THE ROLE OF AUTOLOGOUS STEM CELL TRANSPLANTATION IN PRIMARY CNS LYMPHOMA

Andrés J. M. Ferreri¹ and Gerald Illerhaus²

1) Unit of Lymphoid Malignancies, Division of Onco-hematological Medicine, Department of Onco-hematology, IRCCS San Raffaele Scientific Institute, Milano, Italy;
2) Klinik für Hämatologie, Onkologie und Palliativmedizin; Stuttgart Cancer Center; Tumorzentrum Eva Mayr-Stihl; Klinikum Stuttgart; Stuttgart, Germany.

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Correspondence to: Andrés J. M. Ferreri, MD
Unit of Lymphoid Malignancies
Division of Onco-Hematological Medicine
Department of Onco-Hematology
IRCCS San Raffaele Scientific Institute
Via Olgettina 60, 20132 - Milan, Italy
Phone: 0039-02-26437649
Fax: 0039-02-26437625
E-mail: ferreri.andres@hsr.it

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ABSTRACT
Primary CNS lymphoma (PCNSL) treatment includes two phases: induction and consolidation. Induction consists of high-dose-methotrexate-based polychemotherapy for most patients, with regimen and dose variations according to patient characteristics and country. Several strategies have been proposed for the consolidation phase, with whole-brain irradiation (WBRT) the most common. However, some authorities recommend avoiding WBRT because of its related risk of severe neurotoxicity. The most relevant alternatives to WBRT are high-dose chemotherapy supported by autologous stem cell transplantation (HDC/ASCT) or non-myeloablative chemotherapy, the former supported by several single-arm phase II trials. Moreover, HDC/ASCT is the only strategy that is assessed in comparison with WBRT in ongoing randomized trials. The rationale for the use of HDC/ASCT in PCNSL patients is based on the fact that the delivery of high doses could achieve therapeutic drug concentrations in the brain and cerebrospinal fluid, and that non-cross resistant drugs used for conditioning (e.g. alkylating agents) could favour the elimination of residual chemoresistant lymphoma cells. Worldwide experience with HDC/ASCT is limited to few single-arm phase II trials, but overall results are encouraging, mostly when thiotepa/containing conditioning regimens are used, both in newly-diagnosed and relapsed patients. However, several questions on efficacy and feasibility of HDC/ASCT, as well as the best candidates for this strategy, the optimal conditioning regimen, the best time for response assessment, and acute and late effects remain unanswered. In this review, we critically analyze reported studies on HDC/ASCT in PCNSL, and discuss its current role and future perspectives in treating this aggressive malignancy.

Key words: diffuse large B-cell lymphoma, extranodal lymphoma, primary CNS lymphoma, autologous stem cell transplantation, brain neoplasm.
INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is an aggressive malignancy occurring exclusively in the CNS, i.e. the brain parenchyma, spinal cord, eyes, cranial nerves, and/or meninges. It represents 4% of intracranial neoplasms and 4-6% of all extranodal lymphomas, exhibits peculiar clinical and biological features and constitutes a diagnostic and therapeutic challenge for multidisciplinary clinicians and scientists. Its outcome remains unsatisfactory if compared with that of extra-CNS lymphomas patients at a similar stage and histology, and several factors prevent therapeutic progress. In particular, PCNSL patients often show impaired general conditions and poor performance status (PS), which interferes with patients enrollment in prospective trials. Current therapeutic knowledge is only based on four reported randomized trials, few single-arm phase-II trials and some multicenter retrospective studies. This low level of available evidence induces consequent uncertainties in therapeutic decisions and lack of consensus on primary endpoints for future trials. Moreover, molecular and biological knowledge is insignificant compared to other lymphomas, which limits the identification of new therapeutic targets.

The treatment of PCNSL currently consists of two phases: induction and consolidation. Induction consists of high-dose-methotrexate (HD-MTX)-based polychemotherapy for most patients, with regimen and dose variations according to age, PS, comorbidity and geographical area. Several strategies have been proposed for the consolidation phase, with whole-brain irradiation (WBRT) among the most common. However, increased risk of severe neurotoxicity, especially in elderly patients, has been reported with chemo-radiation therapy. Recent international efforts have focused on establishing valid alternatives to consolidative WBRT, mostly consisting of high-dose chemotherapy supported by autologous stem cell transplantation (HDC/ASCT) or nonmyeloablative chemotherapy. HDC/ASCT is supported by several single-arm phase II trials and is the only one that is compared to WBRT in ongoing randomized trials. In this review, we critically analyze reported studies on HDC/ASCT in PCNSL, and discuss its potential role and future perspectives in the treatment of this poor-prognosis malignancy.

