Published in final edited form as:

Leuk Lymphoma. 2012 December ; 53(12): 2383–2389. doi:10.3109/10428194.2012.697559.

Outcome of Patients with Relapsed/Refractory AIDS-Related Lymphoma Diagnosed 1999–2008 and Treated with Curative Intent in the AIDS Malignancy Consortium

U. D. Bayraktar¹, J. C. Ramos¹, A. Petrich², N. Gupta³, S. Lensing⁴, Page Moore⁴, E. G. Reid⁵, D. M. Aboulafia⁶, L. Ratner⁷, R. Mitsuyasu⁸, Timothy Cooley⁹, D. H. Henry¹⁰, P. Barr¹¹, and A. Noy³

¹Division of Hematology/Oncology, University of Miami, Miami, FL, USA

²Department of Oncology, Montefiore Medical Center, Bronx, NY, USA

³Hematology Division, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

⁴Department of Biostatistics, University of Arkansas for Medical Sciences, Little Rock, AR, USA

⁵Division of Hematology-Oncology, University of California at San Diego, San Diego, CA, USA

⁶Division of Hematology/Oncology, Virginia Mason Medical Center, Seattle, WA, USA

⁷Oncology Division, Washington University in St. Louis, St. Louis, MO, USA

⁸Division of Hematology/Oncology, University of California at Los Angeles, Los Angeles, CA, USA

⁹Department of Medicine, Boston University Medical Center, Boston, MA, USA

¹⁰Division of Medical Oncology, Pennsylvania Hospital, Philadelphia, PA, USA

¹¹Division of Hematology and Oncology, Case Western Reserve University School of Medicine, Cleveland, OH, USA

Abstract

No comparative studies exist for relapsed/refractory (rel/rfr) AIDS-related lymphomas (ARLs). To determine practices over the last decade and to assess the outcomes of salvage chemotherapy with curative intent and autologous stem cell transplantation (ASCT), we retrospectively evaluated treatment outcomes in patients with rel/rfr ARL who were treated in 13 national AIDS Malignancy Consortium (AMC) sites between 1999 and 2008 (N=88). The most commonly used second line therapies were ICE (n=34), dose adjusted EPOCH (n=17), and ESHAP (n=11). The odds of achieving a response were lower for those with non-Hodgkin lymphoma (NHL) than those with HL and for those with primary refractory disease than those with relapse. Overall survival (OS) was significantly longer for those with relapsed disease compared to those with refractory disease and for those with non-Burkitt NHL compared to those with Burkitt. OS was longer in patients who underwent ASCT compared to those who did not (1-year OS: 63.2% vs. 37.2%). However, among 32 patients (36%) who achieved CR/PR after second-line therapy 1-year OS was not different between the 2 groups (87.5% for ASCT vs. 81.8% for non-ASCT). Long-term survival in some patients with rel/rfr ARL may be possible without transplant, although transplant remains the standard of care for chemotherapy sensitive disease.

Keywords

Acquired immune deficiency syndrome; lymphoma; salvage therapy; stem cell transplantation

Introduction

Although the incidence of HIV/AIDS-associated lymphomas (ARL) has decreased and the prognosis has improved since the advent of highly active anti-retroviral therapy (HAART) in 1996[1], ARLs remain one of the major causes of death in HIV-positive individuals[2] with its incidence on HAART anywhere from 25–150 fold higher than in the HIV uninfected population. Even with dose-adjusted etoposide/prednisone/vincristine/cyclophosphamide /doxorubicin (DA-EPOCH), the regimen with the highest reported response rates in ARL patients, 26% of patients fail to achieve complete response (CR) following therapy (primary refractory disease) and about 10% of patients who do achieve a CR later relapse[3]. To date, no comparative studies exist for rel/rfr ARL. Furthermore, the last study on salvage chemotherapy for ARL was published in 2001, early in the HAART era. The available single-arm studies, report overall response rates (ORRs) to second-line chemotherapy ranging between 23–54%[4–8]. The highest ORR was reported with etoposide/methylprednisolone/cytarabine/cisplatin (ESHAP) (CR: 23%, ORR: 54%), originally developed in HIV-negative patients[8, 9]. Without an agreed upon standardized approach, rel/rfr ARL patients have usually been treated with various regimens including the aforementioned ones and ifosfamide/carboplatin/etoposide (ICE) which was also initially developed in HIV-negative patients[10]. Of note, the efficacy of ICE in HIV-positive patients is unknown.

