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Reviews

Hematopoietic Cell Transplantation for Plasmablastic Lymphoma: A Review

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A B S T R A C T

Plasmablastic lymphoma (PBL) is recognized by the World Health Organization as a very aggressive subtype of non-Hodgkin lymphoma. It was initially described in the setting of human immunodeficiency virus (HIV) infection, but it has since been identified in immunocompetent patients, as well. PBL is characterized by CD20 negativity and is associated with Epstein-Barr virus infection. The outcome with available therapy is poor, with median survival of less than 1 year. Multiple adverse prognostic factors have been identified, including HIV-negativity, *MYC* gene rearrangement, high-risk international prognostic index, and not achieving complete remission after induction therapy. The role of intensification of induction chemotherapy is controversial. Novel agents have shown some activity in relapsed setting and may have a role in upfront line of treatment. The outcome for relapsed PBL is dismal. Autologous hematopoietic cell transplantation (AHCT) appears to be feasible and may produce better results than chemotherapy, but definitive data are sparse. Chemosensitivity before transplantation might be required to benefit from such therapy. Some data suggest a better outcome of PBL if consolidation with AHCT is used in first-line setting, particularly for those with high-risk disease.

INTRODUCTION

Plasmablastic lymphoma (PBL) was first described in 1997 by Delecluse and colleagues [1]. In this report, 16 patients, of whom 15 were infected with human immunodeficiency virus (HIV), presented with an oral mass and aggressive clinical behavior, poor response to conventional therapies, and short survival. PBL is now recognized by the World Health Organization as 1 of the lymphomas that is more commonly seen in patients with HIV infection [2].

PBL seems to account for 2% to 3% of all HIV-associated lymphomas, although the actual incidence in HIV-positive, as well as in HIV-negative, patients is unknown. In HIV-negative patients, one third of patients have an underlying immunosuppressive status, such as post–solid-organ or allogeneic hematopoietic cell transplantation (AlloHCT) [3], whereas other HIV-negative patients with PBL appear to be immunocompetent. Based on a literature review, there seems to be a male predominance (4:1 in HIV-positive and 1.6:1 in HIV-negative individuals), with younger age at presentation in HIV-positive (median, 39 years) compared with HIV-negative individuals (median, 58 years) [4].

Pathologically, PBL is characterized by a monomorphic proliferation of large, round- to oval-shaped cells with abundant cytoplasm, eccentric nucleus, and prominent nucleolus. The background is composed of lymphocytes, apoptotic and mitotic figures, and macrophages that impart a “starry-sky appearance” [2]. PBL cells show a plasmacytic immunophenotype, in which classic B cell markers, such as CD20, CD79a, and PAX-5, are lost. However, plasma cell markers, such as CD38, CD138, and MUM1/IRF4, are expressed [2]. The cell of origin appears to be the plasmablast, a blastic proliferating B cell that has switched its phenotype to plasma cells (ie, activated, nongerminal center B cell) [2]. More recently, novel immunohistochemistry stains for *PRDM1/BLIMP1* and *XBP1* have been proposed for the identification of PBL [5]. It is of interest, however, that despite having an immunophenotype that resembles plasma cells, PBL has a genomic profile closer to diffuse large B cell lymphoma (DLBCL), regardless of HIV status [6]. A more recent study published in abstract form has shown repression of several components of the B cell receptor-signaling pathway, with similarities between PBL and extraosseous isolated plasmacytomas when compared

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with DLBCL [7]. These disparate results likely reflect an inherent heterogeneity within PBL.

PBL has been associated with Epstein-Barr virus (EBV) infection, as EBV-encoded RNA can be detected using an in situ hybridization technique in the PBL cells in 80% of HIV-positive and 46% of HIV-negative patients [4]. More recently, *MYC* gene rearrangements have been identified in 40% to 50% of patients with PBL and appear to confer a worse prognosis [8,9]. The mechanisms behind the development of *MYC* gene rearrangement in PBL have not been elucidated, as other lymphomas associated with *MYC* gene rearrangements, such as Burkitt lymphoma and double-hit lymphomas, typically show a germinal center B cell profile [10,11]. Finally, PBL must be differentiated from other CD20-negative lymphoproliferative disorders, such as plasmablastic myeloma, anaplastic lymphoma kinase–positive DLBCL, plasmablastic microlymphoma arising from human herpesvirus 8–positive multicentric Castleman's disease, and primary effusion lymphoma [12]. Selected features of PBL and differential diagnoses are shown in Table 1.

