Biol Blood Marrow Transplant 25 (2019) 1505–1510

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Autologous

Outcomes of Consecutively Diagnosed Primary Central Nervous System Lymphoma Patients Using the Alberta Lymphoma Clinical Practice Guideline Incorporating Thiotepa-Busulfan Conditioning for Transplantation-Eligible Patients

Sheilagh Sanders[1,*], Neil Chua[2], Jean-François Larouche[3], Carolyn Owen[1], Mona Shafey[1], Douglas A. Stewart[1]

[1] Departments of Oncology and Medicine, University of Calgary, Calgary, Alberta, Canada
[2] Department of Oncology, University of Alberta, Edmonton, Alberta, Canada
[3] Department of Medicine, CHU de Quebec, Quebec City, Quebec, Canada

Article history:
Received 23 December 2018
Accepted 2 April 2019

Keywords:
Primary central nervous system lymphoma
Autologous stem cell transplantation

A B S T R A C T

While no widely accepted standard treatment regimen exists for primary central nervous system lymphoma (PCNSL), growing evidence supports an approach that incorporates autologous stem cell transplantation (ASCT) as consolidative therapy when feasible. In November 2011, the Alberta Hematology Tumor Team established a new clinical practice guideline (CPG) for PCNSL involving high-dose methotrexate (HDMTX)/cytarabine-based induction followed by ASCT for eligible patients using a thiotepa and busulfan (TBu) conditioning regimen that omitted cyclophosphamide from the regimen that was used before 2011. This retrospective study analyzed all 64 patients with PCNSL diagnosed consecutively in 3 Canadian centers between November 2011 and December 2017 to evaluate adherence to the 2011 CPG and associated outcomes. Of the 64 patients with PCNSL, 38 were initiated on the transplantation-eligible protocol, of whom 30 underwent successful ASCT, and 26 were deemed transplantation-ineligible, of whom only 7 completed the transplantation-ineligible HDMTX-based protocol. For the transplantation-eligible and -ineligible cohorts, the projected 3-year overall survival (OS) rates were 83.8% and 14.3% and progression-free survival (PFS) rates were 78.1% and 0%, respectively. For the 30 patients who underwent TBu/ASCT, the 3-year OS and PFS rates were 92.7% and 88.9%, respectively, with no treatment-related mortality or significant neurotoxicity. These real-world results highlight the efficacy and tolerability of TBu/ASCT consolidation for PCNSL in patients young and fit enough for an intensive treatment program, along with the significant need for improved therapies for older or less fit patients with PCNSL.

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is a rare variant of extranodal diffuse large B cell lymphoma isolated to brain, leptomeninges, and eyes, with an annual incidence of 4 to 5 per million population [1]. Although there is no consensus regarding the best therapeutic strategy for PCNSL, serial randomized phase II trials suggest that the backbone of induction therapy should include high-dose methotrexate (HDMTX), cytarabine, and possibly rituximab [2]. Whole-brain radiotherapy (WBRT) is active against PCNSL but does not offer long-lasting remission when used alone [3] and leads to significant neurotoxicity when used following HDMTX-based induction, especially in patients age >60 years. The G-PCNSL-SG1 trial demonstrated that WBRT consolidation after HDMTX-based chemotherapy does not significantly prolong overall survival (OS) but increases neurotoxicity [4-6]. Therefore, PCNSL protocols that omit WBRT are appropriate.

Several retrospective series, as well as single-arm and randomized controlled phase II trials have demonstrated approximately 40% to 50% long-term progression-free survival (PFS) when high-dose chemotherapy and autologous stem cell transplantation (ASCT) is used for relapsed/refractory PCNSL [7], and approximately 60% to 85% PFS when used as first remission consolidation, with low rates of neurotoxicity [8,9]. In November 2011, the Alberta Hematology Tumor Team established a new clinical practice guideline (CPG) for PCNSL involving HDMTX/cytarabine-based induction followed by ASCT for eligible patients using a thiotepa and busulfan (TBu) conditioning regimen, without cyclophosphamide. The decision to omit

Financial disclosure: See Acknowledgments on page 1510.