BACKGROUND AND RATIONALE

For decades, WBRT alone was the standard treatment for PCNSL, with both high response and relapse rates. Almost all patients treated with WBRT alone experience
relapse within the first year of follow-up. While the addition of chemotherapy has remarkably improved PCNSL patients’ outcomes, the CHOP regimen, the most commonly used chemotherapy combination in diffuse large B-cell lymphomas (DLBCL), has not resulted in improved survival compared to WBRT alone. Better results have been progressively reported with a wider use of HD-MTX-based polychemotherapy induction in combination with consolidative WBRT. A parallelism with the management of limited-stage, extra-CNS DLBCL can be made. In the pre-rituximab era, anthracycline-based chemotherapy followed by involved-field radiotherapy was the standard treatment in limited-stage DLBCL. With a wider use of rituximab, and 18FDG-PET in particular, the role of consolidative radiotherapy in extra-CNS DLBCL was constrained, even if randomized trials focused on this issue in the rituximab era do not exist. This is mostly due to better disease control with immunochemotherapy and an improved definition of response degree in patients with residual masses at CT scan. Accordingly, post-chemoimmunotherapy 18FDG-PET allows to identify DLBCL patients with metabolic complete response, who can be successfully managed without consolidative radiotherapy. Similarly, a growing inclination to avoid radiotherapy in patients achieving complete remission (CR) after induction chemotherapy has been applied also to PCNSL. This choice is strongly motivated by the above-mentioned association between WBRT and risk of severe neurotoxicity. However, WBRT withdrawal should be considered with caution as the situation is completely different in PCNSL, where the quality of response after chemotherapy is suboptimal compared to DLBCL patients treated with R-CHOP. Moreover, quality of response assessment is worse in PCNSL as PET is not currently used and MRI shows relevant limitations. Most PCNSL patients treated without WBRT experience relapse and only a small proportion of failed patients benefit from salvage treatment, which has not changed with a wider use of rituximab. Two schools of thought were therefore established. On the one hand, some authorities believe that WBRT should remain the standard of care in routine practice, at least until results from randomized trials comparing WBRT with HDC/ASCT are available. On the other hand, some experts are convinced that the level of evidence supporting upfront HDC/ASCT is sufficient to recommend the use of this strategy in routine practice. Guidelines from the European Association of Neuro-Oncology consider upfront HDC/ASCT as an experimental treatment in PCNSL, whereas NCCN guidelines for routine practice refers to HDC/ASCT as an alternative to WBRT in patients who achieve CR after HD-MTX-containing induction.
The use of HDC/ASCT in PCNSL is based on its efficacy in recurrent systemic lymphoma. PCNSL manifests in a sanctuary behind the blood-brain barrier (BBB), escaping control from the host immune system and exposure to most conventionally-dosed cytotoxic drugs. With the exception of some lipophilic drugs that successfully penetrate the BBB at conventional doses, most other drugs must be administered at high doses to achieve cytotoxic concentrations in the brain tissue and cerebrospinal fluid (CSF), which constitutes part of the rationale for the use of HDC/ASCT in PCNSL. In addition, non-cross resistant drugs used for conditioning (e.g. alkylating agents) increase the possibility of eliminating residual lymphoma cells that may be resistant to drugs used for induction. A few single-arm phase II trials and retrospective studies have shown encouraging outcomes with HDC/ASCT in patients with PCNSL both as upfront and salvage treatment (Table 1). Most trials addressing HDC/ASCT included a small number of patients, often with a short follow-up period, and series showed differences in patient and lymphoma characteristics and therapeutic management. Thus, several questions on its efficacy and feasibility, as well as the best candidates for this strategy, the optimal conditioning regimen, the best time for response assessment, and acute and late effects remain unanswered. In addition, one of the main reasons to use consolidative HDC/ASCT instead of WBRT is a putative reduction of the risk of severe neurotoxicity. However, it is important to underline that, with a single exception, a formal neurotoxicity assessment through validated neuropsychological tests has not been performed in retrospective and prospective studies. Thus, reported neurotoxicity rates regard patients with evident neurological symptoms attributed to therapeutic side effects (Table 1), with a consequent underestimation of the incidence of this complication. Accordingly, neurocognitive safety of HDC/ASCT remains to be formally demonstrated.

**ASCT AS SALVAGE THERAPY**

Since the first report of durable remission obtained with HDC/ASCT in a patient affected by relapsed PCNSL, this approach has been used in explorative series and prospective trials on patients with PCNSL. HDC/ASCT was first used in patients with relapsed or refractory PCNSL more than 20 years ago in France, especially among patients with relapsed intraocular lymphoma and it was subsequently applied to every patient with recurrent PCNSL. Twenty-two patients, half of them with relapse limited to the eyes, were treated with two courses of cytarabine-etoposide combination, and patients with
chemosensitive lymphoma were treated with a combination of thiotepa, busulfan and cyclophosphamide followed by ASCT (Table 1). Complete remission rate (CRR) after the full treatment was 80%, with grade-4 neutropenia and thrombocytopenia in all patients, septic complications in 86% of cases and 23% treatment-related mortality (TRM), mostly among patients >60 years old. With this strategy, the 3-year event-free survival (EFS) and overall survival (OS) were 53% and 64%, respectively. Outcome was evidently different among patients with failure limited to the eyes compared to the remaining patients, with a median OS of 33+ months and 12 months, respectively. Discrepancies in outcome between these subgroups suggest biological differences and a potential selection bias. Importantly, 32% of patients developed neurologic toxicity, which was fatal in one-third of the affected patients. This complication, consisting of severe chronic leukoencephalopathy with cognitive dysfunction, had been equally observed both in patients >60 years old who did not receive WBRT and in previously irradiated younger patients.

