle biopsy; blood counts and chemistry; lactate dehydrogenase (LDH) level; computed tomography of the chest, abdomen, and pelvis; bone marrow aspiration and biopsy. Data were collected as to site of lymphomatous involvement and largest mass, age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS), initial and subsequent treatments, response to therapy, complications of therapy, and date and cause of death. Lymphoma diagnosis was determined by pathologists using standard diagnostic criteria [3] including identification of the t(8;14) and/or C-MYC translocation by karyotype analysis or fluorescence in situ hybridization (FISH). Pathology review was performed at the individual institutions at which the patients received treatment. BL risk was defined retrospectively by Magrath [29] and BC Cancer Agency criteria [30]. Low risk by Magrath criteria was ≤1 extranodal site of BL involvement; LDH level of ≤350 IU/L; all other patients were considered high risk. Low risk by BCCA criteria was Ann Arbor stage I, II, or III; bulk <5 cm; normal LDH level; all other patients were considered high risk.

All patients were treated as high risk. The planned Magrath regimen involved two cycles of chemotherapy repeated for a total of four treatments (CODOX-M ± R (treatment A) followed by IVAC ± R (treatment B), then repeated). All patients received central nervous system (CNS) prophylaxis with intrathecal methotrexate (MTX) and cytarabine. One patient received EPOCH instead of the second IVAC-R treatment because of neurotoxicity from ifosfamide. Chemotherapy doses and schedules were CODOX-M ± R: cyclophosphamide 800 mg/m^2 intravenously (IV) on days 1 and 2, doxorubicin 50 mg/m^2 IV on day 1, vincristine 1.4 mg/m^2 IV on days 1 and 8, methotrexate (MTX) 6720 mg/m^2 [29] or 3000 mg/m^2 IV on day 10 (MTX 3000 mg/m^2 was adopted in BC as per BC Cancer Agency guidelines in 2006, the rationale being that 3000 mg/m^2 MTX consistently penetrates the blood-brain barrier but may have less toxicity than higher doses) followed by standard leucovorin rescue [30]. Rituximab 375 mg/m^2, when given, was on day 8.

IVAC-R: cytarabine 2000 mg/m^2 IV every 12 hours on days 1 and 2, ifosfamide 1500 mg/m^2 IV given with MESNA on days 1–5, etoposide 60 mg/m^2 on days 1–5, rituximab 375 mg/m^2, if patients received it, was given on day 4.

EPOCH: etoposide 50 mg/m^2 continuous IV infusion days 1–4, doxorubicin 10 mg/m^2 continuous IV infusion days 1–4, vincristine 0.4 mg/m^2 continuous IV infusion days 1–4, cyclophosphamide 375 mg/m^2 IV day 5, prednisone 60 mg/m^2 orally days 1–5, rituximab 375 mg/m^2 on day 8.

Rituximab was given according to provincial availability; this medication was available for all ten BC patients but not for the four patients treated in Ontario.

For the first patient treated in BC and all Ontario patients (five patients in total), CNS prophylaxis or treatment was planned according to the Magrath regimen for high risk patients. This consisted of two intrathecal injections of cytarabine 70 mg and one injection of MTX 12 mg with cycle A and one MTX 12 mg with cycle B [29]. For subsequent patients from BC (nine patients total), prophylaxis was planned according to BCCA guidelines, which consisted of one injection of cytarabine 50 mg with cycle A and two injections of MTX 12 mg with cycle B [30]; two additional

injections of cytarabine are generally given when feasible for a total of eight intrathecal injections.

Adverse events were graded using the National Cancer Institute Common Toxicity Criteria. Late neutropenia was defined as an absolute neutrophil count less than 0.5×10^9/L at 12 weeks or greater following completion of all chemotherapy. Complete remission (CR) was defined as the disappearance of all evidence of lymphoma maintained for at least 4 weeks following the completion of therapy. Partial remission (PR) was defined as at least a 50% reduction in the sum of the largest diameters of all measurable lesions at 4 weeks following completion of all therapy. Progression was defined as the regrowth of previously responding lesions or the appearance of disease at a new site. Overall survival (OS) was defined as the time from diagnosis to the time of death from any cause. Patients were censored at the last known date of contact. OS was determined by the Kaplan-Meier method using SPSS for windows, version 17.0 (SPSS, Chicago, Ill, USA).