* Correspondence and reprint requests: Sheilagh Sanders, MD, Royal Victoria Hospital, 201 Georgian Drive, Barrie, ON, Canada L4M 6M2.
E-mail address: sheilaghcsanders@gmail.com (S. Sanders).

https://doi.org/10.1016/j.bbmt.2019.04.004
1083-8791/

cyclophosphamide was based on its poor central nervous system (CNS) penetration of only 20% [10], and the hypothesis that its elimination would decrease transplantation-related mortality without compromising efficacy. Transplantation-ineligible patients were to receive HDMTX/cytarabine induction, followed by standard-dose ifosfamide consolidation. Rituximab was added to induction chemotherapy in 2016. This institution-specific protocol was followed at Alberta tertiary provincial cancer centers in Calgary and Edmonton, and subsequently also in Quebec City beginning in 2016.

The objectives of this retrospective study were to analyze all consecutively diagnosed PCNSL patients in Alberta and Quebec City from November 2011 to December 2017 to evaluate adherence to the 2011 CPG, its associated outcomes, and to assess the safety of omitting cyclophosphamide from the thiotepa, busulfan, and cyclophosphamide (TBC) conditioning regimen that was used in Calgary before 2011.

METHODS

Patient Selection and Data Collection

This multicenter retrospective quality improvement project analyzed all HIV-negative patients in Alberta and Quebec City who were newly diagnosed with primary CNS lymphoma. In Alberta, the included patients were diagnosed between November 2011 and December 2017, reflecting the time when Alberta CPGs recommended TBu consolidation for ASCT-eligible patients. Quebec City began following the protocol on February 2, 2016, so these patients were included from February 2016 to December 2017. All consecutively diagnosed PCNSL patients were identified using provincial and local cancer registries, and all patients provided written informed consent before proceeding with ASCT. In Alberta, PCNSL patients are typically treated at the tertiary academic centers in Calgary and Edmonton, and ASCT is performed only at these centers. Electronic medical records were reviewed to gather patient data, including patient and tumor characteristics, treatment, transplantation-specific data, objective response, reported toxicities, and survival.

Protocol

Patients age <65 years with no serious comorbidities were identified as "transplantation-eligible," and those who were age ≥65 years or who had a serious comorbidity were identified as "transplantation-ineligible." Transplant eligibility was in keeping with the Alberta Bone Marrow and Blood Cell Transplant Standard Practice Manual [11]. The patients deemed transplantation-eligible received a 3-step induction regimen. The first step consisted of 2 doses of methotrexate 3.5 g/m^2 i.v. on days 1 and 15; rituximab 375 mg/m^2 on days 0, 4 and 14; and procarbazine 100 mg/m^2 on days 1 to 7. Cytarabine 3 g/m^2 and rituximab were given with step 2, followed by stem cell immobilization and collection. Step 3 consisted of 2 cycles of methotrexate, cytarabine, and rituximab. Of note, rituximab was added to the induction protocol in 2016. The ASCT conditioning regimen consisted of thiotepa 300 mg/m^{2}i.v. on days -5 and -6 and busulfan 3.2 mg/kg i.v. on days -4 to -2 (Figure 1). Transplantation-ineligible patients received methotrexate 3.5 g/m^2 and cytarabine 2 g/m^2, followed by ifosfamide 2 g/m^2 consolidation (Figure 2).

Statistics

Primary outcomes of interest included OS and PFS in all patients with PCNSL, as determined by the Kaplan-Meier method. OS was defined as time in months from diagnosis to time of death from any cause or last follow-up as of August 2018. PFS was defined as the time in months from diagnosis to disease relapse/progression, death, or last follow-up as of August 2018. Response assessments were determined using the criteria established by the International PCNSL Collaborative Group [12]. Data were analyzed with GraphPad Prism version 8.0.0 for Windows (GraphPad Software, La Jolla, CA; www.graphpad.com).

RESULTS

Patient Characteristics

In total, 64 patients from Alberta and Quebec City were diagnosed with PCNSL between November 2011 and December 2017. Baseline patient characteristics are summarized in Table 1. The median age of patients was 63 years, and the median Eastern Cooperative Oncology Group (ECOG) score was 2. The calculated Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) is included in Table 1, but is likely an underestimate, because some of the data included in the HCT-CI were not available. The median International Extranodal Lymphoma Study Group (IELSG) PCNSL prognostic score was 2. Thirty-eight patients were deemed transplantation-eligible at the time of diagnosis, and 26 were deemed transplantation-ineligible. One of the 38 transplantation-eligible patients was age >65 years. Of the 26 patients deemed transplantation-ineligible, 19 were considered so by virtue of age (median age, 73 years; range, 65 to 85 years) and 7 because of significant comorbidities (median age, 64 years; range, 61 to 64 years). These comorbidities included the diagnosis of another concurrent cancer, congestive heart failure with ejection fraction <30%, lung disease, and an ECOG score of 4 at baseline. All patients had diffuse large B cell lymphoma.