Clinically, PBL presents with advanced clinical stage in approximately 60% of the patients, regardless of HIV status. The oral cavity, however, seems to be involved in a higher proportion of patients with HIV infection [4]. PBL has predilection for extranodal disease in the gastrointestinal tract, bone, or skin. PBL can also present in sanctuary sites, such as the central nervous system or testicles, and 30% of patients have bone marrow involvement at the time of diagnosis.

PBL is characterized by poor outcomes. In a retrospective study including 51 HIV-positive PBL patients, the median progression-free (PFS) and overall survival (OS) were 6 and 11 months, respectively, regardless of intensity of therapy [13]. In a univariate analysis, factors affecting survival were achieving complete remission (CR), performance status, clinical stage, *MYC* gene rearrangements, and International Prognostic Index. A German study also identified short survival (median OS of 4 months) in patients with HIV-associated PBL [14]. More recent studies have reported higher response rates and longer OS in PBL patients [15-17]. Outcome data on HIV-negative patients are sparse. A literature review showed a median OS of 9 months; CR after induction chemotherapy was the only factor associated with improved outcomes [3]. Another review showed that HIV-negative but immunosuppressed PBL patients had a worse outcome than immunocompetent PBL patients [18].

NONTRANSPLANTATION THERAPEUTIC OPTIONS

The optimal treatment of PBL has not been identified. Attempts at curative therapy are often complicated by challenges associated with delivering chemotherapy to immunocompromised patients. Given that immunocompetent patients may also have PBL, approaches must be highly customized for individual patients. Prospective studies to define a standard of care are lacking. The majority of what is known about treating this aggressive neoplasm comes from case reports and retrospective case series. The most relevant of these are reviewed here.

Because PBLs are nearly always CD20-negative, there is no role for anti-CD20 monoclonal antibody therapy. Multiagent chemotherapy is typically attempted as first-line therapy. A 10-year retrospective review by the AIDS Malignancy Consortium of 19 newly diagnosed PBL patients treated with a variety of regimens, including CHOP (cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone), showed a 1-year survival of 67% [15]. Although CHOP is often given, there is a suggestion that more aggressive therapy leads to better outcomes. For example, Barta et al. presented a pooled analysis of 1546 patients with HIV-associated non-Hodgkin lymphoma (NHL), demonstrating improved OS with infusional EPOCH (etoposide, prednisone, vincristine, doxorubicin, cyclophosphamide) [19]. PBL, identified only as "other histology" in this paper, constituted only 6% of the patients [19].

In the largest case series of HIV-positive PBL, the majority of patients received CHOP, whereas 37% were given more intensive regimens, such as EPOCH [13]. Although the complete response rate was 66%, the majority of patients relapsed and ultimately died of their disease. The median PFS was 6 months and median OS was 11 months [13]. In this case series and another review [20], the use of regimens more intensive than CHOP did not provide apparent PFS or OS benefits.

Nevertheless, the preference for more aggressive therapy has been advocated by the National Comprehensive Cancer Network guidelines, which state, "standard CHOP is not adequate therapy." The National Comprehensive Cancer Network suggests modified CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, methotrexate/ifosfamide, etoposide, cytarabine), dose-adjusted EPOCH, or HyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with methotrexate and cytarabine) as primary therapy. The evidence supporting these recommendations arises from single-center case series [21]. The MD Anderson group has demonstrated a 38% 5-year OS in PBL patients; approximately one half received HyperCVAD [16]. Given the well-established record of dose-adjusted EPOCH in HIV-associated NHL, this has become the first-line treatment of choice for most clinicians [22,23]. A phase II clinical trial (CTSU 9177) by the Southwest Oncology Group is attempting to study this regimen in a prospective manner in the setting of HIV-related NHL [24].

