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Lymphoma

High-dose thiotepa, busulfan, cyclophosphamide and ASCT without whole-brain radiotherapy for poor prognosis primary CNS lymphoma

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Summary:

Treatment of primary central nervous system lymphoma (PCNSL) with combined high-dose methotrexate (HD-MTX)-based chemotherapy and whole-brain radiotherapy (WBRT) is associated with severe neurotoxicity, but high relapse rates are associated with the use of either modality alone. In an attempt to improve upon these dismal results, we treated seven PCNSL patients with HD-MTX-based induction therapy followed by thiotepa, busulfan, cyclophosphamide (TBC), and autologous stem cell transplant (ASCT), without WBRT. Six of these patients had at least one of the following poor prognostic features: Karnofsky performance status (KPS) $\leqslant$50%, age $>$60 years, or relapsed disease. All but one patient tolerated the treatment well and experienced improvements in neurological function and overall performance status post-transplant. No treatment-induced neurotoxicity (dementia, ataxia, and incontinence) was observed although the follow-up is short. One early treatment-related death occurred in a patient with multiple comorbid medical conditions. The other six patients achieved a complete response (CR) after TBC and ASCT. Five patients are currently alive and relapse-free at 5, 8, 24, 36, and 42 months from diagnosis. One additional patient relapsed and died 33 months after diagnosis. Two of the seven patients received TBC/ASCT as the only treatment after disease progression following their initial chemotherapy and both remain relapse-free at the time of this report, 22 and 31 months post-TBC/ASCT. In conclusion, prolonged CR can be attained after chemotherapy-only treatment of poor prognosis PCNSL. Furthermore, this small series suggests that high-dose chemotherapy for PCNSL should include drugs that penetrate the CNS such as busulfan and thiotepa rather than standard lymphoma regimens such as BEAM.

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Primary central nervous system lymphoma (PCNSL) is an aggressive malignancy that arises from the brain, spinal cord, leptomeninges, or eyes. The incidence in immunocompetent patients has risen more than 10-fold in the past three decades, with a current rate of 0.3/100 000 person-years.[1] Despite marked intrinsic chemo- and radiosensitivity, PCNSL continues to be associated with poor survival and quality of life.[1–3]

The optimal treatment for PCNSL is not yet established. Traditional whole-brain radiotherapy (WBRT) is associated with poor survival rates and severe neurotoxicity.[4–8] Adding CHOP to RT does not improve outcome.[4,9] Although combined modality treatment (CMT) with high-dose methotrexate (HD-MTX)-based chemotherapy and WBRT results in higher disease-free and overall survival rates, it is associated with severe neurotoxicity.[5,10] Treatment-related neurotoxicity manifests as dementia, ataxia, incontinence, and may lead to death in patients who are otherwise 'cured' of their PCNSL. Age over 50 or 60 years has been identified as the most important predictor for delayed neurotoxicity.[10] This is problematic because the median age of onset for PCNSL is 60 years. On the other hand, treating patients with HD-MTX-based chemotherapy alone leads to a higher risk of relapse.[3,11,12]

In order to improve upon the results of single modality chemotherapy and to avoid the neurotoxicity associated with WBRT, we treated a small series of patients with HD-MTX/Ara-C induction therapy followed by thiotepa, busulfan, and cyclophosphamide (TBC) and autologous stem cell transplant (ASCT) for their poor prognosis PCNSL. The TBC high-dose chemotherapy (HDCT) regimen was selected because these agents have good CNS penetration and proven efficacy in treating lymphoid malignancies. Furthermore, this combination of agents has been well studied in high dosage.[13–16]

Patients and methods

Patient characteristics

Between August 1998 and August 2002, we treated seven PCNSL patients with TBC and ASCT without WBRT. All patients were immunocompetent and ranged in age from 41 to 64 years with the median age of 56. Histological