3. HIV Characteristics

Clinical data collected were HIV risk (sexual, injection drug use (IDU), etc.), CD4 count and HIV viral load at lymphoma diagnosis, prior AIDS, coinfection with the hepatitis B and/or hepatitis C viruses, and HAART use. HAART was defined as two nucleoside/nucleotide analogues and at least one protease inhibitor or a nonnucleoside reverse transcriptase inhibitor [31].

This study was performed in accordance with the requirements of the Institutional Research Ethics Board at each centre.

4. Results

Fourteen patients with HIV-associated BL diagnosed between December 2004 and August 2009 who received at least one treatment from the Magrath protocol were identified [30]. Patients were from St. Paul's Hospital, $n = 7$; Vancouver General Hospital, $n = 3$ (Vancouver); St. Michael's Hospital, $n = 2$; Sunnybrook Hospital, $n = 2$; (Toronto). One patient had features intermediate between DLBCL and BL according to the 2008 World Health Organization (WHO) classification, including a documented t(8;14) and a proliferation rate of 80% in the pericardial fluid. The clinical features were considered to be more in keeping with BL than DLBCL and he was treated as such. The C-MYC translocation was confirmed by FISH for MYC in nine patients, t(8;14) in eight, and FISH was unsuccessful in one. The t(8;14) was confirmed by karyotype analysis in one patient. The t(14;18) or BCL-2 was negative by: FISH for t(14;18) in four patients; FISH for BCL-2 in six patients and immunohistochemistry (IHC) for BCL-2 in three patients (one of these patients had focal weak positivity for BCL-2 by IHC, which is accepted in the WHO 2008 classification) [3]. The t(14;18) was negative by karyotype analysis in two patients, and BCL-2 and t(14;18) were not reported in two patients.

The baseline characteristics of the patients are shown in Table 1. Median age at BL diagnosis was 45.5 (range 32–56) years and all patients were male. By Magrath risk criteria [29], eleven patients had high risk BL and three were low risk. By BCCA risk criteria [30], all fourteen patients had high risk BL. One patient had CNS involvement at BL diagnosis. One patient receiving the Magrath regimen had an ECOG performance status of 4 prior to chemotherapy; he improved dramatically with cyclophosphamide administered as a single agent and the remainder of the Magrath regimen was given starting on day 7 with a 50% dose reduction of doxorubicin for an increased bilirubin level as per BCCA guidelines [30].

Two patients with BL not receiving the Magrath regimen as initial therapy over the same time period were identified. The first had CNS involvement at BL diagnosis, was obtunded, had several comorbidities, and received palliation. The second was initially diagnosed as DLBCL and received EPOCH-R as initial therapy; the diagnosis was later amended to BL. The lymphoma progressed following cycle 4 of EPOCH-R, and he was switched to the Magrath regimen with initial control of BL. However, the lymphoma progressed within one month of completing the Magrath regimen, and he received palliative therapy thereafter.

The median CD4 count at BL diagnosis was 375 (range 140–760) cells/mL and HIV viral load <50 (<50–200 000) copies/mL. Ten patients were receiving HAART at BL diagnosis and 13 received HAART concurrent with chemotherapy. Ten patients received rituximab with chemotherapy and HAART. Seven patients received all four planned treatments with rituximab, one patient received three treatments (he declined further therapy and remains in remission at last followup), and two patients received only two rituximab treatments (one patient is still on treatment and in one patient the reason was not clear, but it was apparently not due to toxicity). Five patients received high dose MTX at 6720 mg/m^2 as per the original Magrath protocol [29], and nine received 3000 mg/m^2 as per BC Cancer Agency guidelines [30]. Thirteen patients received hematopoietic growth factor support between chemotherapy cycles with G-CSF.