Relapsed disease is highly problematic. From AIDS Malignancy Consortium data, Noy et al. reported that long-term

Table 1
Differential Diagnosis of PBL

Diagnosis	DLBCL	PBL	PEL	ALK+ DLBCL	HHV8+ LBCL	PCM
Association with HIV	++	+++	+++	–	+	–
Immunocompetent patients	+++	+/–	+/–	+	+/–	++
CD20 expression	+	–	+/–	–	+/–	–
Plasma cell markers	+/–	+	+	+	+	+
Ki67 expression	Intermediate	High	High	High	High	Low
Association with EBV	5-15%	80%	90%	–	–	–
Association with HHV8	–	–	100%	–	100%	–
Other		Oral cavity	Effusions	ALK+	KS, MCD	CRAB

PEL indicates primary effusion lymphoma; ALK, anaplastic lymphoma kinase; HHV8, human herpesvirus 8; DLBCL, Diffuse large B cell lymphoma; LBCL, large B cell lymphoma; PCM, plasma cell myeloma; KS, Kaposi sarcoma; MCD, multicentric Castleman disease; CRAB, hypercalcemia, anemia, renal dysfunction, bone lytic lesions.

survival in patients with relapsed or refractory disease is possible but rare [15]. Autologous hematopoietic cell transplantation (AHCT) is felt to offer the best chance of cure and should be pursued in patients with chemosensitive disease who are candidates for high-dose therapy. Bortezomib is a proteasome inhibitor with activity in multiple myeloma and certain subtypes of NHL. There is growing evidence that it is an active agent in relapsed PBL. Several case reports describe prompt responses to bortezomib, even in highly refractory patients [25-28]. Bortezomib has been safely combined with rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (R-CHOP) in clinical trials for specific subtypes of DLBCL [29] and may be an appealing choice for development in PBL. CD30 expression can be found in approximately 30% of PBL [30-32]. A case report showed that the anti-CD30 antibody-drug conjugate brentuximab vedotin can have activity against PBL [33], and may be a reasonable option for patients with CD30-positive relapsed PBL who are not suitable for more aggressive therapy.

TRANSPLANTATION THERAPEUTIC OPTIONS

The PARMA trial made high-dose antitumor chemotherapy and AHCT the standard of care for relapsed chemosensitive HIV-negative NHL [34]. Several other randomized trials have corroborated this finding [35,36]. Moreover, AHCT has been used to consolidate initial therapy in patients with poor prognostic features CR1 [37-39]. Recently, after the introduction of combination antiretroviral therapy (cART), the role of AHCT in HIV-positive patients with NHL has been entertained and has been shown to be feasible [40-45]. No randomized trials have been reported or conducted in the setting of PBL, and none are likely to be conducted because of the rarity of the disease and the heterogeneity of treatment. Most of the data have been extrapolated from larger phase II trials, retrospective analysis of individual center's experience, or case reports of subtype of DLBCL.

A preliminary data report from the center for International Blood and Marrow Transplant Research (CIBMTR) indicates 20 patients who received a first AHCT for PBL in CR1 or CR2 between 2001 and 2012 are registered with the CIBMTR. HIV status was not reported. Median age at transplantation was 55 (range, 32 to 76). Eleven of 20 (55%) patients underwent transplantation in CR1. Relapse data were not reported, but 1-year and 3-year OS rates were 69% (95% confidence interval [CI], 48% to 87%) and 45% (95% CI, 21% to 71%), respectively. (CIBMTR unpublished data)

AHCT IN REFRACTORY OR RELAPSED PBL

HIV-positive Patients with PBL

In refractory or relapsed HIV-related lymphoma in general, including HIV-positive patients with PBL, treatment was considered mainly palliative with some rare cases of long-term survival. Median survival of patients with HIV-related lymphoma in the pre-cART era was 2.1 months in 1 Italian cohort [46], but better results have been reported since the inclusion of cART into treatment regimens [47-49]. In a retrospective analysis of 70 chemotherapy-treated HIV-positive patients with PBL between 1997 and 2009, the median OS for patients with refractory disease was 3.5 months [20].