Table 1 Patient characteristics at diagnosis

Patient	*Sex/age (years)*	*Diagnosis*		*KPS* (%)	*Involved sites*				*Biopsy diagnosis*	*Comorbid diseases*
		Sx to dx (month)	*New vs relapse*		*B*	*E*	*C*	*S*		
1	M/41	6	R	50	+	–	–	–	B cell DLCL	None
2	F/41	8	N	30	+	+	–	–	T cell IBL	DVT + PE
3	M/54	3	N	30	+	–	–	–	B cell LCL	Pancreatitis, HTN, CAD, DVT
4	M/64	18	N	30	+	–	–	–	B cell IBL	HTN, COPD, smoker, ETOH, depression, BPH
5	M/61	1	N	70	+	–	–	–	B cell LBL	HTN
6	F/56	1	N	70	+	–	–	–	B cell DLCL	None
7	M/62	2	N	60	+	–	–	–	B cell DLCL	None

–: absent; +: present; B: brain; C: CSF cytology; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; DLCL: diffuse large cell lymphoma; DVT: deep venous thrombosis; E: eyes; ETOH: alcohol abuse; HTN: hypertension; IBL: immunoblastic B cell lymphoma; LCL: large cell lymphoma; *N*: newly diagnosed disease; PE: pulmonary embolism; R: relapsed disease; S: systemic involvement; Sx to dx: symptoms to diagnosis.

Week of Therapy											
Treatment	1	2	3	4	5	6	7	8	9	10	12-14
MTX 3.5-5 g/m^2 IV +leucovorin rescue	X		X		X		X				
+/- Procarbazine 100mg/m^2 p.o. x 7 days	X				X						
Ara-C 3g/m^2 IV x 2 days (days 1-2)**								X			
G-CSF 5-10μg/kg/d (day 8 until apheresis)									X		
CD34+ Cell Apheresis day 13, 14, or 15										X	
TBC* and ASCT											X

* Day –8 and –7 Thiotepa 300mg/m^2 *i.v.* per day
Day–6 to –4 Busulfan 9.6mg/kg *i.v.* per day***
Day–3 to –2 Cyclophosphamide 2g/m^2 *i.v.* per day
Day 0 Infusion of autologous blood stemcells

** Patient 1 received an extra cycle of MTX/ Ara-C;
*** Patient 2 received busulfan orally at 12mg/kg total dose.

Figure 1 Treatment flow chart.

diagnoses were established through stereotactic biopsy, open brain biopsy, or vitrectomy. Patient characteristics and histological diagnosis are described in Table 1. All patients were reviewed by our Neuro-Oncology Program and treatment options were discussed. Owing to advanced age and poor performance status of our patients, it was generally felt that combined modality treatment involving HD-MTX and WBRT would likely result in severe neurological sequelae and a poor chance for survival. In all cases, the patients refused WBRT. All patients and often their next of kin provided written informed consent to proceed with the intensive chemotherapy-only treatment protocol described below.

All patients underwent staging investigations, which included magnetic resonance imaging scan of the cranial–spinal axis, ophthalmologic evaluation with slit-lamp examination, chest X-ray, computed tomography (CT) scan of the chest, abdomen and pelvis, bone marrow biopsy, lumbar puncture, and serology testing for human immunodeficiency virus and hepatitis virus. Patient 2 had a right lower lobe lesion revealed on CT scan, and underwent open lung biopsy that revealed pulmonary infarction likely to be secondary to a pulmonary thromboembolism. Adequate pulmonary, cardiac, hepatic, and renal functions were required. Creatinine clearance was calculated based on 24-h urine collection prior to MTX treatment. All patients gave written informed consent before proceeding to stem cell apheresis and TBC/ASCT.