Six patients did not complete the entire four treatments of the Magrath regimen: two patients received three treatments (cycles 1A, 1B, and 2A) and four patients received two treatments (cycles 1A and 1B). Of two patients receiving three Magrath treatments, one received EPOCH-R instead of IVAC-R as the fourth treatment because of prior ifosfamide neurological toxicity. The other did not receive the second IVAC-R because of concern that there might be difficulty with collection of autologous stem cells for transplantation. This patient did not go on to transplant and declined further treatment, but did achieve complete remission and remains in remission at 27.6 months of followup. Two patients who received two Magrath treatments received additional cycles of lower intensity chemotherapy; one had a complete remission and one had no response. A third patient presented with CNS involvement and died of progressive BL following two Magrath treatments. He received eleven intrathecals in total in Magrath doses (cytarabine 70 mg and MTX 12 mg). The CSF was positive on only the first specimen in this patient, and all subsequent samples were negative for BL. Cycle 1B in this patient was complicated by anoxic

Table 1: Clinical characteristics and initial treatment of 14 patients with HIV-associated Burkitt lymphoma.

Characteristic	*n*
Age at BL presentation (years)	
≤45	7
>45	7
Age in years, median (range)	
45.5 (32–56)	
Gender	
Male	14
BL stage	
I	2
II	1
III	4
IV	7
Magrath risk[1]	
Low	3
High	11
BCCA risk[2]	
Low	0
High	14
LDH	
Normal	6
Increased	8
ECOG PS[3]	
0-1	4
≥2	5
Extranodal sites	
≥1	7
HIV risk[4]	
Sexual	9
IDU	3
CD4 at BL diagnosis	
<200	4
≥200	10
Prior AIDS[5]	
No	13
Yes	1
Coinfections	
Hepatitis B	
Known negative	9
Known positive	3
Hepatitis C	
Known negative	10
Known positive	3
HAART[6]	
No	1
Yes	13
G-CSF	
Yes	13
Number of cycles of HD-CT	
1-2	4
3-4	10
Received rituximab	
No	4
Yes	10

[1]Magrath risk: low risk has ≤1 extranodal site of BL and LDH ≤350 IU/L; all others are high risk.
[2]BCCA risk: low risk has Ann Arbor stage I, II, or III; bulk <5 cm; normal LDH level; all others are high risk.
[3]ECOG Performance Status, $n = 5$ not recorded.
[4]HIV Risk, $n = 2$ not recorded.
[5]Kaposi sarcoma, $n = 1$.
[6]HAART usually includes one nucleoside analog, one protease inhibitor, and either a second nucleoside analog or a nonnucleoside reverse transcription inhibitor (NNRTI).
AIDS: acquired immunodeficiency syndrome; BCCA: British Columbia Cancer Agency; BL: Burkitt lymphoma; ECOG PS: Eastern Cooperative Oncology Group; G-CSF: granulocyte colony stimulating factor; HIV: Human Immunodeficiency virus; HAART: highly active antiretroviral therapy; HD-CT: high dose chemotherapy; IDU: injection drug use; LDH: lactate dehydrogenase; *n*: number of patients.

brain injury secondary to sepsis, and he received palliation thereafter. The lymphoma appeared to be responding to treatment at the time that active therapy was discontinued. The fourth patient was still on treatment at the time of data analysis.

Intrathecal prophylaxis or treatment received was as follows. One patient with positive CSF for BL received eleven intrathecal injections of chemotherapy (IT) in Magrath doses (cytarabine 70 mg, MTX 12 mg) though the number of each cytarabine and MTX doses given are uncertain. One patient received nine IT, with five cytarabine 50 mg and four MTX 12 mg. Three patients received eight IT, two patients with four cytarabine 70 mg and four MTX 12 mg, and one received four each of cytarabine 50 mg and MTX 12 mg. One patient received seven IT, with two cytarabine 50 mg and five MTX 12 mg. One patient received five IT, two cytarabine 50 mg, and three MTX 12 mg. Three patients received four IT; one patient received two cytarabine 50 mg combined with MTX 12 mg and four MTX 12 mg and two patients each received two cytarabine 50 mg and MTX 12 mg. Two patients received three IT. One received cytarabine 70 mg and MTX 12 mg, with the number of each uncertain. One received cytarabine 25 mg combined with MTX 9 mg (dose reduced for increased bilirubin level as per BCCA guidelines) then two MTX 12 mg; this patient declined further IT treatments. Finally, two patients received two IT. Both received two cytarabine 70 mg; one declined further IT treatments and one died of lymphoma.