ASCT Data

Of the 38 patients who were considered potentially transplantation-eligible at diagnosis, 30 (79%) ultimately underwent ASCT (Table 2). Of the 38 patients, 35 had rituximab included in their induction regimen. Reasons for not undergoing ASCT were progression during induction (n = 2), poor ECOG score (n = 2), patient refusal (n = 1), and severe toxicities during induction (n = 3), including 1 death due to infection. No patients were excluded from ASCT owing to poor stem cell mobilization. The median time to transplantation was 4.0 months from diagnosis. The median number of CD34$^+$ hematopoietic stem cells

Steps	Week 1	Week 3	Week 5	Week 6	Week 7	Week 8	Week 11	Weeks 14-16
Step 1								
rituximab 375mg/m² days 0, 4, & 14	X							
methotrexate 3.5g/m² IV days 1 &15	X	X						
procarbazine 100 mg/m² days 1-7	X							
Step 2								
rituximab 375mg/m² day 1			X					
cytarabine 3g/m² days 1 & 2			X					
G-CSF 5-10µg/kg days 8-13				X				
Apheresis ~day 14 or 15					X			
Step 3								
rituximab 375mg/m² day 0						X	X	
methotrexate 3.5g/m² IV day 1						X	X	
cytarabine 2g/m² BID days 2-3						X	X	
Step 4								
thiotepa 300 mg/ m² IV days -6, -5								X
busulfan 3.2 mg/kg IV days -4 to -2								X
ASCT day 0								X

Figure 1. Transplantation-eligible protocol. All transplantation-eligible patients were treated according to this protocol. Busulfan doses were targeted to achieve maximum AUC of 4500 μmol min L^{-1} in Calgary and Quebec, where pharmacokinetics were measured.

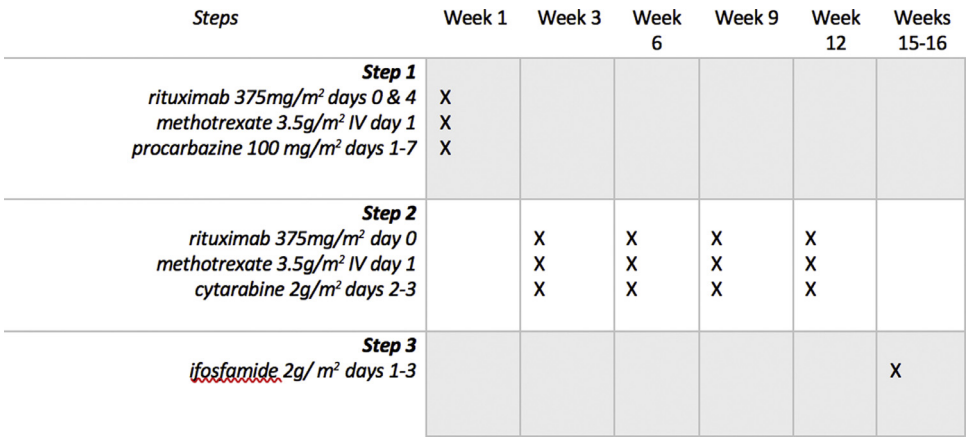

Figure 2. Transplantation-ineligible protocol. All transplantation-ineligible patients followed this protocol.