For HIV-negative patients with rel/rfr lymphoma, autologous stem cell transplantation (ASCT) has the greatest potential for a curative outcome and is the standard of care for younger patients with disease sensitive to second-line therapy[11]. In the treatment of rel/rfr ARL, ASCT has also gained momentum since the earlier studies showed its feasibility in the HAART era[12, 13]. Recently, in a retrospective analysis of 58 HIV-positive and -negative patients with non-Hodgkin lymphoma (NHL) who underwent ASCT, Krishnan et al. reported HIV status did not affect the long-term outcome with a 2-year overall survival (OS) of 75% in both groups[14]. Similar findings were found in an analysis of European Group for Blood and Marrow Transplantation Registry (EBMTR) data[15]. However, preparation of patients with rel/rfr patients for ASCT seems to be challenging, as appreciated in an Italian, multi-center, prospective trial of ASCT in HIV-positive patients with rel/rfr ARL. Re et al. reported the first intent-to-treat analysis, enrolling 50 patients at the time of first relapse or progression. Twenty-three (46%) did not undergo ASCT due to resistance to salvage chemotherapy (n=10), toxic deaths during salvage chemotherapy (n=2), mobilization failure (n=6), early disease progression after successful mobilization (n=4), and consent withdrawal (n=1), demonstrating the need for improvement of second-line chemotherapy[16]. On the other hand, 27 patients who actually underwent ASCT achieved a 5-year OS of 75%, again mimicking the results seen in HIV-negative patients.

To determine the current practices around the nation over the last decade, to investigate the prognostic factors, and to assess the outcomes of salvage chemotherapy given with curative intent and ASCT in patients with rel/rfr ARL, we retrospectively evaluated treatment outcomes in patients with rel/rfr ARL who were treated in 13 national AIDS Malignancy Clinical Trials Consortium (AMC) sites.

Material and Methods

A total of 165 HIV-positive patients with rel/rfr NHL/Hodgkin lymphoma (HL) followed in 13 national AMC sites between 1999 and 2008 were entered in the AML rel/rfr ARL registry. Thirty-seven patients (22%) who did not receive second-line therapy, 37 patients (22%) who received second-line therapy with palliative intent, and 3 patients (2%) with primary central nervous system lymphoma were excluded from the analysis, leaving 88 patients for the current analysis. Palliative intent was defined as chemotherapy that would never be given to a patient with the intention of taking that patient to an autologous or allogeneic transplant.

Using a detailed electronic case report form, each site was required to report the demographics, HIV treatment, baseline laboratory and staging characteristics, first- and second-line ARL treatment details including best response and toxicities, the results of ASCT, if performed, and the survival status as of December 31, 2008 or last follow-up. The EMMES Corporation supervised the quality of reported data, including automated checks. Institutional review boards of each site approved the study protocol, confirming patient consent was not required as data were retrospectively collected and submitted centrally in an anonymized fashion.

Response to treatment was evaluated by each AMC site independently and staging studies were at the discretion of the treating physician. CR was defined as the disappearance of all tumor masses while partial response (PR) was defined as 50% decrease in the measurable lesions. CR and PR comprised overall response (OR). Patients who failed to achieve CR after first-line treatment or progressed through the therapy were considered to have primary refractory disease. PET scanning was not used in the definition of CR/PR as it was not uniformly available at all sites during the time frame of this study.

Descriptive statistics were computed for demographic and clinical characteristics of subjects, and comparisons were made between those who underwent ASCT (ASCT group) and those who did not (non-ASCT group) using chi-square tests or nonparametric Wilcoxon rank sum tests. Chi-square tests were used to identify subject characteristics associated with lower ORR after second-line therapy. Factors significant at the $\alpha=0.10$ level with at least 80% non-missing data were jointly investigated in a multivariable logistic regression model of ORR. ASCT was not included in the logistic regression model, as it was dependent on the response to second-line therapy rather than vice versa. OS was calculated from the initiation of second-line therapy to death or last follow-up. Kaplan-Meier estimates of 1-year survival and corresponding 95% confidence intervals based on complementary log-log transformation were computed and survival distributions compared according to various subject characteristics using log-rank tests to identify prognostic factors on OS. Factors significant at the $\alpha=0.10$ level with at least 80% data non-missing were investigated in a multivariable Cox proportional hazards model. P-values less than 0.05 were considered statistically significant.