Although the use of cART in HIV-positive patients with PBL did not seem to confer a survival advantage in 1 study [13], another retrospective analysis [20] showed a statistical trend towards improved survival. In the Italian cooperative group's experience [17], there was a trend towards a better

Table 2
Transplantation Experience in HIV-Positive Patients with Lymphoma

Ref	Total ASCT, n	PBL, n	Median Age (Range), yr	Gender (M/F)	Disease Status at Transplantation	CD4 Cell/ηL at ASCT	Conditioning Regimen, n	cART during ASCT	Engraftment, Median (Range), d	TRM, %	PFS, %	OS, %	Follow-up, mo
Gabarre et al. [40]	14	NR	37 (27-53)	M = 11 F = 3	CR = 8 PR = 3 RD = 3	300 (77-534)	TBI/CY TBI/Mel BEAM	Yes Short interruption	N = 12 (7-14) *P* = 11 (5-21)	None	29	36	38
Krishnan et al. [41-43]	32	3*	42 (11-68)	M = 29 F = 3	CR1 = 4 CS = 28	156 (25-1064)	CBV = 28 TBI-based = 4	Yes 50% short interruption	N = 10 (5-19) P = NR	6; Cardiac MDS	81 at 2 yr	80 at 2 y	47 (7-107)
Re et al. [44,58]	27	2	39 (28-59)	M = 43 F = 7	CR = 24 PR = 2 RD = 1	190 (88-561)	BEAM	Yes 7 short interruption	N = 10 (8-14) *P* = 12 (8-120)	None	76	74.6	45 (4-70)
Serrano et al. [61]	17	2	43 (31-61)	M = 14 NR = 3	CR1 = 6 CR2 = 9 PR = 2	186 (72-325)	BEAM = 16 TBI-based = 1	Yes	N = 12.5 (9-33) P = NR	11; MDS MOF	55	67	36.5
Balsalobre et al. [45,59]	68	4	41 (29-62)	M = 56 F = 12	CR1 = 16 CS = 44 RD = 8	162 (8-1159)	BEAM = 65 TBI-based = 3	Yes in 95% 22.5% short interruption	N = 11 (8-36) *P* = 14 (6-455)	4.4 at 3 mo 7.5 at 1 yr	56.5 at 3 yr	61 at 3 yr	32

M indicates male; F, female; NR, not reported; PR, partial remission; RD, refractory disease; TBI, total body irradiation; CY, cyclophosphamide; Mel, melphalan; N, neutrophil; P, platelet; CS, chemosensitive disease; CBV, cyclophosphamide, BNCU, and VP16; MDS, myelodysplastic syndrome; MOF, multiorgan failure.

* Personal communications.

Table 3
Main Characteristics of Patients with Relapsed/Refractory PBL Who Underwent Transplantation within GICAT and Updated Outcome

Patient No. [Ref]	Age, yr	Gender	Stage at Relapse	Induction/Salvage Chemotherapy	Disease Status at ASCT	Conditioning	Response after ASCT	Survival after ASCT, mo
1 [58]	43	M	IV A	CHOP14 (RD) ESHAP	PR	BEAM	CR	79+
2 [58]	53	M	IV A	CHOP21/IEV	PR	BEAM	PR	6 (died, PD)
3 [58]	36	M	IV A	R-CDE*/ESHAP	RD	BEAM	RD	4 (died, PD)
4 [17]	30	M	IV A	CHOP21/ESHAP	PR	BEAM	CR	36+
5 [17]	47	M	IV A	CHOP14/ESHAP	PR	BEAM	CR	21+

ESHAP indicates etoposide, methylprednisolone, high-dose cytarabine, and cisplatin; IEV, ifosphamide, epirubicin, and etoposide; PD, progressive disease; R-CDE, rituximab plus infusional cyclophosphamide, doxorubicin, and etoposide; RD, refractory disease.
* Treated upfront with rituximab with CD20 positive disease.

prognosis in patients with PBL in the post-cART era as well (3-year OS 25% versus 83%, $P = .056$). In addition to that, CR has been reported in some cases after starting cART [50]. Furthermore, many relapses have been reported in PBL patients who stopped cART [20,51,52]. Now, intensive chemotherapy [53,54] and AHCT [40-45] are feasible treatment modalities with comparable results to matched HIV-negative patients [43,55].

Multiple experiences with AHCT in HIV-positive patients with lymphoma from single centers or cooperative group have been published (Table 2). All have shown the feasibility and safety of the procedure with treatment-related mortality (TRM) in the range of 5% to 10%. In 2 separate matched case control analyses, HIV status did not influence the outcome of AHCT in patients with NHL [43,55]. Although the opportunistic infections rate was somewhat higher in the HIV-positive group, it did not affect TRM. In almost all patients included in both analyses, cART was continued throughout the procedure, except for short interruptions. Furthermore, immune recovery after AHCT for HIV-related NHL is similar to that observed in HIV-negative patients [56,57].