Six of the patients were very ill prior to treatment with at least one of the following poor prognostic features: Karnofsky performance status (KPS) $\leqslant 50\%$, age >60 years, or relapsed disease. Patient 1 was previously treated with HDMTX/Ara-C and BEAM/ASCT as part of a competing multicenter phase II study. He obtained a CR but relapsed 7 months later in parenchymal brain. He then received TBC/ASCT as his only salvage therapy. Three other patients were not eligible for the competing PCNSL protocol because of a KPS of only 30% at diagnosis (2, 3, and 4). The final three patients (5–7) were treated after the competing protocol had been closed.

Treatment plan

This is summarized in Figure 1.

MTX/Ara-C induction therapy: The first five patients received intravenous MTX 3.5 g/m^2 at biweekly intervals for four to five cycles. To try and increase the response rate to induction therapy, the final two patients (6 and 7) received MTX 5 g/m^2 at biweekly intervals for four cycles

with procarbazine 100 mg/m^2 p.o. daily for 7 days with MTX cycles 1 and 3. No MTX dose adjustment was required as no patient had a low creatinine clearance. For all seven patients, alkalinization with D5/0.45NS with two ampules of sodium bicarbonate and 20 mmol of KCL/l was started 12 h prior to MTX at a rate of 3 l/m^2/day and continued until MTX level was under 0.05 μmol/l. Leucovorin 40–50 mg i.v. four times daily was started 24 h after MTX infusion and continued until the MTX level was less than 0.1 μmol/l, and then at 25 mg i.v. or p.o. until the MTX level was less than 0.01 μmol/l. Ara-C 3 g/m^2 i.v. once daily for two consecutive days was given following the last cycle of MTX. Six patients received one cycle of Ara-C, while patient 1 received two cycles (Figure 1).

Blood stem cell harvesting: Peripheral blood progenitor cells were mobilized with the last cycle of induction therapy. Ara-C 3 g/m^2 i.v. was given once daily on days 1 and 2, followed by G-CSF 5–10 μg/kg s.c. (rounded to the nearest vial size), given once daily starting day 8. Apheresis was performed on day 13, 14, or 15 when blood CD34+ cell counts were over 20×10^6/l (Figure 1). Volume of aphereses ranged from 8.5 to 10.8 l and the number of CD34+ cells collected ranged from 12.1×10^6 to 44.6×10^6/kg.

TBC/ASCT: Thiotepa 300 mg/m^2 i.v. once daily was infused over 24 h on days −8 and −7. Busulfan 4 mg/kg p.o. in divided doses daily was given on days −6 to −4 for one patient, while the other six patients received 3.2 mg/kg i.v. once daily on days −6 to −4. Cyclophosphamide 2 g/m^2 i.v. once daily over 2 h was given on days −3 and −2 followed by ASCT on day 0. G-CSF 300–480 μg s.c. once daily was routinely given from day +7 until the absolute neutrophil count (ANC) was over 1.5×10^9/l. Phenytoin at 5 mg/kg/day p.o. in divided doses to achieve therapeutic blood levels was started 1 week prior to busulfan and continued until completion of busulfan treatment. Continuous infusion of mesna at 4 g/day for 2 days was given with cyclophosphamide. Antimicrobial prophylaxis consisted of ciprofloxacin, acyclovir, nystatin, and trimethoprim-sulfamethoxazole.

Definition of responses: Response was defined according to common criteria used in the evaluation of PCNSL.[10] Complete response (CR) was defined as resolution of the enhancing tumor for at least 1 month. In the patient with eye involvement, a repeat ophthalmologic examination negative for tumor was documented. Patients were off corticosteroid therapy and neurologically stable or improved. Partial response (PR) was defined as an over 50% reduction in tumor size. Patients were neurologically improved or stable on a stable or decreasing dose of corticosteriods. Progressive disease (PD) was defined as unequivocal increase in tumor size or the appearance of new lesions.

Follow-up: Patients were evaluated at 3-month intervals with a targeted history, physical examination, and neuroimaging. Survival and time to progression were measured from date of diagnosis to date of relapse, death, or last clinic visit.