Results

Characteristics of patients with rel/rfr ARLs

Table 1 summarizes the demographic and clinical characteristics of the 88 patients who received second-line therapy for rel/rfr ARL with curative intent. Males predominated 4:1. Median age at the time of ARL diagnosis was 41 years (range: 21–59). Median CD4 cell count at HIV diagnosis and ARL diagnosis were 110/ μ L (n=37, range: 12–1000) and 152/ μ L (n=74, range: 5–803), respectively. The CD4 cell count at the time of ARL diagnosis was <100/ μ L in 23 of 74 patients (31%), and 41 of 83 patients (49%) had a history of

opportunistic infections. At the time of initial diagnosis, 65 patients (74%) had Ann-Arbor stage III-IV disease. In addition, of 34 patients with relapsed disease, 17 had elevated serum LDH levels, 23 (68%) had Ann-Arbor stage III-IV disease, and 6 (18%) had bone marrow involvement at the time of relapse. Of 68 NHL patients evaluable, 52 (76%) had tumors expressing CD20. Of those, 31 (60%) were treated with rituximab in the first-line setting. Diffuse large B-cell lymphoma (DLBCL) was the most common histology followed by Burkitt lymphoma (BL)/variants and HL. Fifty-four patients (61%) had primary refractory disease.

Second line therapy

The second line therapies with curative intent were ICE (n=34), DA-EPOCH (n=17), ESHAP (n=11), high-dose methotrexate (MTX) variants (n=10), Hodgkin specific therapies (n=4), dexamethasone/ cytarabine/cisplatin (DHAP) (n=4), ifosfamide/etoposide (n=4) and others (gemcitabine/cisplatin/dexamethasone in 2, hyperfractionated-CVAD alternating with methotrexate/cytarabine in 1, and mechlorethamine/vincristine/procarbazine/prednisone in one patient with NHL). Of 52 patients with CD20+ NHL, 27 (52%) received rituximab in the second-line setting. Thirty-two patients (36%) had a response to second line therapy (CR, n=21; PR, n=11).

NHL histology and primary refractory disease were found to be associated with lower ORR on univariate analyses (Table 2). The ORR was 80% vs. 31% for HL vs. NHL ($p=0.004$). A logistic regression model incorporating these variables revealed that the odds of achieving OR was 83% lower for those with NHL as compared to those with HL ($p=.038$) and 67% lower for those with primary refractory disease as compared to those who had relapsed ($p=.023$).

Fifty patients (57%) developed one or more grade 3 adverse events during the second-line chemotherapy (Table 3). The most common grade 3 adverse events were thrombocytopenia (n=23) and febrile neutropenia (n=22). Six patients died due to infectious complications, including one with aspergillosis.

Autologous Stem Cell Transplantation

Only 10 of 32 (31%) patients who achieved CR/PR after second-line therapy went onto ASCT likely due to known differences in regional availability and changing treatment paradigms. Four additional patients were transplanted with stable disease and two with refractory disease. None of the 16 transplanted patients received an allo-transplant. The conditioning regimen of BCNU/etoposide/cytarabine/ melphalan (BEAM) was given in 9 patients and busulfan/cyclophosphamide in 7. There were no significant differences in demographic and clinical characteristics between the patients in ASCT and non-ASCT groups except according to race, histology, CD20 expression, and primary refractory versus relapsed disease. The ASCT group contained more subjects with unknown race, and the non-ASCT group contained more patients with DLBCL histology and disease refractory to second-line therapy (Table 1). However, it should be noted that none of the patients with rel/rfr BL underwent ASCT. The ORR was higher in ASCT group (63%) as opposed to those in non-ASCT group (31%, $p<.001$). At post-transplantation day 90, 10 patients (63%) were in CR. These included 4 patients who entered ASCT in PR and converted to CR post-transplant.

Survival

At last follow-up, 29 subjects were alive, 8 lost to follow-up, and 51 had died. Median follow-up was 88 weeks for surviving patients (range: 1–468). Median OS was 38 weeks (95% CI, 27–63). One- and two-year OS rates were 42.1% (95% CI, 30.9–52.8%) and

35.4% (95% CI, 24.5–46.4%), respectively. On univariate analyses, one-year OS was significantly higher for those with relapsed disease as compared to those with primary refractory disease (58.8% vs. 30.7%), for those with any response to second-line therapy as compared to those with no response, and for those with non-BL NHL as compared to those with BL NHL (41.5% vs. 11.9%) (Table 2). One-year survival amongst HL (78%) vs. NHL (38%) approached significance ($p=0.058$). CD4+ cell count did not affect OS. In a proportional hazards model for those with NHL, BL and variants were associated with a 2.3 (95% CI, 1.0–5.0) fold increase in the hazard of death as compared to those with other NHL ($p=0.043$) after adjusting for bone marrow involvement and disease type (primary refractory vs. relapsed disease).

Reflecting the 65% prevalence of patients refractory to second line therapy in the non-ASCT group compared with 13% prevalence in the ASCT group, OS was longer in those who underwent ASCT compared to those who did not (1-year OS: 63.2% vs. 37.2%).