Table 1
Baseline Patient Characteristics

Characteristic	All Patients (N = 64)	Transplantation-Eligible (N = 38)	Transplantation-Ineligible (N = 26)
Age at diagnosis, yr, median (range)	63 (39.2-84.8)	58 (39.2-68.7)	71 (61.4-84.8)
Age >60 yr, n (%)	38 (59.4)	13 (34.2)	26 (100)
ECOG score at diagnosis, n (%)			
0-1	26 (40.6)	15 (39.5)	11 (42.3)
2	24 (37.5)	16 (42.1)	8 (30.8)
3-4	14 (21.9)	7 (18.4)	7 (26.9)
KPS score <70%, n (%)	38 (59.4)	23 (60.5)	15 (57.7)
HCT-CI score, n (%)			
0	34 (53.0)	23 (60.5)	11 (42.3)
1	8 (12.5)	8 (21.1)	0 (.0)
2	6 (9.4)	2 (5.3)	4 (15.4)
3	8 (12.5)	4 (10.5)	4 (15.4)
4	6 (9.4)	1 (2.6)	5 (19.2)
5	2 (3.1)	0 (.0)	2 (7.7)
Elevated LDH, n (%)	9 (14.1)	4 (10.5)	5 (19.2)
Deep brain involvement, n (%)	39 (60.9)	24 (63.1)	15 (57.7)
Elevated CSF protein, n (%)	25 (39.1)	16 (42.1)	9 (34.6)
No LP done, n (%)	26 (40.6)	14 (36.8)	12 (46.2)
IELSG prognostic score, n (%)			
Low risk (0-1)	18 (28.1)	13 (34.2)	5 (19.2)
Intermediate risk (2-3)	38 (59.4)	22 (57.9)	16 (61.5)
High risk (4-5)	8 (12.5)	3 (7.9)	5 (19.2)
Center of treatment, n (%)			
Calgary, AB	25 (39.1)	16 (42.1)	9 (34.6)
Edmonton, AB	19 (29.7)	12 (31.6)	7 (26.9)
Lethbridge, AB	1 (1.5)	0 (.0)	1 (3.8)
Quebec City, QC	19 (29.7)	10 (26.3)	9 (34.6)
Immune suppression drugs, n (%)	6 (9.4)	5 (13.2)	1 (3.8)
DLBCL, n (%)			
By histology	61 (95.3)	36 (94.7)	25 (96.2)
By CSF cytology	3 (4.7)	2 (5.3)	1 (3.8)
Craniotomy and resection, n (%)	20 (31.3)	12 (31.6)	8 (30.8)

This table compares baseline characteristics of included patients. Fisher's exact p value comparing ASCT-eligible and -ineligible groups for IELSG prognostic risk groups was $P = .27$, suggesting no statistically significant difference among high-risk, intermediate-risk, and low-risk patients at baseline between the 2 groups.
CSF indicates cerebrospinal fluid; DLBCL, diffuse large B cell lymphoma.

reinfused was 8.5×10^6/kg, and all patients achieved prompt hematopoietic recovery, with a median duration of hospitalization of 21.5 days. The most common complications of transplantation were infectious, with 22 patients with grade 3-4 febrile neutropenia and 9 patients developing bacteremia (4 of 9 were gram-negative organisms). Three patients had

Table 2
Outcomes of Transplantation-Eligible Patients

Characteristic	Transplantation-Eligible Patients (n=38)
Transplantation-eligible	
Underwent ASCT	30 (78.9%)
Did not complete ASCT	
Declined ASCT	1 (2.6%)
Progression during induction	2 (5.3%)
Poor ECOG score	2 (5.3%)
Toxicity preventing ASCT	2 (5.3%)
Death due to infection before ASCT	1 (2.6%)
Transplantation data	
Median hospital stay, d	21.5
Median time to ANC >.5 × 10^9/L, d	10
Median time to platelet count >100, d	14
Median follow-up, mo	19.7
3-year PFS, %	
All transplantation-eligible	78.1
Transplantation received	92.7
3-year OS, %	
All transplantation-eligible	83.8
Transplantation received	88.9
Grade 3-4 toxicity during ASCT, n (%)	
Febrile neutropenia	21 (70.0)
Bacteremia	9 (30.0)
Mucositis	4 (13.3)
Neurotoxicity	0 (.0)
Transplantation-related mortality	0 (.0)

enterocolitis (10%). The most common grade 1-2 toxicities were stomatitis (57%) and skin rash (17%). There were no treatment-related deaths, intensive care unit admissions, seizures, episodes of veno-occlusive disease, or neurotoxicity post-transplantation.

Response and Survival Outcomes

The median duration of follow-up for the 39 surviving patients was 24.1 months (range, 6.8 to 84.1 months). For all 64 patients included in the study, the projected 3-year PFS was 48.3%, and the projected 3-year OS was 55.9%. The median time to death for the 25 deceased patients was 5.3 months (range, .4 to 67.7 months).