Results

Hematological recovery and toxicity

Median time to ANC $\geqslant 0.5 \times 10^9$/l was 10 days and platelet $\geqslant 20 \times 10^9$/l was 11 days post-ASCT. Six patients developed culture negative febrile neutropenia (Table 2). All received systemic antimicrobial therapy.

Nonhematological toxicity

All patients tolerated the MTX/Ara-C induction therapy well, with no grade 3 or 4 toxicity except chemotherapy-induced severe cytopenia. Patient 4 developed septic shock secondary to aspiration pneumonia and polymicrobial neutropenic sepsis during transplantation. He required ventilator support and died on day +6 post-ASCT secondary to sepsis and his multiple comorbid medical conditions. Patient 5 experienced hemorrhagic cystitis, herpes zoster, and prolonged noninfectious diarrhea, but has since made a full recovery. Patient 3 developed cholestasis with a peak total bilirubin of 151 μmol/l on

Table 2 Response to therapy and survival from diagnosis

Patient	*Response to therapies*		*Best ↑in KPS*	*Current KPS (%)*	*Survival (month)*
	MTX/Ara-C	*TBC/ASCT*			
1[a]	CR	CR	20	70	42
2	PR	CR	50	—	33
3	PR	CR	60	90	36
4	PR	CR[b]	0	—	2
5	PD	CR	20	90	24
6	PR	CR	0	70	8
7	PR	CR	20	80	5
Summary		100%	Median 20	Median 80	Median 24

[a]Patient 1 had a CR after his MTX/Ara-C treatment prior to BEAM/ASCT. He relapsed 7 months later after BEAM/ASCT and was treated on TBC/ASCT protocol without reinduction MTX-Ara-C. He remains event-free 31 months post-TBC/ASCT.
[b]Patient 4 had no residual microscopic diseases on autopsy. Best ↑in KPS: best KPS post-transplant minus best KPS prior transplant.