Surprisingly, 1-year OS among patients who achieved CR/PR after second-line therapy was 87.5% (95% CI, 38.7–98.1%) for ASCT and 81.8% (58.5–92.8%) for non-ASCT (Figure 1). Only one patient with BL survived a year without ASCT, but succumbed to the disease.

Rituximab

In regards to previous rituximab therapy, amongst 52 patients with CD20+ NHL, rituximab was given in the first-line in 31 (60%). Although there was a trend for a lower response rate among those receiving front-line rituximab therapy as compared to those who did not (ORR: 23% vs. 48%, $p=0.059$), OS did not differ amongst patients who had and who did not have first-line rituximab (1-year OS: 40.6% [95% CI, 30.8–50.1%] vs. 40.6% [95% CI, 29.6–51.3%], $p=0.960$). Therefore, first-line rituximab therapy was not included in the Cox model.

Discussion

In this multi-center, retrospective study of 88 patients with rel/rfr ARL, we described the outcomes after second-line chemotherapy with curative intent in patients who underwent ASCT and those who did not. The patients were not randomly assigned to ASCT. Rather, patients achieving CR/PR went on to ASCT based on regional availability and changing treatment paradigms. Surprisingly, ASCT was not associated with longer OS among patients achieving a CR/PR after second line therapy with more than 80% of patients surviving 1 year in both groups. However, the numbers in this subset were very small and the survival in the non-SCT group inexplicably high.

ICE was the most commonly used second line regimen in the current cohort. High-dose cytarabine and cisplatin based regimens, ESHAP and DHAP, were also commonly used. A recent multi-center prospective trial, the CORAL study, did not demonstrate any difference between R-ICE and R-DHAP regimens with regards to response, mobilization rates, and survival in HIV-negative patients with relapsed CD20-positive DLBCL[17]. Therefore, it is not likely that switching from ICE to a different currently standard second line therapy would improve outcomes in rel/rfr ARL. The follow up Bio-CORAL study did suggest an advantage of DHAP for germinal center type DLBCL by Hans Criteria and this could be explored in HIV + patients[18, 19].

Rituximab was used in most of the patients with CD20 expressing lymphomas in accordance with the suggested improved response rates after addition of rituximab to the conventional chemotherapy regimens[20, 21]. However, CORAL demonstrated that R-ICE or R-DHAP was less efficacious in rituximab-experienced patients compared to historical controls[17]. It

is possible that using a different antibody as part of second-line combination chemoimmunotherapy may be advantageous.

The discouraging ORR of 37% in our patient cohort may be due to factors that cannot be ascertained within the limits of this retrospective study such as reduction of the chemotherapy dose intensity or excessive delays between the chemotherapy cycles. Regardless, the lower ORRs reported in our and previous studies in rel/rfr ARLs compared to those reported in HIV-negative patients demonstrate the need for better treatment strategies.

In our retrospective cohort, NHL histology vs. HL and refractory disease to the first-line therapy were independently associated with lower ORRs to the second-line therapy. Association of NHL with low CD4+ cell counts in contrast with HL, might have led to a higher prevalence of advanced HIV infection in the NHL group and a poorer prognosis. However, we did not find any impact of CD4+ cell count on the response to second-line therapy in univariate analyses. Additionally, those with relapse after CR to first line therapy rather than primary refractory disease had higher response rates to salvage therapy and longer OS suggesting that the nature of the lymphoma rather than the stage of HIV infection is the driving force behind the therapy failures. Although, International Prognostic Index (IPI) correlated with survival in HIV-negative patients with aggressive lymphomas[22], we were unable to correlate the response to second line therapy with the IPI score as the performance status was not evaluable in one quarter of the patients. Specifically, amongst the 41 CD20+ DLBCL patients, only 31 had performance status available, which is an insufficient sample size for Cox modeling.

The hematologic toxicity rates in our study were comparable to those previously reported in patients with rel/rfr ARL treated with cyclophosphamide/doxorubicin/etoposide (CDE)[7], DHAP, and ESHAP[8] and those in HIV-negative patients treated with DHAP and ICE[17]. Our number of chemotherapy-related deaths due to infections (n=6, 7%) appears higher than the 1% reported with DHAP and ICE, although our population may have been sicker than those admitted to a randomized trial with a minimum performance status requirement. Nonetheless, this demonstrates the importance of infection surveillance and treatment in these heavily pretreated, immunosuppressed patients undergoing intensive chemotherapy.

