Chemotherapy in newly diagnosed primary central nervous system lymphoma

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Abstract: Primary central nervous system lymphoma (PCNSL) accounts for only 3% of brain tumors. It can involve the brain parenchyma, leptomeninges, eyes and the spinal cord. Unlike systemic lymphoma, durable remissions remain uncommon. Although phase III trials in this rare disease are difficult to perform, many phase II trials have attempted to define standards of care. Treatment modalities for patients with newly diagnosed PCNSL include radiation and/or chemotherapy. While the role of radiation therapy for initial management of PCNSL is controversial, clinical trials will attempt to improve the therapeutic index of this modality. Routes of chemotherapy administration include intravenous, intraocular, intraventricular or intra-arterial. Multiple trials have outlined different methotrexate-based chemotherapy regimens and have used local techniques to improve drug delivery. A major challenge in the management of patients with PCNSL remains the delivery of aggressive treatment with preservation of neurocognitive function. Because PCNSL is rare, it is important to perform multicenter clinical trials and to incorporate detailed measurements of long-term toxicities. In this review we focus on different chemotherapeutic approaches for immunocompetent patients with newly diagnosed PCNSL and discuss the role of local drug delivery in addition to systemic therapy. We also address the neurocognitive toxicity of treatment.

Keywords: blood–brain barrier disruption, chemotherapy, high-dose chemotherapy, intra-arterial chemotherapy, intraocular chemotherapy, intrathecal chemotherapy, methotrexate, neurocognitive toxicity, primary central nervous system lymphoma

Introduction

Primary central nervous system lymphoma (PCNSL) is a rare cancer accounting for less than 3% of brain tumors [CBTRUS, 2009]. The vast majority of PCNSLs are diffuse large B-cell lymphomas, and unlike systemic diffuse large B-cell non-Hodgkin lymphoma (NHL), PCNSL remains confined to the CNS (brain parenchyma, leptomeninges, eyes and the spinal cord) in most patients. In addition, unlike systemic lymphoma, durable remissions remain uncommon. The mean age of patients is approximately 60 years [Abrey *et al.* 2006; Ferreri *et al.* 2003]. Several treatment modalities have been employed for these patients: combined modality therapy with whole brain radiation therapy (WBRT); systemic chemotherapy alone; intrathecal (IT) chemotherapy; and intraocular chemotherapy. A major difficulty in defining the optimal therapy for patients with PCNSL is the low incidence of these tumors making adequately powered phase III trials difficult to conduct [Muldoon *et al.* 2007]. This paper reviews the role of various routes of chemotherapy delivery for the treatment of immunocompetent patients with newly diagnosed PCNSL.

Although combined chemotherapy and radiation therapy has produced response rates of up to 80–90% and median overall survival (OS) close to 5 years in PCNSL [Shah *et al.* 2007; Gavrilovic *et al.* 2006; Omuro *et al.* 2005b; DeAngelis *et al.* 2002; Abrey *et al.* 2000], neurocognitive toxicity has been a major limitation of this paradigm [Abrey *et al.* 1998, 2000]. Delayed neurotoxicity presents with memory deterioration and personality changes early in the course, followed by gait disturbance and urinary incontinence; these complications are generally permanent [Abrey *et al.* 1998, 2000]. Risk factors for

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neurotoxicity include radiotherapy, older age (particularly over 60 years), IT chemotherapy and chemotherapy after WBRT [Illerhaus *et al.* 2009; Omuro *et al.* 2005a; Correa *et al.* 2004; Abrey *et al.* 1998; Blay *et al.* 1998] although some studies do not agree entirely with the above correlations. For example Blay and colleagues reported no association between age or IT chemotherapy and late neurotoxicity [Blay *et al.* 1998] and Illerhaus and colleagues reported no clinical signs of severe neurotoxicity in elderly patients provided they were treated without WBRT [Illerhaus *et al.* 2009]. Up to 83% of patients older than 60 years of age who receive WBRT for the treatment of PCNSL develop neurotoxicity [Abrey *et al.* 2000]. As a result, older patients who survive may have a poor quality of life. In addition, this study failed to demonstrate a survival advantage to the use of WBRT as part of a combined treatment regimen in this population of patients (32 versus 33 months for patients who received WBRT versus deferred WBRT, respectively) [Abrey *et al.* 2000]. These findings raise the question as to whether patients with PCNSL should receive WBRT at diagnosis and if it could be avoided without compromising response rate or survival.