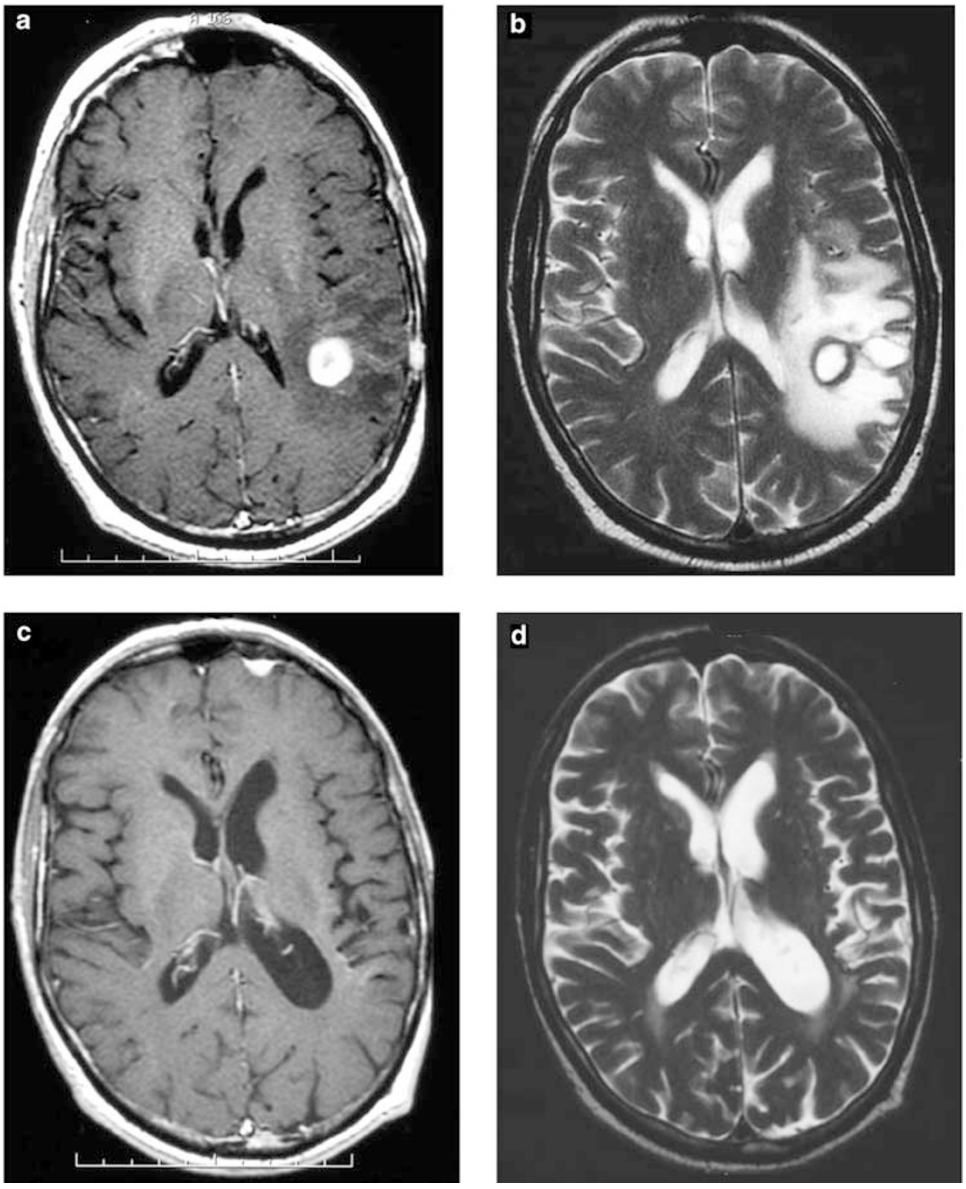

Figure 2 Brain MRI scans for patient #5, immediately before and 20 months after TBC/ASCT. Brain MRI after HDMTX/Ara-C induction chemotherapy and prior to TBC/ASCT: (a) T1 and (b) T2 weighted images. Brain MRI 20 months after TBC/ASCT: (c) T1 and (d) T2 weighted images.

day +8 of his transplant; he recovered uneventfully. Mucositis was limited to grade 1 (two patients) and 2 (five patients). There were no cases of veno-occlusive disease.

Response and survival

One patient had a CR, five a PR, and one patient had PD after induction therapy with HD-MTX/Ara-C (Table 2). All six evaluable patients had CR after TBC and ASCT. Two of these patients (1 and 5) received TBC/ASCT as the only treatment after disease progression following their initial chemotherapy and both remain relapse-free 22 and 31 months post-TBC. The pre- and post-TBC/ASCT MRI scans of one of these patients are shown in Figure 2. The only patient who did not survive TBC/ASCT (patient 4) had no microscopic evidence of residual brain lymphoma or lymphoma elsewhere in his body at autopsy.

Five patients (1, 3, 5, 6, 7) are alive with event-free survivals of 5, 8, 24, 36, and 42 months from diagnosis. One patient relapsed 28 months post-ASCT and received palliative cranial radiotherapy. She died 1 month post-radiation, and 33 months from diagnosis.

Quality of life (QOL)/performance status

Six of the seven patients experienced improvements in their neurological function and overall performance status post-transplant (Table 2). Patient 1 presented with severe

neurological compromises, loss of self-care, a 45 lb weight loss, and a KPS of 50%. He improved steadily post-TBC/ASCT and returned to work. Patient 2 was bedridden and extremely drowsy at presentation with a KPS of 30%. She was only able to follow simple commands after repetition. Her neurological functioning progressively improved and she had a KPS of 80–90% for more than 2 years until her PCNSL relapsed 28 months post-TBC/ASCT. Patient 3 presented with severe neurological compromises requiring two-person assistance, elevated LDH, and KPS of 30%. He also returned to work. Patients 5 and 7 were over 60 years of age at diagnosis. They have made a full neurological recovery and one has returned to work as a pianist with a KPS of 100%. Patient 6 presented with a generalized seizure and memory difficulty, and was found to have a large frontal lobe lymphoma. She has recovered from TBC/ASCT and plans to return to work next month.