Despite important TRM and risk of neurotoxicity, these results led the same authors to conduct a second phase II trial on relapsed/refractory patients, treated according to the same above-described strategy. In this trial, 43 PCNSL patients (median age: 52 years) with relapse (n=22), refractory disease (n=17), or partial response to first-line treatment (n=4) were enrolled. Patients with failure limited to the eyes constituted only 14% of cases. CRR after the full treatment was 60%, with expected hematological toxicity and 16% TRM. Severe neurotoxicity was observed in 12% of cases, but this rate is probably underestimated considering that prospective neuropsychological assessment had not been performed and that many patients dying early due to lymphoma or toxicity had been considered as censored for this analysis. With a median follow-up of 36 months, the 2-year OS was 45%. Interestingly, 12 patients with stable or progressive disease after induction chemotherapy had been referred to HDC/ASCT obtaining transient CR in 11 cases, with a median progression-free survival (PFS) of 9 months. Chemosensitivity, defined as objective response to induction chemotherapy, was independently associated with better outcomes.

These results compare favorably with other conventional-dose salvage treatments used both as mono- and poly-chemotherapy. In fact, median PFS and 2-year OS were 10-15 months and 33% for topotecan, 3 months and 21% for temozolomide, and 26 months and 70% (1-year OS) for HD-MTX re-treatment. Salvage polychemotherapy was associated with median PFS of 5 months and 1-year OS of 41%. However, these trials
included patients selected by using less restrictive criteria compared to PCNSL trials testing salvage HDC/ASCT. This is of crucial importance if we consider that only 40% of patients <70 years old with relapsing/refractory PCNSL currently receive HDC/ASCT. The gap in results with conventional-dose salvage and HDC/ASCT are less impressive when comparing similarly selected populations. Moreover, the promising results yielded with salvage HDC/ASCT should be taken into account with caution considering that this strategy is associated with relevant TRM and severe neurotoxicity in elderly or previously irradiated patients. Although it was not addressed in well-designed prospective trials, our experience shows that patients with relapsed PCNSL are more frail than other lymphoma patients referred to salvage ASCT, and exhibit higher rates of fatal complications both during induction therapy and ASCT. Poor performance status and severe neurological deficits often result in prolonged immobilization, with consequent higher rates of deep venous thrombosis, pulmonary embolism and septic complications. These major concerns suggest that this strategy should be used carefully out of well-designed clinical trials, and recent, small retrospective series managed with thiotepa-based conditioned/ASCT showed that adequate selection of candidates is associated with excellent feasibility and safety profiles, and encouraging survival figures.

**ASCT AS UPFRONT TREATMENT**

*Induction chemotherapy regimens*

With anecdotal exceptions, only patients with PCNSL responsive to induction phase are referred for HDC/ASCT. Accordingly, the choice of induction treatment is extremely important both to achieve high response and ASC collection rates, with the obvious consequence to offer HDC/ASCT to a higher proportion of treated patients. All prospective trials reporting on HDC/ASCT in the first-line setting used different variations of HD-MTX as induction treatment, reflecting the heterogeneity across study groups and countries of treatment approaches in newly-diagnosed PCNSL. In this setting, HD-MTX was used as a single agent, as part of sequential programs, and included in polychemotherapy combinations. HD-MTX monotherapy, at a dose of 8 g/m², was used in a single trial, CRR after induction was 13%, and 69% of patients proceeded to HDC/ASCT, most of them with residual disease at transplantation. Sequential protocols mostly used combinations of HD-MTX and high-dose cytarabine (HD-ARAC). A combination of five biweekly HD-MTX (3.5 g/m²) cycles followed by two monthly courses of
HD-ARAC (2 x 3 g/m²) resulted in 50% of patients proceeding to HDC/ASCT²⁹,³⁰. Two prospective German studies addressed a sequential induction before HDC/ASCT⁶,¹⁸; CRR was 15% after induction with HD-MTX (8 g/m²), 27% after intensification with HD-ARAC (2 x 3 g/m²) and thiotepa (2 x 5 mg/kg) combination and 77% after HDC/ASCT¹⁸. This observation suggests that HDC/ASCT is active per se, resulting in encouraging outcomes, even among patients with residual disease at the time of conditioning.

The most encouraging results were reported with HD-MTX (3 or 3.5 g/m²) in combination with alkylating agents (i.e., carmustine, procarbazine, thiotepa) and/or HD-ARAC. These polychemotherapy combinations have resulted in high ASC mobilization rates and CRR of up to 66%, with up to 81% of patients proceeding to ASCT¹⁹, ³¹ (Table 1). The anti-CD20 monoclonal antibody rituximab is another important component of induction treatment. As salvage monotherapy, rituximab has been associated with an overall response rate (ORR) of 42%³², and its combination with HD-MTX-based chemotherapy is feasible³³, but there are many doubts about its capability to cross the blood-brain barrier³⁴. A few retrospective studies using historical controls suggested that the addition of rituximab is associated with improved response rates, but effect on survival is unclear due to small number of patients and follow-up duration imbalances³⁵, ³⁶. Recently, results from the first randomization of the IELSG32 trial aimed to establish the most active induction regimen were presented³⁷. The combination of HD-MTX, HD-ARAC, thiotepa and rituximab (called MATRix regimen) was associated with an ORR of 87% and a 2-year PFS of 62%³⁷; as for other HD-ARAC-based combinations³¹, MATRix allows successful ASC collection in 94% of cases.