Thirteen patients were documented to have received prophylaxis for PCP infection (trimethoprim-sulfamethoxazole, $n = 10$; dapsone, $n = 2$; not specified, $n = 1$), eight for herpes simplex virus/varicella zoster virus (HSV/VZV (valacyclovir, $n = 6$; acyclovir, $n = 2$)), and four for fungal infections (fluconazole, $n = 2$; amphotericin B, $n = 2$). Of

Table 2: Treatment-related toxicity in 14 patients with HIV-related Burkitt lymphoma receiving intensive chemotherapy with CODOX-M/IVAC ± rituximab.

Treatment-related toxicity	Grade 1-2		Grade 3-4	
	n (episodes)	*n* (patients)	*n* (episodes)	*n* (patients)
Bacterial infection[1]	5	3	15	4
Culture negative febrile neutropenia	—	—	7	7
Late neutropenia	5	4		
Opportunistic infection[2]	1	1	1	1
Grade 3 or 4 hematotoxicity	—	—	14	14
Cardiac syndrome[3]	—	—	1	1
Stomatitis	3	3[4]	—	—
Increased liver enzymes	2	2	—	—
Skin reaction	1	1	—	—
Peripheral neuropathy	1	1	1	1
Hallucinations	1	1	—	—
Neurotoxicity from ifosfamide	—	—	1	1
Chemotherapy dose reductions, delays, or changes due to toxicity[5]	—	—	5	4

[1] Included: bacteremia, $n = 12$ episodes in 7 patients; urinary tract infection, $n = 4$ in 2 patients; clostridium difficile diarrhea; $n = 3$ in 3 patients; cellulitis, $n = 1$ in 1patient.
[2] Oral thrush in 1 patient, presumed HSV esophagitis in 1 patient.
[3] Poorly defined cardiac syndrome; possible CHF following day 1 of cycle 1A, requiring admission to the Coronary Care Unit; patient recovered and completed treatment modified for other toxicities.
[4] In one of these patients the grade was not reported.
[5] Dose reductions/delays: Vincristine was held in cycle 2 due to severe peripheral neuropathy in one patient. One patient did not receive day 2 cyclophosphamide in cycle 1A due to developing a cardiac syndrome, in this patient cycle 2A was given without incident. One patient presented with a bilirubin level of 361 (normal < 20) umol/L from BL hepatic infiltration. He received dexamethasone 4 mg qid (day-1) followed by cyclophosphamide 1000 mg/m^2 (day1), and by day 6 the bilirubin was 67. He received the remainder of day 1-2 chemotherapy on day 7 (doxorubicin was given at 50% dose for increased bilirubin as per BCCA guidelines), rituximab on day 8 and high dose MTX on day 15. The bilirubin normalized by day 26. The patient who had a cardiac syndrome with cycle 1A later developed ifosfamide neurotoxicity with cycle 1B. He received 2 of 5 doses of ifosfamide, 3 of 5 doses of cytarabine, and completed cycle 1B with day 3–5 etoposide given on days 15–17. For cycle 2B, he received EPOCH-R. One patient receiving full Magrath doses had cycle 2A high dose MTX delayed by 6 days because of grade 4 neutropenia.

three patients known to be hepatitis B positive, all received prophylaxis (emtricitabine, $n = 2$; lamivudine, $n = 1$).

The toxicity of treatment is shown in Table 2. No fatal toxic events were observed. The most common grade 3-4 adverse events were bacterial infection, $n = 15$; hematologic toxicity, $n = 14$; febrile neutropenia, $n = 7$. There were only two opportunistic infections, oral thrush and presumed HSV esophagitis.