ASCT is considered to be the treatment of choice in patients with ARL since the demonstration of its feasibility[12, 13] and achievement of long-term results similar to those observed in HIV-negative patients[14] despite the lack of any comparative studies.[23]. Re et al. reported the largest prospective trial of ASCT in 50 patients with rel/rfr ARL, achieving a long-term OS and progression-free survival (PFS) of 50% where only 27 patients actually underwent ASCT[16]. In a recent retrospective analysis of 68 patients with rel/rfr ARL reported to EBMTR, PFS and OS were 56% and 61%, respectively[24]. Curiously, in those in CR/PR after second line therapy, ASCT did not affect outcome in our study. Specifically, with a median follow up of 117 weeks, we reported a 1-year OS of 88% for those who underwent ASCT and 82% for those who did not, among patients who achieved CR/PR after second-line therapy. We cannot easily explain this finding which flies in the face of randomized studies in HIV-negative patients[11]. Regardless, currently ASCT remains the current standard of care in rel/rfr ARL when feasible. A joint AMC and Bone Marrow Transplant Clinical Trials Network study currently underway may shed some light on the feasibility of ASCT in a larger setting, though no comparator arm exists.

Finally, patients with rel/rfr BL and variants in our cohort neither underwent ASCT nor survived. In the post-HAART era, although survival in HIV-positive patients with DLBCL improved to be commensurate with HIV-negative patients, mixed results have been reported

for BL, ranging from 6 month median survival using CHOP type regimens[25] to one-year OS in the 80% range with dose-intense regimens such as CODOX-M/IVAC[26] and variants[27], or hyperCVAD[28]. Our findings demonstrate a uniformly poor prognosis in HIV-positive patients with rel/rfr BL is poor, similar to those without HIV infection.

The major limitation of our study is its retrospective nature leading to reporting and selection biases with respect to treatment. Therefore, comparisons, particularly for those undergoing ASCT or not have to be interpreted with caution. Notably, almost half of the patients registered in the database were excluded either because they had not received any second-line therapy or received it palliative regimens inappropriate for transplant eligible patients. The underlying reasons likely include the reluctance of clinicians/patients to pursue aggressive therapy, poor performance status or comorbidities of HIV-positive patients. Although we found no differences between second line therapies with respect to ORR or OS, our power to detect relevant differences was limited by sample size. Finally, it is possible that the inclusion of patients treated in the early years of HAART, biased our study to include those with prior opportunistic infections and, hence, a poor prognosis.

In summary, the success of second-line chemotherapy is of utmost significance in the treatment of rel/rfr ARLs and prospective studies are desperately needed to improve salvage strategies. Whether ASCT is associated with a greater chance of survival cannot be addressed by our study due to its limitations, but some patients survived without transplant and the OS did appear surprisingly similar when one limited the analysis to patients who achieved CR/PR after second-line therapy.

Acknowledgments

Mary Crowe, a study coordinator from UCLA, provided assistance with data collection.

Funding: This work was supported by grant NIH UO1 CA121947 to the AIDS Malignancy Consortium.

References

1. Besson C, Goubar A, Gabarre J, et al. Changes in AIDS-related lymphoma since the era of highly active antiretroviral therapy. *Blood*. 2001; 98:2339–2344. [PubMed: 11588028]
2. Engels EA, Goedert JJ. Human immunodeficiency virus/acquired immunodeficiency syndrome and cancer: past, present, and future. *J Natl Cancer Inst*. 2005; 97:407–409. [PubMed: 15769998]
3. Little RF. Highly effective treatment of acquired immunodeficiency syndrome-related lymphoma with dose-adjusted EPOCH: impact of antiretroviral therapy suspension and tumor biology. *Blood*. 2003; 101:4653–4659. [PubMed: 12609827]
4. Tirelli U, Errante D, Spina M, et al. Second-line chemotherapy in human immunodeficiency virus-related non-Hodgkin's lymphoma: evidence of activity of a combination of etoposide, mitoxantrone, and prednimustine in relapsed patients. *Cancer*. 1996; 77:2127–2131. [PubMed: 8640681]
5. Kaplan, LD.; Moran, T.; Song, L.; Northfelt, D. Continuous infusion ifosfamide/MESNA with daily etoposide for refractory HIV-associated non-Hodgkin's lymphoma. 1998 ASCO Annual Meeting; 1998.
6. Levine AM, Tulpule A, Tessman D, et al. Mitoguanzone therapy in patients with refractory or relapsed AIDS-related lymphoma: results from a multicenter phase II trial. *J Clin Oncol*. 1997; 15:1094–1103. [PubMed: 9060550]
7. Spina M, Vaccher E, Juzbasic S, et al. Human immunodeficiency virus-related non-Hodgkin lymphoma: activity of infusional cyclophosphamide, doxorubicin, and etoposide as second-line chemotherapy in 40 patients. *Cancer*. 2001; 92:200–206. [PubMed: 11443628]
8. Bi J, Espina BM, Tulpule A, et al. High-dose cytosine-arabioside and cisplatin regimens as salvage therapy for refractory or relapsed AIDS-related non-Hodgkin's lymphoma. *J Acquir Immune Defic Syndr*. 2001; 28:416–421. [PubMed: 11744828]