With the limitations of comparison among single-arm phase II trials, available literature suggests that HD-MTX-based polychemotherapy should be preferred to mono-therapy or sequential programs as pre-ASCT induction. Higher toxicity is compensated with high response and ASC collection rates. Although randomized trials comparing different induction regimens containing HD-MTX, alkylating agents and rituximab do not exist, we suggest using MATRix regimen as standard induction approach to patients ≤70 years old with newly diagnosed PCNSL because it is the sole induction regimen addressed in a randomized trial and is supported by the highest level of evidence in this field.

Concluding remarks

Conditioning regimens

BEAM regimen

BEAM (Table 2) is the most commonly used conditioning regimen in patients with relapsed or refractory DLBCL¹⁰. Since its well-known feasibility, safety profiles and efficacy, it was
one of the first conditioning combinations used in PCNSL\textsuperscript{29, 31, 38}. When the most consistent trials were considered, median time to engraftment after BEAM was 8 days for neutrophil recovery \( \geq 500/\mu L \) and 9 days for platelet recovery \( \geq 2,000/\mu L \)\textsuperscript{29, 31}, which is not significantly different to engraftment after thiotepa-based conditioning\textsuperscript{18}. Toxicity after BEAM was intermediate between those reported after the combination of high-dose busulfan and thiotepa and after BCNU-thiotepa conditioning\textsuperscript{6, 18}, with a TRM of 13\% in patients treated with HD-busulfan-thiotepa combination\textsuperscript{28}, 4\% after BEAM\textsuperscript{29, 31} and 0\% after BCNU-thiotepa conditioning\textsuperscript{6, 18}. TRM is currently attributed to the frequent and prolonged immobilization of PCNSL patients, recurrently associated with pulmonary embolism and fatal pneumonia\textsuperscript{28}.

Two trials addressed a HD-MTX-based induction followed by BEAM-conditioned ASCT\textsuperscript{29, 31}. In a French multicenter prospective trial\textsuperscript{31}, 25 patients with newly diagnosed PCNSL were administered two courses of MVBP regimen (HD-MTX, carmustine, etoposide and methylprednisolone); patients with responsive lymphoma were treated with ARAC-ifosfamide combination and BEAM-conditioned ASCT, whereas patients with unresponsive disease were treated with etoposide-ARAC combination and WBRT. Contribution of BEAM/ASCT to response rate was modest, with a 44\% CRR after MVBP induction and 52\% after BEAM, with a 4-year EFS and OS for the whole series of 46\% and 64\%, respectively\textsuperscript{31}. Notably, all enrolled patients received intrathecal chemotherapy and WBRT, which prevents drawing definitive conclusions on the effect of BEAM on survival. The only phase II trial addressing BEAM-conditioned ASCT in a radiotherapy-free program was a mono-institutional experience from the Memorial Sloan Kettering Cancer Center\textsuperscript{29}. In this trial, a sequential combination of high doses of MTX and ARAC followed by BEAM/ASCT resulted in 57\% ORR after induction, with half of enrolled patients receiving ASCT. Even in this trial, contribution of BEAM regimen to response rate was modest, with a median EFS of only 9 months and a 2-year OS of 60\%; 57\% of transplanted patients experienced relapse within the first 6 months of follow-up, whereas late relapses were not recorded because follow-up of survivors was usually shorter than 3 years\textsuperscript{29, 31}.

Overall results obtained with BEAM-conditioned ASCT are unsatisfactory, which could be explained at least in part by the low capability to cross the BBB of drugs included in this combination. In fact, while drugs used in other conditioning regimens\textsuperscript{18, 28, 39} (see below), like busulfan, thiotepa and BCNU, have excellent CNS penetration, with CSF levels in excess of 80\% serum levels for busulfan and thiotepa, and of 50\%-80\% for BCNU, CNS penetration rates for agents in the BEAM regimen are very low, such as 5\% for etoposide,
6%–22% for ARAC and 10% for melphalan\textsuperscript{40}. Therefore, disappointing results and CNS bioavailability data led most specialists to abandon BEAM as conditioning regimen in the first-line treatment of PCNSL.