One patient developed an altered level of consciousness after receiving two doses of ifosfamide. Mental status returned to normal within 48 hours after ifosfamide was held, but deteriorated when rechallenged and recovered fully within 36 hours with administration of methylene blue [32, 33]. This patient received the EPOCH-R regimen in substitution for cycle 2B. Two patients had elevated liver enzymes: one with known hepatitis C coinfection and the other had involvement of the biliary tract with BL at presentation. Dose reductions or changes in regimen were required in three patients because of therapy-related toxicity. Dose reductions and delays were as follows. Vincristine was held in cycle 2 due to severe peripheral neuropathy in one patient. One patient did not receive day 2 cyclophosphamide in cycle 1A due to developing a cardiac syndrome. In this patient, cycle 2A was given without incident. This same patient developed ifosfamide neurotoxicity with cycle 1B. He received 2 of 5 doses of ifosfamide, 3 of 5 doses of cytarabine, and completed cycle 1B with day 3–5 etoposide given on days 15–17. For cycle 2B he received EPOCH-R. One patient presented with a bilirubin level of 361 (normal < 20) umol/L from BL hepatic infiltration. He received dexamethasone 4 mg four times daily (from day-1) followed by cyclophosphamide 1000 mg/m^2 (day 1) and by day 6 the bilirubin was 67. He received the remainder of day 1-2 chemotherapy on day 7 (doxorubicin was given at a 50% dose reduction for increased bilirubin as per BCCA guidelines), rituximab on day 8, and high dose MTX on day 15. The bilirubin normalized by day 26. One patient who received full Magrath doses of MTX had cycle 2A high dose MTX delayed by 6 days because of grade 4 neutropenia. Late neutropenia occurred in five patients; all responded to administration of G-CSF.

Toxicity did not appear to occur more frequently according to the type of HAART used, for example comparing protease-inhibitor (PI) based to non-PI-based regimens, the occurrence of any toxicity, the number of toxic episodes, peripheral neuropathy, increased liver function tests, and late neutropenia did not differ between groups, nor did the requirement for chemotherapy dose reductions. The episode

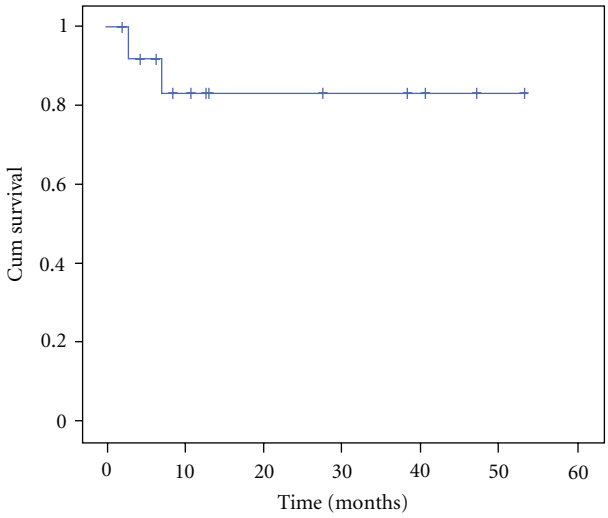

Figure 1: Overall survival of 14 patients with HIV-associated Burkitt lymphoma receiving CODOX-M/IVAC chemotherapy, 13 with HAART and 10 with rituximab.

of oral thrush, mucositis, and skin reaction (one each), however, all occurred in patients receiving PI-based HAART.

CD4 counts and HIV VL measurement were available six months following the completion of chemotherapy in five patients; the CD4 count was >250 cells/mL and HIV VL <50 copies/mL in four.

5. Survival and Causes of Death

At a median followup of 11.7 (2.0–53.2) months, 12 of 14 patients (86%) are alive and in remission (Figure 1). All 10 patients who received HAART, intensive chemotherapy, and rituximab are alive. Eleven of 12 survivors had high-risk BL and 10 had a CD4 count >200 cells/mL at BL diagnosis. There were 2 deaths, at 2.9 and 6.9 months from lymphoma diagnosis, both from progressive lymphoma. The CD4 count at BL diagnosis in these patients was 140 and 180 cells/mL. One patient presented with CNS involvement by BL and received chemotherapy without HAART or rituximab. The second patient received chemotherapy and HAART but no rituximab, and received only two cycles of therapy as he suffered anoxic brain injury secondary to sepsis, prompting a change in direction of care to palliative management. He ultimately died of progressive BL.