Systemic delivery of chemotherapy

Combination chemotherapy

Different combinations of chemotherapy have been used in the treatment of PCNSL (Table 1). Because systemic NHL is treated with combination chemotherapy rather than monotherapy, one could argue that optimal management requires this approach in treatment of PCNSL as well.

Most methotrexate (MTX)-based combination regimens use significantly lower doses than are used in monotherapy (MTX dose 1–5 g/m^2 versus 8 g/m^2 in monotherapy) [Illerhaus *et al.* 2009; Pels *et al.* 2009; Omuro *et al.* 2007; Hoang-Xuan *et al.* 2003]. The response rates and median survival range between 48% and 100% and 15 and 50 months, respectively [Illerhaus *et al.* 2009; Pels *et al.* 2003, 2009; Omuro *et al.* 2007; Hoang-Xuan *et al.* 2003; Sandor *et al.* 1998]. Although the data suggest that younger patients [Angelov *et al.* 2009; Pels *et al.* 2009; Sandor *et al.* 1998] may have improved response rates with combination chemotherapy compared with older patients [Illerhaus *et al.* 2009; Hoang-Xuan *et al.* 2003], the regimens differ significantly making generalizations difficult to assert.

The prognosis and outcome of treatment appears to differ between younger and older patients. Among studies that included mostly younger patients, one of the best response rates achieved was reported in a small number of patients by Sandor and colleagues, in which all 14 patients achieved a complete or partial response [Sandor *et al.* 1998]. The patients were relatively younger (median age 57) compared with other studies where WBRT was excluded from the treatment. The dose of MTX in this study was higher than all other combination chemotherapy regimens (8.4 g/m^2 over 24 h). Although the regimen consisted of thiotepa, vincristine and high-dose MTX, it also included IT MTX and cytarabine. High-grade toxicities included severe leukoencephalopathy, grade 3–4 neutropenia in 50% of cycles, ileus and seizures. The three patients with leukoencephalopathy were 66, 67 and 69 years old, confirming the adverse effect of age on the toxicities of high-dose MTX or other drugs used in this regimen [Sandor *et al.* 1998]. Some more recent studies with different regimens have replicated good responses or survival outcomes with different regimens. A recent study of combination chemotherapy in a relatively small number of young patients (median age 53 years) showed a response rate of 77% but high relapse rates with the omission of IT therapy [Pels *et al.* 2009]. An older study from the same group, where IT chemotherapy was part of the protocol, however, demonstrated a much lower relapse rate in the younger patient population [Pels *et al.* 2003]. Median time to treatment failure and OS were not reached after median follow up of 32 months in the patient group younger than 60 years, which was more consistent with some other studies dedicated to younger patients.

Other recent studies on younger patients, have reported outcome with different regimens and modalities of therapy, including single-agent MTX [Yang *et al.* 2009], intra-arterial (IA) chemotherapy [Angelov *et al.* 2009], high-dose chemotherapy followed by stem-cell rescue [Illerhaus *et al.* 2008; Montemuro *et al.* 2007], and regimens which include WBRT as part of protocol [Shah *et al.* 2007; Omuro *et al.* 2005b; DeAngelis *et al.* 2002]. The median age in all of these reports is in the fifties and with few exceptions [Yang *et al.* 2009; Illerhaus *et al.* 2008]

Table 1. Chemotherapy-only regimens for initial therapy of primary central nervous system lymphoma.