**Busulfan-thiotepa regimens**

Different combinations of high doses of busulfan and thiotepa, with or without other drugs, have been used as conditioning regimen in some PCNSL series (Table 2). Busulfan and thiotepa are two drugs with excellent CNS bioavailability and a good profile of non-hematological toxicity. The use of busulfan-thiotepa combination after single-agent MTX 8 g/m\textsuperscript{2} in PCNSL patients 18-65 yo has been associated with an 83% ORR, but feasibility has been suboptimal, with less than half of the patients receiving full treatment, and a 2-year OS of 48%\textsuperscript{28}, which seems to be related to a poor quality response to induction therapy. Importantly, TRM was 13%, and an additional 10% of patients died of severe neurotoxicity\textsuperscript{28}. Busulfan-thiotepa regimen has often been used in combination with high-dose cyclophosphamide (TBC regimen: thiotepa 250-300 mg/m\textsuperscript{2}/d, days –8 and –7; busulfan 3.2-9.6 mg/kg BW/d, days –6 to –4; cyclophosphamide 2 g/m\textsuperscript{2}/d, days –3 and –2) in PCNSL patients (Table 1). Preliminary studies on TBC combination were performed on small and heterogeneous retrospective series, sometimes combining patients with PCNSL and secondary CNS lymphoma, as well as with untreated and relapsed disease, with consequent difficulties to interpret results\textsuperscript{27, 41-43}. In the largest retrospective series, the 5-year OS of patients treated with HD-MTX-based induction followed by TBC-conditioned ASCT was 44%\textsuperscript{41}. Post-ASCT relapses displayed notable aggressiveness and chemorefractoriness. In a recent phase II trial\textsuperscript{19}, 32 PCNSL patients were treated with HD-MTX-based chemoimmunotherapy, with 81% of responders performing TBC-ASCT (thiotepa 250 mg/m\textsuperscript{2}/d, days -9, -8 and -7; busulfan 3.2 mg/kg/d, days -6, -5 and -4; cyclophosphamide 60 mg/kg/d, days -3 and -2). Assessment by formal neuropsychological tests showed significant improvement in some cognitive functions, with no evidence of neurological decline. At a median follow-up of 45 months, the PFS and OS were 81%, but these encouraging results should be considered cautiously, with only 19% of the study group having high risk scores\textsuperscript{19}. Overall, these studies have suggested TBC regimen is active in patients with newly diagnosed PCNSL responsive to HD-MTX-based induction, but toxicity remains a major concern\textsuperscript{41-43}. In fact, a median length of hospital stay of 24-28 days, median time to neutrophil and platelet recovery of respectively 9 and 13 days have
been reported\textsuperscript{19,41,43}. Importantly, septic complications, mostly bacterial infections, occur in one third of treated patients\textsuperscript{19,41,43}, with grade $\geq 3$ febrile neutropenia in 42\% of patients, grade $\geq 3$ infections in 23\%, non-relapse mortality of up to 24\%, and a TRM of up to 19\%. These complications are more common among patients over 60 years\textsuperscript{41}, but, overall, these rates seem to be higher than those with other thiotepa-based regimens (see below). Grade 3-4 mucositis is a major complication, reported in up to 81\% of treated patients, with 16\% requiring total parenteral nutrition\textsuperscript{43}. More specific complications, like hemorrhagic cystitis, prolonged noninfectious diarrhea (15\%), cholestasis, rash and other skin toxicities, reversible acute neurotoxicity (delirium, ataxia, dysphagia, weakness - 22\% of cases) and peripheral edema have often been reported with TBC regimen\textsuperscript{41,42,43}. TBC regimen needs adjunctive therapy including multiple daily showers during thiotepa treatment, and delivery of phenytoin or lorazepam and mesna to prevent some of these toxicities. Accordingly, TBC is an effective conditioning regimen, but its use should be restricted to experienced centres because of related toxicity\textsuperscript{19}.

BCNU-thiotepa regimens

Two German phase-II trials addressed BCNU-thiotepa combination as conditioning in PCNSL patients\textsuperscript{6,18}. Patients under 65 years old were managed with sequential induction chemotherapy, including three cycles of HD-MTX (8 g/m\textsuperscript{2}) and HD-ARAC-thiotepa combination. In the first trial\textsuperscript{18}, thiotepa dose at conditioning was 5 mg/kg body weight and all patients received WBRT. This conditioning regimen was well tolerated, with no relevant acute or late extra-hematological toxicity, with the exception of grade 1-2 mucositis in 26\% of transplanted patients. At a median follow-up of 63 months, the 5-year OS was 69\% for all patients and 87\% for those completing HDC/ASCT. In the second trial\textsuperscript{6}, induction chemotherapy was intensified, the thiotepa dose doubled and only those patients who did not achieve CR after induction therapy underwent WBRT. Importantly, CRR after induction was 31\%, while CRR after ASCT stood at 85\%, demonstrating that BCNU-thiotepa combination is active \textit{per se}, suggesting an excellent CNS bioavailability and non-cross resistant efficacy. Likewise, an increase in CRR after ASCT has been reported in a phase II trial on American patients managed with TBC regimen\textsuperscript{19}. Interestingly, survival curves of patients with pre-transplantation CR or partial response were similar in a retrospective study that analyzed patients with PCNSL and SCNSL together\textsuperscript{43}, These figures contrast with NCCN guidelines that recommend ASCT only for PCNSL patients who achieve CR.
after HD-MTX-based induction therapy\textsuperscript{14}. Although based on a small number of treated patients, cumulative evidence suggests that thiotepa-conditioned ASCT should be offered even to patients with partial response after induction treatment.

BCNU-thiotepa-conditioned ASCT was generally well tolerated, no patients died of toxicity, and increased dose of thiotepa did not result in increased side effects. The 3-year OS was 77\% and, CRs achieved long-term remission without WBRT, suggesting a potential curative effect. Similar encouraging results have been reported in small case-series treated in other countries\textsuperscript{44}. BCNU-thiotepa-conditioned ASCT was used, following MATRix induction in five HIV-related PCNSL patients, resulting in lymphoma remission longer than 2 years in two patients\textsuperscript{45}. Overall, HDC/ASCT should be used with caution in HIV-positive patients with PCNSL because of the high risk of fatal complications\textsuperscript{45}. However, this strategy merits further evaluation in these high-risk subgroup of patients, mostly to identify the best candidates and establish the best conditioning regimen. Currently, BCNU-thiotepa regimens seem to be the best compromise between safety and efficacy as conditioning regimens in patients with newly-diagnosed PCNSL.