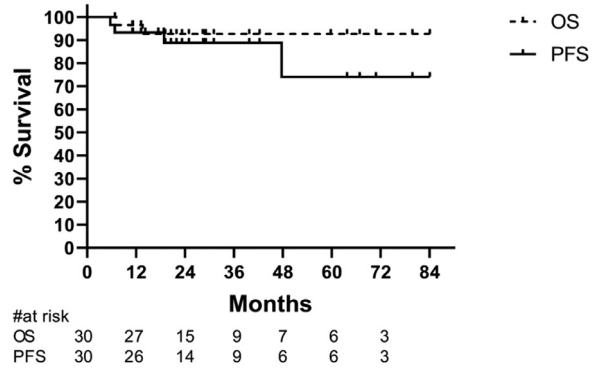

Figure 4. OS and PFS of patients with PCNSL who received TBu/ASCT. The OS and PFS for the 30 patients who underwent successful ASCT were 88.9% and 92.7%, respectively.

The projected 3-year PFS and OS rates were 78.1% and 83.8%, respectively, for the 38 patients who were initially deemed transplantation-eligible and 88.9% and 92.7%, respectively, for the 30 patients who successfully underwent ASCT (Figures 3 and 4). Following induction, 13 of 38 patients achieved a complete remission (CR) or unconfirmed complete remission (CRu), and 20 of the 38 achieved partial remission (PR). Following transplantation, 20 of the 30 patients had achieved CR, 7 had achieved PR, and 3 were of unknown status. Two patients experienced late relapse; 1 relapsed at 48 months and was salvaged with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen), and the other relapsed at 60 months and went on to receive radiation treatment.

For the transplantation-ineligible patients, the projected 3-year PFS was 0% and the projected 3-year OS was 14.3%. Of those 26 patients, 5 were palliated at time of diagnosis without chemotherapy or radiation, and 1 received WBRT alone. Of the 20 patients who started HDMTX/ARA-C-based non-ASCT therapy, only 7 completed the full protocol, and none of these 7 achieved 3-year PFS. The remaining patients did not complete the protocol due to lymphoma progression (n = 7), regimen-related toxicity (n = 3), patient/physician preference (n = 2), or comorbid disease (n = 1). Of the 7 patients who completed the protocol, 6 achieved CR or CRu and 1 had progressive disease.

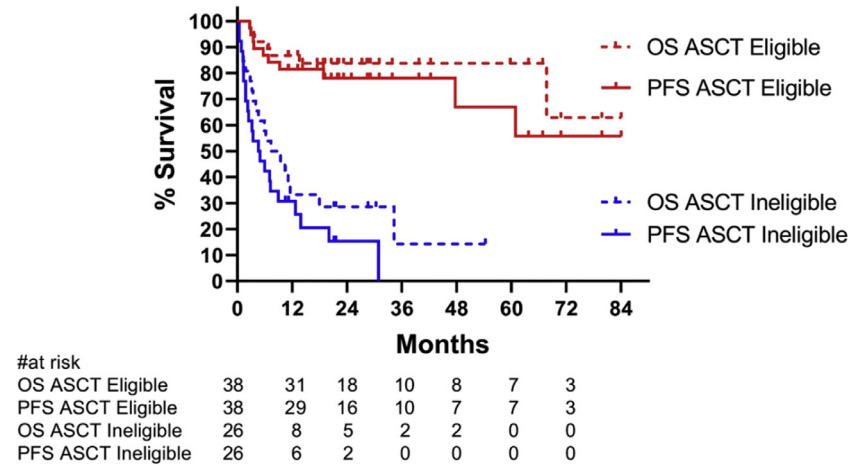

Figure 3. OS and PFS of patients with PCNSL according to eligibility for ASCT protocol. The 3-year PFS and OS rates for the 38 patients who were initially deemed transplantation-eligible were 78.1% and 83.8%, respectively. For the transplantation- ineligible patients, the projected 3-year PFS was 0% and the projected 3-year OS was 14.3%.