The effectiveness of such therapy (ie, DFS and OS) was not significantly different between HIV-positive and HIV-negative group of patients [43,55]. In the Italian Cooperative Group on AIDS and Tumors (GICAT) study [58], the median OS of patients who did not proceed to AHCT according to study protocol (either due to chemoresistant disease, progression of disease before transplantation, or mobilization failure) was 7 months with a 3-year PFS of 13%, compared with 76% for patients who received a transplant ($P < .001$, log-rank test), but this may be because of selection bias. On the other hand, the low relapse rate (12% to 15%) and the plateau in PFS 12 to 18 months after transplantation in multiple reports are encouraging [39,40,58]. However, the small number of patients, and, in particular, PBL patients (Table 3), precludes any firm conclusions.

In a registry-based analysis from the European Group for Blood and Marrow Transplantation (EBMT), 8% of patients with NHL had PBL [59]. Age older than 50 years was associated with higher TRM. On the other hand, histology consistent with PBL, delayed referral to AHCT, and not being in CR at the time AHCT were associated with higher risk of disease relapse.

Some case reports have been presented in the literature describing cases of HIV-positive patients with PBL, in particular with mixed results (Table 4). In 1 case report [51], authors suggested that demonstration of an *IgH/MYC* fusion, which was shown in multiple retrospective analyses to confer poor prognosis in PBL [8,13,20], might account for the rapid proliferation, aggressive clinical course, and poor outcome despite the use of AHCT in relapse settings. It was postulated that AHCT earlier in the course of disease might have overcome this adverse feature.

HIV-negative Patients with PBL

The Moffitt Cancer Center presented a single-institution experience on 9 consecutive HIV-negative patients diagnosed with PBL between 1999 and 2010 [18]. The median age at diagnosis was 58 years (range, 46 to 67 years). Five of 9 patients (55%) had an age-adjusted International Prognostic Index (aaIPI) ≥ 2. Seven of 9 (78%) patients received CHOP. Four of them received rituximab, 1 patient for EBV-reactivation after AlloHCT, and 3 others for no reported reason. Two of 9 patients (22%) were treated with Hyper-CVAD regimen. Seven (78%) patients achieved CR with chemotherapy. One patient had partial response adequate for AHCT consolidation and 1 required additional therapy. The overall response rate was 89%. Four patients (44%) with an aaIPI ≥ 2 underwent AHCT after achieving CR1 (Table 5). The median OS was not reached at the time of report.

Authors of this article also presented a literature review on 70 HIV-negative PBL patients [18]. Sixty percent of

Table 4
Case Reports of Relapsed HIV-Positive Patients with PBL and Their Reported Outcome in Literature

Patient No. [Ref]	Age, yr	Gender (M/F)	Stage	aaIPI	CD4 Count before ASCT Cell/micL	Induction Regimen/ Salvage Tx	Disease Status before ASCT	Conditioning Regimen	Disease Status after ASCT	Outcome	OS at Last Follow-up, mo
1 [21]	36	M	IV	4	167	CHOP X8 PD: DHAP	CR2	BCNU/CY	CR	A-NED	25
2 [51]	36	M	IE	1	192 (on diagnosis)	CHOP PD: IVAC	PR2	CBV	CR	PD 4 mo	14
3 [52]	51	M	IE	2	100	CHOP/RT PD: mESHAP and ICE	PR2	MEAM	CR	A-NED	16

Tx indicates treatment; DHAP, dexamethasone, high-dose cytarabine, and cisplatin; A-NED, alive with no evidence of disease; IVAC, ifosfamide, etoposide, and cytarabine; RT, radiation; mESHAP, modified etoposide, methylprednisolone, high-dose cytarabine, and cisplatin; ICE, ifosfamide, carboplatin, and etoposide; MEAM, MCNU, etoposide, cytarabine, and melphalan.
R-CHOP: rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone.