Thiotepa-free regimens other than BEAM
To date, two thiotepa-free conditioning regimens other than BEAM have been explored in patients with newly-diagnosed PCNSL (Table 1). Both regimens were assessed in small retrospective series of Asian patients\textsuperscript{30, 46}. BUCYE regimen (busulfan 3.2 mg/kg/d, days -7 to -5; cyclophosphamide 50 mg/kg/d, days -3 & -2; etoposide 200 mg/m\textsuperscript{2}, twice a day, days -5 & -4) was tested after induction with sequential high-dose MTX and ARAC in 11 Korean patients with PCNSL\textsuperscript{30}. This regimen was associated with grade-3 diarrhea in two patients, and febrile neutropenia in 10; no patients died of toxicity. All patients achieved CR before ASCT, six out of eight patients with a follow-up of over one year experienced relapse; at a median follow-up of 25 months, EFS was 30\% (median 15 months) and OS was 89\%. However, these results should be considered with caution because treated series was small, follow-up was short and salvage therapy showed a remarkably positive effect\textsuperscript{30}. Overall, these results are similar to those reported with BEAM\textsuperscript{29, 31}, and appear inferior to that reported with thiotepa-based regimens (see above). LEED conditioning regimen (cyclophosphamide 60 mg/kg/d, days -4 & -3; etoposide 250 mg/m\textsuperscript{2} every 12 h days -4 to -2; melphalan 130 mg/m\textsuperscript{2} once daily on day -1;
Dexamethasone 48 mg/d, days -4 to -1) was tested after induction with sequential MVP (methotrexate, vincristine, procarbazine) and HD-ARAC in 13 Japanese patients with PCNSL. In spite of good initial response rate, only half of the patients received ASCT. All transplanted patients achieved engraftment and there were no toxic deaths. Actuarial survival figures were encouraging (3-year OS: 75%), and, conversely to those reported in all the other ASCT studies in this field, transplanted and not transplanted patients showed similar survival (3-year OS: 80% vs. 71%; p= 0.25). Actually, the small number of transplanted patients and the use of WBRT in more than half of patients render this preliminary experience of hard interpretation.

ONGOING TRIALS

Large ongoing trials in PCNSL patients are mostly focused on improving activity of induction combinations and enhance efficacy of consolidation treatment, both following the main goal to reduce overall toxicity, late neurotoxicity in particular. Four large, ongoing randomized trials aim to compare HDC/ASCT with WBRT or with non-myeloablative chemotherapy as consolidation treatment. The first two compare the effect of HDC/ASCT and WBRT as consolidation after HD-MTX-based polychemotherapy in patients with newly diagnosed PCNSL. The accrual of the IELSG #32 trial (NCT01011920) was recently completed; 227 patients were enrolled in 53 centers in five European countries. The trial consisted of a double randomization addressing the effect of the addition of rituximab and/or thiotepa at high doses of MTX and ARAC in the first randomization, and addressing WBRT and HDC/ASCT as consolidation in the second comparison. CRR and PFS are the primary endpoints of the first and second randomizations, respectively. Preliminary results suggest increased activity with the addition of both rituximab and thiotepa, and more mature data on the second randomization are expected next year. PRECIS (NCT00863460) is a French multicenter randomized phase II trial comparing the same chemoimmunotherapy (sequential high-dose-MTX and ARAC-based chemotherapy plus rituximab) followed by WBRT or HDC/ASCT, with 2-year PFS as primary endpoint. The IELSG #32 and PRECIS trials could provide different results as they vary in design and patient selection. In particular, the upper age limit is 60 years in the PRECIS trial and 70 years old in the IELSG #32 trial; randomization was performed at trial registration in the PRECIS trial and only after confirmation of response to induction chemotherapy in the IELSG #32 trial; and conditioning regimens are different: TBC in the PRECIS trial and
BCNU-Thiotepa in the IELSG #32 trial. Although these relevant differences should be considered cautiously at results interpretation, both trials will provide relevant conclusions on the role of HDC/ASCT and will establish the subgroup of PCNSL patients as the best candidates for this intensified strategy.

Based on the encouraging results of the Alliance/CALGB 50202 trial, this American Intergroup is performing a multicenter randomized phase II trial that compares BCNU-Thiotepa-conditioned ASCT and non-myeloablative combination of high doses of etoposide and ARAC (etoposide 40 mg/kg continuous IV over 96 hours, days 1-4; ARAC 2 g/m² IV over 2 hours, every 12 hours, for 8 doses; days 1-4) in 160 patients ≤70 years old with PCNSL responsive to induction combination of methotrexate, temozolomide and rituximab (NCT01511562). A similar international trial sponsored by the IELSG (IELSG43) compares BCNU-Thiotepa-conditioned ASCT with conventional-dose ifosfamide-based chemotherapy as consolidation in 250 patients with PCNSL responsive to MATRix chemoimmunotherapy (NCT02531841). As an overall strategy, these randomized trials will establish the best consolidative strategy as part of first-line treatment in PCNSL patients, but, at the same time, will suggest which of these strategies could be kept to consolidate responses to chemotherapy in patients with relapsed/refractory disease. This is an important aspect considering that failed patients often achieve response to salvage chemotherapy. This is often short-lived, mostly due to the unavailability of feasible and effective consolidative strategies.