Chemotherapy regimen	*N*	Median age	Median KPS	MTX dose (g/m^2)	Response rate % (CR + PR)	Median OS (months)	Median PFS (months)	Comment	Reference
MTX alone									
MTX	31	63	40	8	100	30	16.6	Followed by maintenance	Guha-Thakurta *et al.* [1999]
MTX	37	60	70	8	35	25	10		Herrlinger *et al.* [2005]
MTX	25	60	80	8	74	55Ŧ	12.8		Batchelor *et al.* [2003]
MTX	16	52	90	8	57	50	NR		Yang *et al.* [2009]
MTX	31	74	70	3.5–8	97	37	7.1	30 patients started with 8 g/m^2	Zhu *et al.* [2009]
Combination									
MTX, TMZ	23	68	60	3	55	35	8		Omuro *et al.* [2007]
MTX, thiotepa, VCR, dexamethasone and IT CXT	14	57	NR	8.4	100	NR	16.5	MTX 1.5 g/m^2 over 1 h, then 300 $mg/m^2/h \times 24$ h	Sandor *et al.* [1998]
MTX, CCNU, PCB, methylprednisolone and IT CXT	50	72	50	1	48	14	6.8		Hoang-Xuan *et al.* [2003]
MTX, VCR, ifosfamide, cytarabine, cyclophosphamide, dexamethasone and IT CXT	65	62	70	5	71	50	21*	MTX 0.5 $g/m^2 \times 30$ min, then 4.5 $g/m^2 \times 23.5$ h	Pels *et al.* [2003]
MTX, PCB, VCR, IT CXT and post-radiation cytarabine	57	65	70	3.5	90§	29#	7#	26 were treated with CXT alone	Gavrilovic *et al.* [2006] (update from Abrey *et al.* [2000])
MTX, VCR, ifosfamide, cytarabine, cyclophosphamide, dexamethasone	18	53	80	5	77	NR	8*	MTX 0.5 $g/m^2 \times 30$ min, then 4.5 $g/m^2 \times 23.5$ h	Pels *et al.* [2009]
MTX, PCB, CCNU	30	70	60	3	71	15	5.9		Illerhaus *et al.* [2009]
IA MTX with BBBD and combinations with etoposide, cyclophosphamide, PCB	149	54	70	2.5‡	82	37	21.6	Retrospective study; various CXT combinations	Angelov *et al.* [2009]
HDC/ASCT									
MTX, cytarabine, BEAM	28	53	70	3.5	57	NR	5.6**		Abrey *et al.* [2003]
MTX, busulfan, thiotepa	23	55	70	8	83	20	17**	Response-adapted WBRT	Montemurro *et al.* [2007]
MTX, cytarabine, thiotepa, carmustine	13	54	90	8	62	25	≥25Ŧ	Response-adapted WBRT	Illerhaus *et al.* [2008]

*Time to treatment failure.
**Event-free survival.
‡2.5 g days 1 and 2 (5 g/cycle).
#Data for the 26 patients treated with CXT alone.
ŦNot mentioned directly in paper: data extrapolated from Kaplan–Meier plot.
§ORR post-induction CXT.
ŦŦUpdate per Gerstner *et al.* [2008].
BEAM, carmustine/etoposide/cytarabine/melphalan; CCNU, lomustine; CR, complete response rate; CXT, chemotherapy; HDC/ASCT, high-dose chemotherapy followed by autologous stem-cell transplant; IT, intrathecal; KPS, Karnofsky performance score; MTX, methotrexate; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response rate; TMZ, temozolomide; PCB, procarbazine; VCR, vincristine; WBRT, whole brain radiation therapy.

where response rate has been in the range of 50–60%, response rates to chemotherapy in this young population has ranged between 80% and 90% [Angelov *et al.* 2009; Montemuro *et al.* 2007; Shah *et al.* 2007; Omuro *et al.* 2005b; DeAngelis *et al.* 2002]. Comparison of survival outcomes between these studies is more difficult because of the different modalities and inclusion of WBRT in some of the protocols.

Studies in older patients have attempted to develop regimens that are more appropriate for patients unable to undergo radiation therapy. Hoang-Xuan and colleagues reported results of a MTX (1 g/m^2)-based combination chemotherapy in patients with median age 72 years and median Karnofsky performance score (KPS) of 50%. Response rates were 48% and OS was only 14 months, which is only slightly better than historical survival rates with WBRT alone [Hoang-Xuan *et al.* 2003; Nelson *et al.* 1992]. The high-grade toxicities were mainly hematological, hepatic and renal and resulted in dose reductions in 26% of the patients and discontinuation of treatment in 8% of patients. While most of the patients preserved their cognitive function and their performance status or showed some improvement until disease progression, 8% of patients manifested neurologic decline based on the mini-mental state examination (MMSE) test, and 12% developed worsening performance status. The results of this study were still encouraging because it offered a treatment option for vulnerable patients with a lower rate of long-term side effects compared with standard radiation treatment while preserving a similar or slightly better outcome [Hoang-Xuan *et al.* 2003].