DISCUSSION

This report describes the characteristics and outcomes of a consecutively diagnosed series of 64 patients with PCNSL treated according to the November 2011 Alberta clinical practice guideline, which included consolidation therapy using high dose TBu conditioning and ASCT for transplantation-eligible patients. This retrospective real-world quality improvement study found that 59% of all patients were initially deemed suitable to receive the transplantation-eligible protocol, of whom 79% eventually underwent TBu/ASCT, achieving a projected 3-year PFS rate of 78.1%. Unfortunately, the projected 3-year PFS was 0% for the 26 patients who were initially deemed transplantation-ineligible. These results, along with the fact that only 7 of the 26 patients (26.9%) completed the transplantation-ineligible protocol, strongly suggest that sequential intensive HDMTX and cytarabine combination therapy is not effective, tolerable, or feasible for most transplantation-ineligible patients in the real world.

Our study is limited by its relatively small sample size and retrospective design without a concurrent control arm. However, the objective of the study was to evaluate adherence to and corresponding outcomes of the Alberta November 2011 clinical practice guideline for PCNSL. This guideline recommended different treatment strategies for transplantation-eligible and -ineligible patients based on age and comorbidities. Nevertheless, the outcomes are susceptible to selection bias owing to the initial interpretation of transplantation-eligible status by treating physicians. Indeed, survival within the transplantation-ineligible group declined rapidly within the first 6 months of diagnosis, perhaps suggesting that these patients were frailer. In addition, our transplantation-eligible patients had relatively low HCT-CI scores, which may have had an impact on the low associated toxicity with the TBu regimen, given that the TBC regimen has been associated with greater toxicity [13]. Of note, rituximab was not added to the induction regimen until 2016. Although the IELSG-32 study results suggest that omitting rituximab from induction may have adversely impacted our results [14], the recently reported results of the HOVON 105/ALLG NHL 24 phase III trial found that 6 doses of rituximab did not improve the overall response rate, CR rate, or long-term outcomes when added to HDMTX-based induction therapy in 199 randomized patients with PCNSL [15].

Strengths of this multicenter real-world study include a consecutive series of patients, with no exclusions for age, comorbidities, or performance status. In addition, the report not only includes Albertan PCNSL patients treated in Calgary and Edmonton, but also patients treated at a third city in the province of Quebec.

Our results are consistent with those from several other retrospective and prospective phase II trials that suggest an important role for high-dose consolidation therapy and ASCT for PCNSL. Two recently reported randomized phase II trials are particularly relevant to this discussion: the IELSG-32 trial and the PRECIS trial.

In the IELSG-32 trial, the two goals were to identify the most effective induction regimen and to assess consolidation with either ASCT or WBRT [16]. The authors concluded that MATRix induction followed by ASCT should be considered the new standard of care therapy for PCNSL, based on a 4-year OS of 67% in all MATRix recipients and less toxicity in those patients receiving ASCT rather than WBRT. Of note, however, although the 4-year OS was 67% in all MATRix patients, it was 84% in the 47 patients who received consolidation, compared with only 39% in the 28 patients who did not receive consolidation. Although based on the results of a fairly large prospective randomized phase II trial, this conclusion is perhaps overstated. Only 54% of the initial 219 patients proceeded to the second randomization evaluating consolidation therapy. The study report did not clearly explain why consolidation rates were >20% lower than the overall response rate following induction; however, the reasons patients why did not proceed to consolidation were distributed fairly equally among poor response to induction and toxicity, refusal, and poor stem cell mobilization. Our study as well as previous reports suggest a transplantation rate of approximately 80% after other, less-intensive induction regimens based on HDMTX-rituximab. If a goal of PCNSL therapy is to optimize ASCT rates, subjecting patients to toxicity of highly intensive induction therapy may not be the best overall strategy. Indeed, the 4-year OS of 64% in the MATRix arm of IELSG-32 is inferior to that reported in our study, and to other studies that used less-intensive induction, but still achieved higher transplantation rates.