OPEN QUESTIONS FOR FUTURE TRIALS

Based on available evidence, HDT/ASCT is associated with high remission rates and excellent long-term outcomes in eligible patients. As outlined above, several important questions are currently being addressed in ongoing randomized trials. However, many unanswered questions remain, in particular, the establishment of the best candidates for upfront ASCT. In current practice, only young patients, without relevant comorbidity, with preserved neurocognitive functions, and chemosensitive lymphoma are referred to HDC/ASCT as part of first-line treatment. Patients with these characteristics represent only a part of PCNSL population. In fact, the proportion of enrolled patients in prospective trials that are successfully referred to HDC/ASCT oscillated between 46% and 81%, with higher rates among patients younger than 65 years (Table 1). Unfortunately, HDC/ASCT will hardly contribute to improve outcome in elderly patients. There is currently no consensus
on the upper age limit to define “elderly patients” in the field of PCNSL and to identify patients eligible for HDC/ASCT. This strategy is not advised to patients over 65 years in some institutions, whereas it is proposed to selected patients over 70 years in others. Thus, it is conceivable that most patients over 70 years and a good proportion of those over 65 are not referred to ASCT, which is an important limitation as alternative to WBRT considering that the most relevant actinic toxicity is observed in this subgroup of patients. Since both ASCT and WBRT may be associated with unacceptable toxicity, other consolidative strategies, like maintenance with immunomodulators or cytostatics, should be assessed in elderly PCNSL patients. The establishment of molecular and imaging markers able to distinguish the best candidates for HDC/ASCT is an important issue. For instance, the predictive effect of early MRI assessment and brain PET deserve further investigation in this setting. A wider use of reliable prognostic factors (a.e., IELSG score\(^48\)) may also result in personalized induction treatment, with a consequent better patient selection, improved feasibility and a higher proportion of patients being referred to consolidative ASCT. Although available evidence, exclusively provided by single-arm phase II trials, seems to support higher efficacy and better tolerability of BCNU-thiotepa combination, the best conditioning regimen remains to be established as randomized comparisons among different myeloablative combinations do not exist. Finally, salvage ASCT used in anecdotal cases of PCNSL relapsed after upfront ASCT should be further investigated as a valid option to avoid the use of consolidation WBRT, and its related neurotoxicity. The number of available effective therapeutic tools against PCNSL is progressively increasing. ASCT will play a central role in the near future, hopefully as part of upfront and salvage therapies. International efforts should be focused on improving feasibility and efficacy of this important strategy.
ACKNOWLEDGMENTS
AJMF and GI conceived the review, performed literature research, collected information, performed data analysis and interpretation, wrote the manuscript and approved final version before submission.

CONFLICT OF INTEREST DISCLOSURE
Authors declare no competing financial interests.
REFERENCES


Table 1. Reported studies focused exclusively on autologous stem cell transplantation in PCNSL

<table>
<thead>
<tr>
<th>Ref</th>
<th>N°</th>
<th>Median age (range)</th>
<th>Therapy Line</th>
<th>Therapy (induction intensification)</th>
<th>CRR to induction</th>
<th>Transplanted patients</th>
<th>Conditioning regimen</th>
<th>WB RT</th>
<th>Median f-up (months)</th>
<th>Overall survival</th>
<th>Neuro toxicity</th>
<th>TRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>22</td>
<td>53 (27-64)</td>
<td>Salvage</td>
<td>ARAC+VP16</td>
<td>36%</td>
<td>91%</td>
<td>Bu/TT/Cy</td>
<td>No</td>
<td>41</td>
<td>3-yr: 64%</td>
<td>32%</td>
<td>4%</td>
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<tr>
<td>17</td>
<td>43</td>
<td>52 (23-65)</td>
<td>Salvage</td>
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<td>35%</td>
<td>63%</td>
<td>Bu/TT/Cy</td>
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<td>2-yr: 45%</td>
<td>5%</td>
<td>12%</td>
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<tr>
<td>26</td>
<td>45</td>
<td>57 (19-72)</td>
<td>Salvage</td>
<td>ICE¥</td>
<td>51%</td>
<td>40%</td>
<td>Bu/TT</td>
<td>No</td>
<td>53</td>
<td>5-yr: 40%</td>
<td>NR</td>
<td>5%</td>
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<tr>
<td>29</td>
<td>28</td>
<td>53 (25-71)</td>
<td>First</td>
<td>HDMTX➔ARAC</td>
<td>29%</td>
<td>50%</td>
<td>BEAM</td>
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<td>28</td>
<td>2-yr: 55%</td>
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<tr>
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<td>25</td>
<td>52 (21-60)</td>
<td>First</td>
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<td>68%</td>
<td>BEAM</td>
<td>Yes</td>
<td>34</td>
<td>4-yr: 64%</td>
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<td>4%</td>
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<td>53 (30-66)</td>
<td>First</td>
<td>MBVP➔IFO+ARAC</td>
<td>2/6</td>
<td>6/6*</td>
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<td>41</td>
<td>2-yr: 40%</td>
<td>2/6</td>
<td>0/6</td>
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<tr>
<td>30</td>
<td>11</td>
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<td>HDMTX➔ARAC</td>
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<td>25</td>
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<tr>
<td>46</td>
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<td>56 (35-65)</td>
<td>First</td>
<td>MPV➔ARAC</td>
<td>31%</td>
<td>46%</td>
<td>LEED</td>
<td>Yes$</td>
<td>44</td>
<td>3-yr: 76%</td>
<td>0%</td>
<td>0%</td>
</tr>
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<td>23</td>
<td>55 (18-69)</td>
<td>First</td>
<td>HDMTX➔ARAC</td>
<td>13%</td>
<td>69%</td>
<td>Bu/TT</td>
<td>Yes$</td>
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<td>2-yr: 48%</td>
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<td>57 (23-67)</td>
<td>First</td>
<td>R-MPV➔ARAC</td>
<td>66%</td>
<td>81%</td>
<td>Bu/TT/Cy</td>
<td>No</td>
<td>45</td>
<td>3-yr: 81%</td>
<td>0%</td>
<td>12%</td>
</tr>
<tr>
<td>41</td>
<td>21</td>
<td>56 (34-69)</td>
<td>First</td>
<td>MPV➔ARAC</td>
<td>24%</td>
<td>100%*</td>
<td>Bu/TT/Cy</td>
<td>No</td>
<td>60</td>
<td>5-yr: 44%</td>
<td>0%</td>
<td>24%</td>
</tr>
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<td>18</td>
<td>30</td>
<td>54 (27-64)</td>
<td>First</td>
<td>HDMTX➔ARAC+TT</td>
<td>33%</td>
<td>77%</td>
<td>BCNU/TT</td>
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<td>63</td>
<td>5-yr: 69%</td>
<td>17%</td>
<td>3%</td>
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<td>54 (38-67)</td>
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<td>31%</td>
<td>85%</td>
<td>BCNU/TT</td>
<td>Yes$</td>
<td>72</td>
<td>5-yr: 77%</td>
<td>0%</td>
<td>0%</td>
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</tbody>
</table>