9. Velasquez WS, McLaughlin P, Tucker S, et al. ESHAP--an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. *J Clin Oncol.* 1994; 12:1169–1176. [PubMed: 8201379]
10. Moskowitz CH, Bertino JR, Glassman JR, et al. Ifosfamide, carboplatin, and etoposide: a highly effective cytoreduction and peripheral-blood progenitor-cell mobilization regimen for transplant-eligible patients with non-Hodgkin's lymphoma. *J Clin Oncol.* 1999; 17:3776–3785. [PubMed: 10577849]
11. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med.* 1995; 333:1540–1545. [PubMed: 7477169]
12. Molina A, Krishnan AY, Nademanee A, et al. High dose therapy and autologous stem cell transplantation for human immunodeficiency virus-associated non-Hodgkin lymphoma in the era of highly active antiretroviral therapy. *Cancer.* 2000; 89:680–689. [PubMed: 10931469]
13. Gabarre J, Azar N, Autran B, et al. High-dose therapy and autologous haematopoietic stem-cell transplantation for HIV-1-associated lymphoma. *Lancet.* 2000; 355:1071–1072. [PubMed: 10744095]
14. Krishnan A, Palmer JM, Zaia JA, et al. HIV status does not affect the outcome of autologous stem cell transplantation (ASCT) for non-Hodgkin lymphoma (NHL). *Biol Blood Marrow Transplant.* 2010; 16:1302–1308. [PubMed: 20353830]
15. Diez-Martin JL, Balsalobre P, Re A, et al. Comparable survival between HIV+ and HIV-non-Hodgkin and Hodgkin lymphoma patients undergoing autologous peripheral blood stem cell transplantation. *Blood.* 2009; 113:6011–6014. [PubMed: 19307667]
16. Re A, Michieli M, Casari S, et al. High-dose therapy and autologous peripheral blood stem cell transplantation as salvage treatment for AIDS-related lymphoma: long-term results of the Italian Cooperative Group on AIDS and Tumors (GICAT) study with analysis of prognostic factors. *Blood.* 2009; 114:1306–1313. [PubMed: 19451551]
17. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol.* 2010; 28:4184–4190. [PubMed: 20660832]
18. Thieblemont C, Briere J, Mounier N, et al. The germinal center/activated B-cell subclassification has a prognostic impact for response to salvage therapy in relapsed/refractory diffuse large B-cell lymphoma: a bio-CORAL study. *J Clin Oncol.* 2011; 29:4079–4087. [PubMed: 21947824]
19. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood.* 2004; 103:275–282. [PubMed: 14504078]
20. Sparano JA, Lee JY, Kaplan LD, et al. Rituximab plus concurrent infusional EPOCH chemotherapy is highly effective in HIV-associated B-cell non-Hodgkin lymphoma. *Blood.* 2010; 115:3008–3016. [PubMed: 20023215]
21. Boue F, Gabarre J, Gisselbrecht C, et al. Phase II trial of CHOP plus rituximab in patients with HIV-associated non-Hodgkin's lymphoma. *J Clin Oncol.* 2006; 24:4123–4128. [PubMed: 16896005]
22. Blay J, Gomez F, Sebban C, et al. The International Prognostic Index correlates to survival in patients with aggressive lymphoma in relapse: analysis of the PARMA trial. *Parma Group Blood.* 1998; 92:3562–3568.
23. Mounier N, Spina M, Gisselbrecht C. Modern management of non-Hodgkin lymphoma in HIV-infected patients. *British Journal of Haematology.* 2007; 136:685–698. [PubMed: 17229246]
24. Balsalobre P, Diez-Martin JL, Re A, et al. Autologous stem-cell transplantation in patients with HIV-related lymphoma. *J Clin Oncol.* 2009; 27:2192–2198. [PubMed: 19332732]
25. Lim ST, Karim R, Nathwani BN, et al. AIDS-related Burkitt's lymphoma versus diffuse large-cell lymphoma in the pre-highly active antiretroviral therapy (HAART) and HAART eras: significant differences in survival with standard chemotherapy. *J Clin Oncol.* 2005; 23:4430–4438. [PubMed: 15883411]
26. Wang ES, Straus DJ, Teruya-Feldstein J, et al. Intensive chemotherapy with cyclophosphamide, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine (CODOX-