Table 5
Case Reports of HIV-Negative Patients with PBL and Their Reported Outcome in Literature

Patient No. [Ref]	Age, yr	Gender (M/F)	Stage	Immune Status	aaIPI	Induction Regimen	Disease Status before AHCT	Conditioning Regimen	Disease Status after AHCT	DFS after AHCT, mo	OS at Last follow-up, mo
1 [18,21]	23	M	IV	Competent	2	HyperCVAD × 2 PD: IVAC × 3	PR2	BEAM	CR	5	12 (died)
2 [18,75]	57	M	IV	Cardiac transplant (cyclosporine)	2	Cyclosporine w/d Cy/MTX PD: ICE × 3	PR2	Chemo-based	PD	PD	6 (died)
3 [18]	63	F	IV	Competent	5	HyperCVAD × 4	CR1	BEAM	CR	2	13.3 (died)
4 [18]	60	F	IV	Competent	3	HyperCVAD × 4	PR1	BEAM	CR	14	36.5 (died)
5 [18]	64	M	IIE	Competent	2	R-CHOP × 6	CR1	BEAM	CR	A-NED	25.3
6 [18]	67	M	IV	Competent	3	CHOP × 1 R-CHOP × 5	CR1	BEAM	CR	A-NED	46.7
7 [60]	36	M	IV	Competent	2	ProMACE/CytaBOM	CR1	BEAM	CR	NR	16.9 (died)
8 [60]	52	F	II	Competent	1	CHOP × 6 PD: MiniBEAM	PR2	Cy-TBI	CR	2.5	17.2 (died)
9 [60]	50	M	II	Competent	0	CHOP: RD MiniBEAM: RD ICE	RD/CR1	BEAM	PD	PD	14 (died)

W/d indicates withdrawal; MTX, methotrexate; R-CHOP, rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone; ProMACE/CytaBOM, cyclophosphamide, doxorubicin, etoposide cytozar, bleomycin, vincristine, methotrexate and prednisone.

patients were treated with CHOP or a CHOP-like regimen. Two patients with primary refractory disease (Table 5) received AHCT and survived 6 and 12 months. The median OS was 9 months. The authors concluded that age, extranodal disease, and immunosuppression were adverse prognostic features associated with poor outcome. The authors attributed the improved outcome in their single institutional experience in comparison with historical data to the upfront utilization of AHCT in patients with high-risk disease.

Some case reports have been presented in literature describing the feasibility of AHCT in HIV-negative PBL (Table 5). In 1 case series [60], association with *TP53* gene deletion and activated B cell phenotype were proposed as possible mechanisms for PBL chemoresistance and poor outcome.

AHCT CONSOLIDATION IN CR1 FOR HIGH-RISK PBL

Multiple studies have reported that up to 60% of patients with relapsed or refractory lymphoma in general will progress before reaching AHCT [34,44,58,61]. Furthermore, the outcome of patients with relapsed or refractory PBL is very poor [12,13,20]. Because the outcome is significantly superior in patients with relapsed NHL who received AHCT compared with those who did not [35-37,58], it seems rational to explore the use of AHCT earlier in the course of disease, at least in the subgroup of patients with high-risk disease.

In an EBMT registry study [59], some NHL histologies (eg, plasmablastic) have increased risk of relapse compared with DLBCL (relative risk, 3.4; 95% CI, 1.1 to 10.4; $P = .03$) and possible tendency for poorer survival. It was suggested that AHCT in CR1 could be of benefit to this subset of patients. Another study showed poor clinical outcome of patients with relapsed PBL histology compared with standard DLBCL histologies (centroblastic and immunoblastic) even to AHCT in CR2 (median OS of 14 months compared with not reached, with 5-year survival of 57% in other histologies, $P = .002$) [60]. Moreover, the International Prognostic Index has been reported as a useful prognostic factor in patients with HIV-positive and HIV-negative lymphoma [62-64], and specifically for PBL, as well [13]. Furthermore, in previous investigational experiences, an aaIPI more than 1 or 2 (in some trials) has been used as an eligibility criterion for consolidation therapy with AHCT for patients in both groups in CR1 [39,42,61,65].