6. Discussion

In recent years, there has been a shift in treatment goals for patients with HIV-associated NHL. Prior to the HAART era, infectious deaths occurred frequently, as immunosuppression and myelosuppression from HIV made intensive chemotherapy regimens needed to effectively treat aggressive lymphomas difficult to deliver and lower-dose chemotherapy regimens given with palliative intent were recommended [24]. In the HAART era, it has become clear that standard dose chemotherapy for DLBCL [16, 34], and now intensive regimens for BL can be considered and used with success [26, 28, 35–37]. In this study, we reviewed 14 HIV-positive patients with BL treated with CODOX-M/IVAC±R. Most of our patients were receiving HAART at BL diagnosis and this was reflected in their relatively preserved immune parameters; the median CD4 count was 375 cells/mL and HIV VL <50 copies/mL. Previous series [38] have shown some success with intensive chemotherapy in HIV-associated BL. Wang et al. compared patients infected with HIV ($n = 8$ patients) to HIV-negative patients treated with the same regimen and found that toxicity from CODOX-M/IVAC was similar between groups, with similar rates of myelosuppression and infectious complications to HIV-negative patients [38]. A recent study of 30 patient receiving CODOX-M/IVAC and HAART showed a 3-year OS rate of 52% [39]. In addition, in a recent update from the AMC, 33 patients with HIV-associated BL were treated with modified CODOX-M/IVAC-R in which high dose MTX was given at 3000 mg/m^2. At a median followup of 9 months, the one year OS was 82% with no treatment related mortality [40]. Similarly, in 29 BL patients treated with dose-adjusted EPOCH-R, 10 of whom were HIV-positive, at a median followup of 57 months, the OS was 100% [41]. Our CR rate of 86% compares favorably with this experience, as does the projected one and two year OS of 83% (median followup 11.7 months) and tolerability of the regimen. The outcomes are similar to those described in HIV-negative patients with BL [42]. Relapses of BL tend to occur early, within a few months of diagnosis [43]. At a median followup of 11.7 months, only two patients died, both within seven months of diagnosis, and both of BL. Of the twelve other patients, none have relapsed, though two are less than six months from BL diagnosis. Moreover, ten of twelve survivors had high-risk features at presentation by Magrath criteria and all twelve survivors were high risk by BCCA criteria, suggesting that this therapeutic approach can overcome high-risk BL.

The role of immunotherapy with rituximab added to chemotherapy in HIV-BL has been a topic of discussion, though updated results from the AMC trial indicate that this agent can be safely administered concurrently with chemotherapy (EPOCH) and HAART, with good outcomes [20]. Our patients received at most four doses of this agent. The combination of eight doses of rituximab with the hyper-CVAD regimen in HIV-negative patients with BL was compared to historical patients treated with hyper-CVAD alone. There was a significant reduction in relapse rate favoring the inclusion of rituximab (7% versus 34%, $P = 0.008$), and improved 3-year OS (89% versus 53%, $P < 0.01$) [15]. Eight doses of rituximab have also been combined with an intensive chemotherapy regimen in a cohort of HIV-positive and HIV-negative patients with similar results, including a CR of 88% and 84%, respectively [36]. Whether more than four doses of rituximab included with short-course high-intensity chemotherapy such as CODOX-M/IVAC would confer additional benefit is unknown but may be an area worthy of future investigation.

In our ten patients receiving rituximab with BL therapy, the only evidence of additional complications was the occurrence of late neutropenia in five; all responded to G-CSF.

This complication appears to be rituximab related, as has been described in HIV-negative patients. Although late neutropenia appeared to be equally distributed among patients receiving PI-based versus non-PI-based HAART, interactions between antiretroviral agents and chemotherapy medications resulting in increased marrow toxicity cannot be ruled out [44, 45].