The second recently reported randomized phase II trial was the PRECIS study, comparing consolidation therapy with WBRT to TBC and ASCT. Following identical induction therapy in both arms, the PRECIS trial reported a 2-year PFS of 86.8% (95% confidence interval [CI], 76.6% to 98.3%) for patients who received TBC/ASCT compared with 63.2% (95% CI, 49.5% to 80.5%) for those who received WBRT. The CR rate improved from 45% pre-ASCT to 82% post-ASCT [17]. We previously reported a 5-year PFS rate of only 44% using TBC/ASCT consolidation after initial induction therapy for 21 patients with PCNSL in Alberta, including 3 patients who experienced early nonrelapse mortality (NRM) [18]. Early post-TBC/ASCT NRM was 2.6% in the PRECIS study, and early post-thiotepa/carmustine NRM was 3.4% in the IELSG-32 study. In contrast to these results, no patient experienced early post-TBu/ASCT NRM or major organ toxicity in our real-world study, despite the fact that efficacy seemed well preserved, with a projected 3-year PFS rate of 87.5% for the 30 patients who received TBu/ASCT. The lower toxicity of TBu relative to TBC is expected, in view of the fact that TBu not only omits cyclophosphamide, but also reduces the total dose of thiotepa from 750 mg/m^2 to 600 mg/m^2.

Our transplantation-ineligible PCNSL patients experienced dismal outcomes, regardless of whether or not they completed the protocol. One option to improve their outcome would be to extend the age limit for ASCT from 65 years up to 70 years. A recent study of ASCT in patients age >65 years suggests that a thiotepa-based ASCT is safe and effective in selected elderly patients, with a 2-year PFS of 80% reported for 15 patients who underwent transplantation in first response [19]. Perhaps these elderly patients would further benefit from TBu, which is a slightly reduced-intensity conditioning protocol relative to other options for PCNSL. The number of cycles and intensity of pre-ASCT induction therapy should be kept relatively low, however, considering that few of our patients tolerated HDMTX/cytarabine. These patients likely would be unable to tolerate 4 cycles of MATRix induction. Novel agents for PCNSL include BTK inhibitors, immunomodulatory agents, checkpoint inhibitors, m-TOR inhibitors, and PI3K inhibitors [20]. These novel agents offer the potential to improve outcomes in PCNSL, particularly in transplantation-ineligible patients [21]. Further data are needed to assess how to incorporate these agents into upfront treatment, particularly for older or unfit patients.

In conclusion, patients with newly diagnosed PCNSL who are transplantation-eligible should receive well-tolerated induction aimed at improving performance status, obtaining some tumor response, and optimizing stem cell mobilization and ASCT rates. For these patients, we have demonstrated that a TBu conditioning regimen is relatively safe and effective. Ideally, a prospective

randomized trial comparing TBu to TBC or thiotepa/carmustine will be done in the future. Further research is also needed to investigate how best to treat patients who are elderly or transplantation-ineligible and how to incorporate effective novel agents in a concurrent or sequential design, and to determine whether decreasing the intensity of induction is associated with improved overall outcomes, perhaps by omitting HDMTX in MATRix or using fewer than 4 cycles of MATRIX.

ACKNOWLEDGMENTS

Financial disclosure: S.S. has received honoraria from Pfizer and Bristol-Myers Squibb. N.C. has received honoraria for advisory board meetings with Eisai, Merck, BMS, Amgen, Roche, and Bayer, and has received research funding from Roche and Millenium. J-F.L. has no financial disclosures. C.O. has received honoraria from AbbVie, Janssen, Roche, Gilead, Teva and Astrazeneca. M.S. has received honoraria from Janssen, Abb-Vie, Roche, Lundbeck, Gilead Sciences, SGEN, and Teva. D.S. has received honoraria for ad hoc advisory boards from Roche, Lundbeck, Merck, AstraZeneca, Seattle Genetics, Gilead, Janssen, AbbVie, Servier, Amgen, and Celgene, and has received funding for clinical trials from Janssen, Gilead, AbbVie, Roche, Celgene and Merck.

Conflict of interest statement: There are no conflicts of interest to report.