GICAT presented an interim analysis of a phase II multicenter trial of early consolidation with AHCT in HIV-positive patients with NHL [66] and later published their experience specifically in HIV-positive patients with PBL [17]. Twenty newly diagnosed HIV-positive patients with aggressive NHL and an aa-IPI of 2 or 3 were enrolled in this study between 2007 and 2012. The induction therapy used in this protocol was CHOP ± rituximab. Peripheral stem cell collection with high-dose cyclophosphamide and granulocyte colony–stimulating factor was initiated when chemosensitivity was confirmed. All patients received cART during the entire treatment program. At the time of presentation, 10 patients of the entire group underwent AHCT. The procedure was well tolerated; there were no transplantation-related deaths. All patients who underwent transplantation were alive and free of progression after a median follow-up of 43 months (range, 4 to 58 months). Four patients in this study had PBL [66,17]. One patient had prolonged cytopenia during induction therapy and was excluded from study (she is still in CR1 at +34 months). The other 3 patients received transplantation with BEAM (BCNU, etoposide, cytarabine, melphalan) conditioning regimen in CR1, as planned after induction therapy. All of them are alive and in remission at +24, +19, and +13 months (Table 6). In the entire series, with a median follow-up of 19.5 months (range, 4 to 65), the 2-year PFS and OS were 73% and 76%, respectively (Figures 1 and 2).

Two additional HIV-positive patients with high-risk PBL were treated with AHCT as upfront consolidation after induction with CHOP in a GICAT center in Italy, and the results were reported separately [17]. One patient is still alive in CR at +83 months, but the other progressed and died 4 months after transplantation (Table 6).

Comparable to the Italian cooperative group's and the Moffitt Cancer Center's experiences, patients with PBL registered with the CIBMTR were stratified by disease status; 7 of 11 (64%) patients who underwent AHCT in CR1 were alive at most recent follow-up, with a median follow-up of 25 months (range, 4 to 43 months) compared with 4 of 9 (44%) patients who underwent AHCT in CR2 after a median follow-up of 62 months (range, 12 to 104 months). (CIBMTR

Table 6
Main Characteristics of Patients with PBL and aaIPI of Two or Greater Who Underwent Transplantation in CR1 from GICAT and Their Updated Outcome

Patient No. [Ref]	Age, yr	Gender	Stage	Disease Status at ASCT	Induction Chemotherapy	Conditioning	Response after ASCT	Survival after ASCT, mo
1 [17]	36	M	IV A	CR1	CHOP-21	BEAM	CR	83+
2 [66]	46	M	IV A	CR1	CHOP-14	BEAM	CR	24+
3 [66]	38	M	IV A	CR1	CHOP-14	BEAM	CR	19+
4 [66]	54	M	IV A	CR1	CHOP-14	BEAM	CR	13+
5 [17]	35	M	IV B	CR1	CHOP-14	BEAM	PD	4 (died)

unpublished data) However, the number of cases was too small to draw any statistical conclusion.

Ideally, randomized studies must be conducted to establish the merit of AHCT in PBL. Until then, and based on the available data, we propose that PBL patients with the following high-risk features should be considered for consolidation with AHCT in first-line setting: aaIPI score of more than 2, HIV-negative status, *MYC* gene rearrangement, *TP53* gene deletion, or any response to induction chemotherapy other than CR (partial response or refractory disease).

ALLOHCT FOR PBL

The literature on AlloHCT in HIV-positive patients with NHL in general, and PBL in particular, is considerably more limited compared with AHCT. An early enthusiasm for AlloHCT in patients with HIV infection was tempered by several challenges, casting serious doubts about the feasibility of this curative modality in HIV-positive patients with hematologic malignancies [67-69]. Among those challenges presented: significant exposure to opportunistic infection, a high incidence of concomitant infections (ie, viral hepatitis), complex drug-drug interactions between antiretroviral and transplantation-related medications, and effect of HIV on T cell number and function, bone marrow microenvironment, and cytokine milieu, all reflecting not only on increased TRM but also on mortality related to HIV-infection itself.