- M/IVAC) for human immunodeficiency virus-associated Burkitt lymphoma. *Cancer*. 2003; 98:1196–1205. [PubMed: 12973843]
27. Noy A, Kaplan L, Lee J. Feasibility and Toxicity of a Modified Dose Intensive R-CODOX-M/IVAC for HIV-Associated Burkitt and Atypical Burkitt Lymphoma(BL): Preliminary Results of a Prospective Multicenter Phase II Trial of the AIDS Malignancy Consortium (AMC). *Blood*. 2009; 114:1415–1416.
28. Cortes J, Thomas D, Rios A, et al. Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone and highly active antiretroviral therapy for patients with acquired immunodeficiency syndrome-related Burkitt lymphoma/leukemia. *Cancer*. 2002; 94:1492–1499. [PubMed: 11920506]

Figure 1. Overall survival among patients who achieved complete or partial remission after second-line therapy. AHSCT represents those who underwent autologous hematopoietic stem cell transplantation after salvage therapy.

Table 1

Demographic and clinical characteristics of the patients

Characteristic	All (N=88), n (%) [*]	ASCT (N=16)	Non-ASCT (N=72)	P [†]
Male sex	72 (82)	14 (88)	58 (81)	0.726
Ethnicity/Race				
Hispanic	29 (33)	4 (25)	25 (35)	0.021
White	27 (31)	4 (25)	23 (32)	
Black	23 (26)	3 (19)	20 (28)	
Other/unknown	9 (10)	5 (31)	4 (6)	
History of opportunistic infections	41/83 (49)	10/16 (63)	31/67 (46)	0.243
Ever received HAART	85 (97)	16 (100)	69 (96)	0.622
At initial diagnosis				
Median age, yrs (range)	42 (21–59)	42 (32–59)	42 (21–59)	0.535
Median CD4 count, mL ⁻¹ (range)	152 (5–803)	150 (12–335)	153 (5–803)	0.977
CD4 < 100/mL	23/74 (31)	3/13 (23)	20 (33)	0.536
ECOG performance status ²	25/64 (39)	3/13 (23)	22/51 (43)	0.186
Histology				
DLBCL	53 (60)	6 (38)	47 (65)	0.018
BL and variants	12 (14)	0 (0)	12 (17)	
PBL	5 (6)	2 (13)	3 (4)	
T cell lymphomas	5 (6)	2 (13)	3 (4)	
Other type of NHL	3 (3)	1 (6)	2 (3)	
HL	10 (11)	5 (31)	5 (7)	
CD20 positivity (among NHL)	52/68 (76)	6/11 (45)	47/57 (82)	0.016
Ann-Arbor Stage				
I	6/87 (7)	0/15 (0)	6 (8)	0.051
II	16/87 (18)	5/15 (33)	11 (15)	
III	16/87 (18)	5/15 (33)	11 (15)	
IV	49/87 (56)	5/15 (33)	44 (61)	
>1 involved extranodular sites	29 (33)	3 (19)	26 (36)	0.181
Bone marrow involvement	20 (23)	2 (13)	18 (25)	0.354
LDH ULN	49/68 (72)	5/9 (56)	44/59 (75)	0.431
On HAART	43/83 (52)	9 (56)	34/67 (51)	0.692
Therapy				
Primary refractory disease	54 (61)	6 (38)	48 (67)	0.030
Second-line chemotherapy (±rituximab)				
ICE	34 (39)	9 (56)	25 (35)	0.256
EPOCH	17 (19)	2 (13)	15 (21)	
ESHAP	11 (13)	1 (6)	10 (14)	

Characteristic	All (N=88), n (%) [*]	ASCT (N=16)	Non-ASCT (N=72)	P [†]
HD MTX variants	10 (11)	0 (0)	10 (14)	
DHAP	4 (5)	1 (6)	3 (4)	
Hodgkin specific	4 (5)	1 (6)	3 (4)	
Ifosomide/Etoposide	4 (5)	0 (0)	4 (6)	
Others	4 (5)	2 (13)	2 (3)	
Rituximab in 2 nd -line therapy	30 (34)	4 (25)	26 (36)	0.396
Best response to 2 nd -line therapy				
CR	21 (24)	5 (31)	16 (22)	<0.001
PR	11 (13)	5 (31)	6 (8)	
SD	7 (8)	4 (25)	3 (4)	
Refractory	49 (56)	2 (13)	47 (65)	

^{*} Where relevant, numbers indicate the number of patients with the certain characteristic followed by the number of patients for whom data was available. Number in parenthesis always indicates the prevalence of the characteristic in percentage.