REFERENCES

1. Villano JL, Koshy M, Shaikh H, Dolecek TA, McCarthy BJ. Age, gender, and racial differences in incidence and survival in primary CNS lymphoma. *Br J Cancer*. 2011;105:1414–1418.
2. Grommes C, DeAngelis LM. Primary CNS lymphoma. *J Clin Oncol*. 2017;35:2410–2418.
3. Nelson DF, Martz KL, Bonner H, et al. Non-Hodgkin's lymphoma of the brain: can high-dose, large-volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG): RTOG 8315. *Int J Radiat Oncol Biol Phys*. 1992;23:9–17.
4. Thiel E, Korfel A, Martus P, et al. High-dose methotrexate with or without whole-brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial. *Lancet Oncol*. 2010;11:1036–1047.
5. Korfel A, Thiel E, Martus P, et al. G-PCNSL-SG-1 randomized phase III trial of high-dose methotrexate with or without whole-brain radiotherapy for primary central nervous system lymphoma: long-term follow-up. *J Clin Oncol*. 2014;32:8527.
6. von Baumgarten L, Illerhaus G, Korfel A, Schlegel U, Deckert M, Dreyling M. The diagnosis and treatment of primary CNS lymphoma. *Dtsch Arztebl Int*. 2018;115:419–426.
7. Soussain C, Hoang-Xuan K, Taillandier L, et al. Intensive chemotherapy followed by hematopoietic stem-cell rescue for refractory and recurrent primary CNS and intraocular lymphoma: Société Française de Greffe de Moëlle Osseuse-Thérapie Cellulaire. *J Clin Oncol*. 2008;26:2512–2518.
8. Illerhaus G, Kasenda B, Ihorst G, et al. High-dose chemotherapy with autologous haemopoietic stem cell transplantation for newly diagnosed primary CNS lymphoma: a prospective, single-arm, phase 2 trial. *Lancet Haematol*. 2016;3:e388–e397.
9. Omuro A, Correa DD, DeAngelis LM, et al. R-MPV followed by high-dose chemotherapy with TBC and autologous stem-cell transplant for newly diagnosed primary CNS lymphoma. *Blood*. 2015;125:1403–1410.
10. Arndt CA, Balis FM, McCully CL, Colvin OM, Poplack DG. Cerebrospinal fluid penetration of active metabolites of cyclophosphamide and ifosfamide in rhesus monkeys. *Cancer Res*. 1988;48:2113–2115.
11. Albert Health Services, Alberta, Canada. Alberta Bone Marrow and Blood Cell Transplant Program: standard practice manual. Available at: https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-bmt-manual.pdf. Accessed February 8, 2019.
12. Abrey LE, Batchelor TT, Ferreri AJ, et al. International Primary CNS Lymphoma Collaborative Group. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. *J Clin Oncol*. 2005;23:5034–5043.
13. Scordo M, Bhatt V, Hsu M, et al. A comprehensive assessment of toxicities in patients with central nervous system lymphoma undergoing autologous stem cell transplantation using thiotepa, busulfan and cyclophosphamide conditioning. *Biol Blood Marrow Transplant*. 2017;23:38–43.
14. Ferreri AJ, Cwynarski K, Pulczynski E, et al. Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomization of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial. *Lancet Haematol*. 2016;3:e217–e227.
15. Bromberg J, Issa S, Bukanina K, et al. Effect of rituximab in primary central nervous system lymphoma - results of the randomized phase III HOVON 105/ALLG NHL 24 study. *Blood*. 2017;130:582.
16. Ferreri AJM, Cwynarski K, Pulczynski E, et al. Whole-brain radiotherapy or autologous stem-cell transplantation as consolidation strategies after high-dose methotrexate-based chemoimmunotherapy in patients with primary CNS lymphoma: results of the second randomisation of the International Extranodal Lymphoma Study Group-32 phase 2 trial. *Lancet Haematol*. 2017;4:e510–e523.
17. Houillier C, Taillandier L, Dureau S, et al. Radiotherapy or autologous stem-cell transplantation for primary CNS lymphoma in patients 60 years of age and younger: results of the Intergroup ANOCEF-GOELAMS Randomized Phase II PRECIS Study. *J Clin Oncol*. 2019;37:823–833.
18. Alimohamed N, Daly A, Owen C, Duggan P, Stewart DA. Upfront thiotepa, busulfan, cyclophosphamide, and autologous stem cell transplantation for primary CNS lymphoma: a single-center experience. *Leuk Lymphoma*. 2012;53:862–867.
19. Schorb E, Fox CP, Fritsch K, et al. High-dose thiotepa-based chemotherapy with autologous stem cell support in elderly patients with primary central nervous system lymphoma: a European retrospective study. *Bone Marrow Transplant*. 2017;52:1113–1119.
20. Rubenstein JL. Biology of CNS lymphoma and the potential of novel agents. *Hematology Am Soc Hematol Educ Program*. 2017;2017:556–564.
21. Illerhaus G, Schorb E, Kasenda B. Novel agents for primary central nervous system lymphoma: evidence and perspectives. *Blood*. 2018;132:681–688.