N°= Assessable patients; CRR= complete remission rate; WBRT= whole-brain irradiation; TRM= treatment-related mortality.
ARAC= cytarabine; BCNU= carmustine; BEAM= carmustine, etoposide, cytarabine, and melphalan; Bu= busulfan; Cy= cyclophosphamide; IFO= ifosfamide; ICE (regimen)= ifosfamide, carboplatin, etoposide; MBVP (regimen)= methotrexate, carmustine, etoposide, and methylprednisolone; MPV (regimen)= methotrexate, vincristine, and procarbazine; R-MPV (regimen)= MPV plus rituximab; OS= overall survival; TT= thiotepa; VP16= etoposide.
¥ Some patients with relapsed disease were retreated with HD-MTX.
# Performed ASCT was a selection criteria.
§ Only for patients not achieving a complete remission
* One patient received the treatment as salvage therapy.
Table 2. Conditioning combinations used in patients with newly diagnosed or relapsed PCNSL

REGIMENS WITHOUT THIOTEPA

BEAM regimen\textsuperscript{29,31}
BCNU 300 mg/m\textsuperscript{2} day -7
Etoposide 100 mg/m\textsuperscript{2} every 12 hours, days -6 to -3
Cytarabine 200 mg/m\textsuperscript{2} every 12 hours, days -6 to -3
Melphalan 140 mg/m\textsuperscript{2}, day -2.

BUCYE regimen\textsuperscript{30}
Busulfan 3.2 mg/kg/d, days -7 to -5
Cyclophosphamide 50 mg/kg/d, days -3 & -2
Etoposide 200 mg/m\textsuperscript{2}, twice a day, days -5 & -4.

LEED regimen\textsuperscript{46}
Cyclophosphamide 60 mg/kg/d, days -4 & -3
Etoposide 250 mg/m\textsuperscript{2} every 12 h days -4 to -2
Melphalan 130 mg/m\textsuperscript{2} once daily on day -1
Dexamethasone 48 mg/d, days -4 to -1.

THIOTEPA-CONTAINING REGIMENS

Busulfan-thiotepa combination\textsuperscript{28}
Busulfan four oral daily doses of 4 mg/kg BW/d, days -8 to -5
Thiotepa 5 mg/kg body weight on days -4 and -3.

TBC regimen\textsuperscript{41-43}
Thiotepa 250-300 mg/m\textsuperscript{2}/d, days –8 and –7
Busulfan 3.2-9.6 mg/kg BW/d, days –6 to –4
Cyclophosphamide 2 g/m\textsuperscript{2}/d, days –3 and –2.

TBC regimen\textsuperscript{19}
Thiotepa 250 mg/m\textsuperscript{2}/d, days -9, -8 and -7
Busulfan 3.2 mg/kg/d, days -6, -5 and -4
Cyclophosphamide 60 mg/kg/d, days -3 and -2.

BCNU-thiotepa regimen\textsuperscript{18}
Carmustine 400 mg/m\textsuperscript{2}, day -6
Thiotepa 5 mg/kg BW/d, days -5 and -4.

BCNU-thiotepa 10 regimen\textsuperscript{6}
Carmustine 400 mg/m\textsuperscript{2}, day -6
Thiotepa 2 x 5 mg/kg BW/d, days -5 and -4.
The role of autologous stem cell transplantation in primary CNS lymphoma

Andrés J.M. Ferreri and Gerald Illerhaus