In the pre-cART era, AlloHCT attempts were unsuccessful in the setting of HIV-related malignancies [70-72]. A retrospective study from the EBMT confirmed the negative outcome in the pre-cART era, but it showed that the introduction of cART improved the OS of patients undergoing AlloHCT [71]. In a retrospective study of 23 patients with various hematologic malignancies from the CIBMTR [72], patients underwent matched sibling (n = 19) or unrelated donor (n = 4) AlloHCT between 1987 and 2003. The median age at transplantation was 32 years (range, 9 to 43 years). Forty-three percent of patients had NHL. Seventy-eight percent of patients received bone marrow stem cells. Most patients (87%) were conditioned with myeloablative regimens and 70% of patients received cyclosporine-based graft-versus-host disease (GVHD) prophylaxis with or without methotrexate. Median time to neutrophil engraftment was 16 days (range, 7 to 30 days). Engraftment failure rate was 20%. TRM at 100 days was high at 46% and was likely due to regimen-related toxicity (ie, pulmonary toxicity among patients receiving total body irradiation) and infections. With a median follow-up of 59 months, the cumulative incidence of grade II to IV acute GVHD, chronic GVHD, and survival at 2 years were 30% (95% CI, 14% to 50%), 28% (95% CI, 12% to 48%), and 30% (95% CI, 14% to 50%), respectively. There was a difference in survival in patients who underwent transplantation before and after 1996, after availability of cART. Before 1996, 2 of 14 patients (15%) survived, but after 1996, 4 of 9 patients (45%) survived. This study revealed that reduction of TRM and control of HIV infection together are imperative in carrying out successful AlloHCT in this population.

Because the development of reduced-intensity conditioning regimens has improved the outcomes of AlloHCT in general due to decrease in TRM, its role in the HIV-positive patients remains to be defined. The feasibility of the procedure was demonstrated when a 51-year-old HIV-positive man with PBL and a hematopoietic cell transplant comorbidity index of 4 (high risk) underwent AlloHCT from matched unrelated donor [73]. He was conditioned with fludarabine, busulfan, and antithymocyte globulin. GVHD prophylaxis included methotrexate and tacrolimus. He was alive at the time of report 2 years after transplantation with no evidence of disease and off immunosuppression. He had grade II acute GVHD and limited grade chronic GVHD. The patient was continued on cART throughout the procedure. His $CD4^+$ count was 472/μL on day 100 after transplantation.

Currently, a formal study of AlloHCT for treatment of hematologic malignancies in HIV patients by the Blood and Marrow Clinical Trials Network is recruiting [74].

There has been no report in the literature describing AlloHCT in HIV-negative PBL patients.

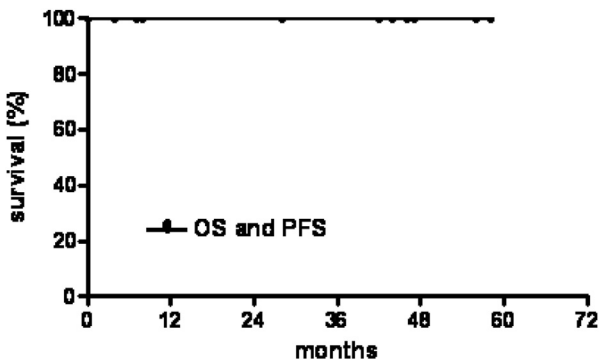

Figure 1. Survival after transplantation (10 patients).

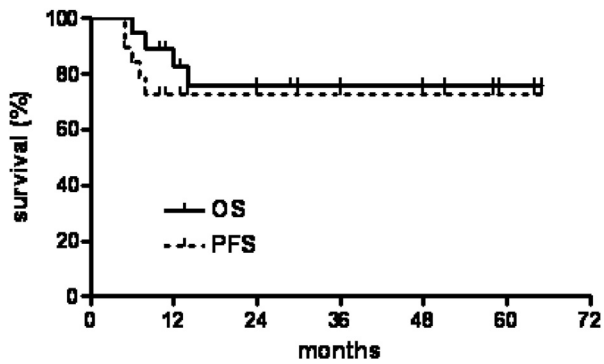

Figure 2. Survival from study entry (20 patients).

CONCLUSION

PBL is an aggressive and rare subtype of NHL, often associated with HIV and EBV infections. Results of current available chemotherapy regimens remain poor. Intensification of induction chemotherapy to achieve better results is controversial. AHCT appears to be feasible and possibly beneficial compared with multiagent chemotherapy in the setting of relapsed and refractory disease. With the dismal outcome of salvage chemotherapy and with the large number of patients with progressive disease waiting for transplantation, AHCT in CR1 should be considered, at least in high-risk patients, in an attempt to improve outcome of this disease. Prospective clinical trials are needed; some are ongoing and might help improve our approach to a better treatment.

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