Another toxicity noted in HIV-DLBCL with rituximab was an increase in herpes virus infections [16]. For HIV-positive patients receiving rituximab with chemotherapy for NHL, we recommend HSV/VZV prophylaxis and monitoring for cytomegalovirus reactivation in those with culture negative fever. Although these measures were documented in only eight of our BL patients, there was only one presumed herpes virus infection in the current study. In the AMC trial, a higher incidence of infectious toxicity was associated with rituximab in patients with a CD4 count of <50 cells/mL [17]. Although none of our patients had a CD4 count <50 cells/mL at BL diagnosis, all ten patients who received rituximab with intensive chemotherapy and HAART are alive. It should be noted that rituximab in patients with active Kaposi sarcoma (KS) may result in severe KS flares [46].

In general, the toxicity of therapy experienced by our patients, largely bacterial infections, febrile neutropenia and grade 3-4 bone marrow suppression, was in keeping with what one would expect in HIV-negative patients receiving this chemotherapy protocol. Opportunistic infections occurred in only two patients, oral thrush in one patient and presumed HSV esophagitis in another. The only HIV-specific form of prophylaxis routinely given was for PCP, which was given regardless of CD4 count, since the CD4 count may decrease on chemotherapy. However, Montoto et al. documented a CD4 count >200 cell/mL and undetectable HIV VL at six months following the completion of BL therapy in 58% and 88% of patients, respectively, indicating good immunological recovery and virological control despite intensive chemotherapy, and our findings are in keeping with this [39].

There was a low rate of mucositis in this series, with two patients experiencing grade 1-2 stomatitis, and a third patient experiencing stomatitis with the grade not specified. One patient was treated for presumed grade 3 HSV esophagitis, and it is possible that this patient actually had mucositis. Of note, nine of the 14 patients in this series received high-dose MTX at 3000 mg/m^2 [30] as compared to the dose of 6720 mg/m^2 used in the original Magrath protocol [29], and this could have resulted in lower than expected rates of mucositis. However, the possibility that episodes of grade 3-4 mucositis were not clearly documented and recognized retrospectively cannot be ruled out.

More than half of patients (8 of 14) received all four planned Magrath treatments. Of six who received fewer intensive treatments, only two were due to toxicity. One patient had ifosfamide neurotoxicity from which he fully recovered [32, 33]; he received EPOCH-R as cycle 2B and had no evidence of lymphoma at four months. A second patient suffered anoxic brain injury secondary to sepsis and was subsequently palliated. These results are in contrast to our experience with HIV-BL in the pre-HAART era; although not fully documented and formally compared, many of our patients suffered toxic deaths despite suboptimal lymphoma chemotherapy.

Limitations of this study include its retrospective nature and small number of patients reviewed. As the study was nonrandomized, selection bias must be considered, as these results may not apply to all patients with HIV-BL. The 14 patients reported here, however, were all the HIV-BL seen over this time period with two exceptions. The first had CNS involvement at BL diagnosis, a very poor performance status, and received palliation. The second had an initial diagnosis of DLBCL made which was later amended to BL; because of the initial diagnosis, the Magrath regimen was not used as first-line treatment and this patient was not included for purposes of this report. Thus, the patients reported here represent a reasonably unselected group of HIV-BL seen over this time period. Even though two patients with HIV-BL during this period did not receive the Magrath regimen, some who did receive Magrath did not receive all planned cycles or rituximab and one did not receive HAART, CODOX-M/IVAC chemotherapy with HAART and rituximab was feasible in the majority of patients, was well tolerated by most, and resulted in acceptable lymphoma control and reasonable immunological recovery and virological suppression. As with other NHL in the HAART era [47], our data suggest that the clinical outcome of BL has improved to the point that it may be comparable to outcomes in HIV-negative patients with similar lymphomas [36, 37].

7. Conclusion

In this review of patients with HIV-associated BL treated with the intensive Magrath (CODOX-M/IVAC) chemotherapy regimen and HAART, patients had acceptable tolerance of therapy even when it included rituximab. Of ten patients who received chemotherapy, rituximab, and HAART, none has died. Eleven of twelve survivors had high-risk features, suggesting that this therapeutic approach can overcome high-risk BL. These results suggest that if HIV control is optimized, patients with HIV-associated BL who receive intensive chemotherapy and rituximab could achieve survival similar to HIV-negative BL patients without undue therapy-related toxicity.

Conflict of Interests

The authors have no relevant conflict of interests to disclose.

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