[†] P value from the comparison of ASCT and non-ASCT groups using the Wilcoxon rank sum or chi-square test.

Table 2

Univariate analyses of overall response rates and overall survival

Characteristics	Strata (n)	ORR, n (%)	P*	1-year OS (95% CI)	P*
All patients	(88)	32 (37)		42.1 (30.9–52.8)	
Age	40 (36)	12 (33)	.623	41.9 (24.6–58.3)	.988
	>40 (52)	20 (38)		42.4 (28.0–56.2)	
CD4	<100 (23)	8 (35)	.838	36.7 (16.4–57.4)	.440
	100 (51)	19 (37)		47.6 (32.4–61.3)	
ECOG PS	0–1 (39)	16 (41)	.289	46.5 (29.4–62.0)	.094
	2–4 (25)	7 (28)		30.8 (13.5–50.0)	
Histology	NHL (78)	24 (31)	.004	37.4 (38.1–94.3)	.058
	HL (10)	8 (80)		78.8 (26.0–48.8)	
Histology	BL&variants (12)	2 (17)	.324	11.9 (0.7–40.2)	.005
	Other NHL (66)	22 (33)		41.5 (28.8–53.8)	
Ann-Arbor Stage	I–III (38)	16 (42)	.267	49.0 (31.0–64.8)	.114
	IV (49)	14 (29)		35.3 (21.6–49.3)	
Number of extranodal sites	0–1 (59)	23 (39)	.466	46.8 (33.0–59.5)	.131
	>1 (29)	9 (31)		31.3 (14.3–50.1)	
Bone marrow involvement	No (68)	25 (37)	.885	44.8 (31.9–56.9)	.053
	Yes (20)	7 (35)		31.6 (11.9–53.5)	
LDH	<ULN (19)	10 (53)	.063	46.8 (23.7–67.0)	.494
	ULN (50)	14 (29)		35.1 (21.3–49.2)	
Rituximab in 2nd-line therapy	No (58)	22 (38)	.671	49.0 (34.8–61.8)	.785
	Yes (30)	10 (33)		29.5 (13.7–47.3)	
Disease	Relapsed (34)	19 (56)	.003	58.8 (39.6–73.7)	.022
	Refractory (54)	13 (24)		30.7 (18.0–44.4)	
Second-line chemotherapy among patients with NHL	ICE (31)	10 (32)		38.2 (20.3–56.0)	
	DA-EPOCH (17)	4 (23)	.824	24.5 (6.3–49.0)	.657
	ESHAP/DHAP (14)	6 (43)		55.6 (26.4–77.2)	
	HD MTX variants (10)	2 (20)		27.8 (4.4–59.1)	

Characteristics	Strata (n)	ORR, n (%)	P*	1-year OS (95% CI)	P*	
Response to 2 nd line therapy	Ifosfamide/Etoposide (4)	1 (25)		25.0 (0.8–66.5)	<.001	
	Other (2) [†]	1 (50)		50.0 (0.6–91.0)		
	CR or PR (32)			83.3 (64.5–92.7)		
	SD or Refractory (57)			16.0 (7.1–28.0)		

ORR: Overall response rate, OS: Overall survival, ECOG PS: ECOG performance score, LDH: Serum lactate dehydrogenase level, NHL: Non-Hodgkin lymphoma, HL: Hodgkin lymphoma, BL: Burkitt lymphoma, ULN: Upper limit of normal, ICE: Ifosfamide/ carboplatin/etoposide, DA-EPOCH: Dose adjusted etoposide/prednisone/vincristine/ cyclophosphamide/doxorubicin, ESHAP: Etoposide/ methylprednisolone/ cytarabine/cisplatin, DHAP: dexamethasone/cytarabine/cisplatin, HD MTX: High dose methotrexate, CR: Complete remission, PR: Partial remission, SD: Stable disease

* ORR compared using chi-square tests and OS compared using log-rank tests.

[†] Mechlorethamine/vincristine/procarbazine/prednisone and Hyperfractionated cyclophosphamide/vincristine/doxorubicin/dexamethasone alternating with methotrexate/cytarabine

Table 3

Grade III/IV toxicities due to second-line therapy

Grade III/IV toxicity	n (%) (N=88)
Any grade III/IV	50 (57)
Thrombocytopenia	23 (26)
Febrile neutropenia	22 (25)
Anemia	17 (19)
Nausea/vomiting	14 (16)
Fatigue	6 (7)
Diarrhea	5 (6)
Renal insufficiency	3 (3)