Discussion

The best reported outcomes of treating PCNSL are with HD-MTX-based chemotherapy combined with WBRT. Nevertheless, this combined modality treatment results in median survivals of only 33–60 months, 5-year survival rates of only 20–50%, and frequent neurotoxicity with dementia, ataxia, and incontinence.[5,10,17] Patients over 60 years of age and with poor performance status tend to have particularly poor outcomes.[2,10] Better treatments are, therefore, needed for PCNSL. Despite the major limitations of our study including small patient numbers and relatively short follow-up, our series demonstrates that HD-MTX/Ara-C induction followed by TBC/ASCT can achieve prolonged CR in a population of poor prognosis PCNSL patients.

The rationale for the different components of the regimen was that the chosen agents all have activity against lymphoma and all penetrate well into the CNS at high dosage. MTX and Ara-C have proven efficacy in treating CNS lymphoma.[3,10,11,18–20] Both drugs achieve good CNS penetration and Ara-C achieves therapeutic concentration in intraocular fluid.[13] Furthermore, HD-MTX and Ara-C act synergistically by prolonging the exposure of proliferating cells to S-phase cytostatics.[2] Therapeutic MTX level of $>10\,\mu$M can be achieved in CSF with intravenous dose of $3\,g/m^2$. This approach is supported by preliminary studies that suggest that adequate meningeal treatment without intrathecal MTX is suitable in both CSF− and CSF+ patients.[2] The MTX/Ara-C regimen needs to be further improved; however, because only one of our patients achieved a CR with this induction therapy. Our more recent patients were treated with a higher MTX dose and procarbazine was given for two cycles, but neither achieved a CR to induction. Perhaps newer agents like temozolomide should be incorporated into the induction regimen.

We chose TBC as the pretransplant conditioning regimen because the agents cross the blood brain barrier (BBB) well and because they are active against high-grade lymphoid malignancies.[15,16] This regimen was also employed by Soussain's group in treating relapsed PCNSL.[13,14] Busulfan achieves therapeutic levels in CSF and in brain parenchyma in animal models.[21,22] Thiotepa and its active metabolite tepa penetrate the BBB very well and achieve therapeutic concentrations in the CSF and brain parenchyma.[15,23] Cyclophosphamide theoretically does not cross the intact BBB well because of its hydrophilic property, but it appears to achieve potentially therapeutic concentrations in the brain parenchyma and especially in tumor tissue in both animal models and clinical practice.[15,24] The reported CNS penetration of thiotepa and busulfan is both $>80\%$, while that of cyclophosphamide is 20–30%.[22] The excellent CNS penetration of the TBC regimen is in opposition to that of agents in the BEAM regimen, where CNS penetration of BCNU is 15–70%, etoposide is $<5\%$, Ara-C is 6–22%, and melphalan is 10%.[22] Although BCNU and Ara-C do penetrate into the CNS to some degree, the doses of these agents in BEAM are not particularly high relative to their maximal doses without ASCT. In other words, the degree to which BCNU and Ara-C can be dose-escalated by ASCT support is very small compared to the substantial dose-escalation possible for thiotepa and busulfan.

Although HDCT/ASCT is widely utilized to treat poor prognosis and relapsed systemic non-Hodgkin's lymphoma, it is not established practice for PCNSL at the present time. Nevertheless, data supporting the use of HDCT/ASCT for CNS lymphoma exist. Van Besien *et al*[24] reported 20–40% disease-free survival rates following HDCT for adults with lymphoma or lymphoid leukemia who had a history of CNS involvement, in one series. Most clinical experiences with HDCT/ASCT for PCNSL are in the setting of relapsed disease. One case of durable remission at 6-year follow-up was reported in a 30-year-old patient who was treated with salvage HDCT and autologous transplantation for relapsed PCNSL.[25] Soussain *et al*[13] used HDCT and autologous bone marrow transplantation to treat five patients who had intraocular lymphoma (IOL) that was refractory to chemotherapy and WBRT. All five patients achieved a CR and three continued in CR at a median follow-up of 26 months. Based on the above experience, the same group later treated an additional 22 immunocompetent patients with high-dose TBC followed by ASCT for recurrent or refractory PCNSL or IOL. The probability of 3-year overall and event-free survival was 63.7 and 53%, respectively.[14]

Application of HDCT/ASCT as first line therapy for PCNSL has the theoretical benefit of maintaining the potential for cure while eliminating the need for WBRT and, therefore, the neurotoxicity associated with WBRT. One small pilot study explored the possibility of utilizing HDCT as first-line therapy to improve relapse-free survival and reduce neurotoxicity in six patients with PCNSL under the age of 65 years.[26] This study concluded that first-line HDCT produces CR with acceptable toxicities for patients less than 65 years of age.

Preliminary results from a multicentre phase II study of first remission consolidation of PCNSL patients with BEAM/ASCT were disappointing.[27] At the time of initial reporting, 24 patients had enrolled on the study and two were too early in treatment to evaluate.[27] Of the remaining 22 patients, 10 did not respond to induction chemotherapy and, therefore, did not proceed to BEAM/ASCT. With a

median follow-up of only 4 months, five of the 12 patients treated with BEAM/ASCT already had relapsed. Our patient 1 was enrolled in this BEAM study and relapsed 7 months after treatment. He subsequently received TBC/ASCT as the only salvage treatment and continues in second CR now 31 months from TBC/ASCT. This observation suggests that HDCT for PCNSL should include drugs that penetrate the CNS extremely well rather than standard regimens used to treat systemic lymphoma such as BEAM, which do not penetrate well into the CNS.[4,9,12,27]

This pilot study is also encouraging in that patients experienced an improvement in their neurological performance and QOL following the TBC/ASCT. This is consistent with previous studies that demonstrate HD-MTX-based chemotherapy alone without WBRT is associated with much less late onset neurotoxicity.[3,11,12] WBRT-based treatment is reported to have a high rate of delayed CNS toxicity leading to impaired QOL.[5,18,28] MTX-based chemotherapy and WBRT act synergistically causing a 26% rate of leukoencephalopathy at 68 months.[5,18] The rate increases to nearly 80% in patients over 60 years of age, 1 year after treatment.[5] Median survival is less than 12 months for patients who develop neurotoxicity despite continuous remission.[18] All had a significant decline in KPS and most required custodial care. This may represent a minimum estimate as no data on QOL, return to work, and neuropsychiatric tests were collected prospectively, and therefore, only overt clinical and radiographic neurotoxicity was recorded.

In conclusion, prolonged CR is attainable after TBC/ASCT following HD-MTX/Ara-C without WBRT in a population of poor prognosis PCNSL patients. HDCT for PCNSL should include drugs that penetrate the CNS extremely well such as busulfan and thiotepa rather than standard lymphoma regimens such as BEAM. The MTX/Ara-C-TBC regimen is associated with minimal neurotoxicity consistent with other reported studies. A multicentre phase II trial is warranted to evaluate the role of TBC/ASCT as first-line therapy for PCNSL. Although the risk of acute toxicity is worrisome in patients over 60 years of age, TBC/ASCT may still be a reasonable alternative to WBRT in patients of this age group who do not achieve CR in response to HD-MTX-based chemotherapy. Further studies in PCNSL should include formal neuropsychiatric evaluation as a clinically important outcome.

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