A recent European study reported on patients over 65 years of age or patients with comorbidities, who were felt not to be eligible for a concurrent trial of high-dose chemotherapy with autologous stem-cell rescue [Illerhaus *et al.* 2009]. Thirty patients with a median age of 70 years received 3 cycles of MTX (3 g/m^2), procarbazine and lomustine (CCNU). WBRT was reserved for patients who did not respond to chemotherapy. Two patients received WBRT after relapse. Only 9 of 30 patients were able to complete all three cycles of therapy. Ten patients stopped therapy due to toxicities and two had fatal toxicities. The median OS was 15 months, and the 5-year OS estimate was 33%. This result was encouraging for older patients and patients with comorbidities, although this regimen had significant toxicities. The addition of procarbazine and CCNU to MTX appeared to improve survival but at the expense of added hematological toxicities and poor tolerance in this vulnerable population [Illerhaus *et al.* 2009]. Thoughtful patient selection is critical to minimize toxicity for this subgroup of patients.

Other studies of combination chemotherapy without WBRT achieved response and survival rates closer to that achieved by regimens that include WBRT (see Table 1 for details on response rates and survival). Abrey and colleagues reported excellent response rates and OS data on a group of patients who received combination chemotherapy including IT chemotherapy followed by WBRT and postradiation chemotherapy [Abrey *et al.* 2000]. High-dose MTX, IT MTX, procarbazine and vincristine were included in the preradiation induction regimen. Of the 52 patients enrolled, 30 patients received radiation and the other 22 patients did not receive radiation, mainly due to their age. Upon completion of induction chemotherapy, objective response rate (ORR) was 90%. The ORR at completion of all treatment was 94% and the median OS for the 52 patients was 60 months. This study showed older age and worse performance status predicted poor outcomes regardless of the treatment modality. Interestingly, the addition of radiation to the treatment regimen of elderly patients did not improve outcome when compared those who did not receive radiation. The cause of death between the two groups were, however, very different; the group which deferred radiation mostly died of progressive disease but the group who received radiation died of complications of treatment [Abrey *et al.* 2000].

More recently, Gavrilovic and colleagues updated the study by Abrey *et al.* [2000]. This report published a 10-year follow up and confirmed the previous findings of worse survival in older patients, regardless of the use of WBRT. The median OS, however, decreased from 60 months to 51 months in all patients but was not reached in younger patients (age <60 years). By contrast, the median survival in the older patients was 29 months, similar to the subgroup which received only chemotherapy (this group also consisted of mainly older patients) [Gavrilovic *et al.* 2006]. Interestingly, the median progression-free survival (PFS) was very long (129 months), and the authors concluded that the combined

modality regimen was likely responsible for the prolonged survival unlike some other studies where salvage chemotherapy may play a major role in survival [Gavrilovic *et al.* 2006]. A multicenter study with regimen similar to that used in the Abrey *et al*. study also produced a very high ORR (94% response rate to pre-irradiation chemotherapy). This study again showed the impact of age on outcome. The median OS was 50 months for younger patients (age <60 years) compared with 22 months in older patients [DeAngelis *et al.* 2002].

Owing to concerns about treatment-related toxicities in the older patients, single-agent chemotherapy has also been evaluated, and the results appear promising. As discussed in more detail in the following section, a study of 31 patients with median age of 74 reported an excellent ORR (97%) and median survival of 37 months. The regimen was generally well tolerated with less than 10% grade 3 or 4 toxicities [Zhu *et al.* 2009].

There is no consensus on the optimal combination regimen or dose of MTX. There remains active debate regarding the best route of drug delivery and about the role of intraventricular or IA chemotherapy [Angelov *et al.* 2009; Pels *et al.* 2003, 2009; Omuro *et al.* 2007.]. The most significant acute toxicities of combined chemotherapeutic regimens include myelosuppression, hepatitis, renal dysfunction, venous thrombosis, vincristine-induced neuropathy, mucositis, sepsis, Ommaya reservoir infection, allergic reaction to procarbazine and ileus [Illerhaus *et al.* 2009; Pels *et al.* 2003, 2009; Omuro *et al.* 2007; Hoang-Xuan *et al.* 2003; Abrey *et al.* 2000]. These side effects must be weighed against the potential benefits with consideration of the population being treated.

MTX alone

In an attempt to minimize acute and late toxicities in management of PCNSL, many studies have investigated the role of single-agent chemotherapy (MTX unless patient has renal insufficiency) and deferred WBRT (see Table 1).

Guha-Thakurta and colleagues reported the results of induction MTX (8 g/m^2) followed by indefinite maintenance therapy at 3.5 g/m^2 at 3-month intervals [Guha-Thakurta *et al.* 1999]. This study reported response rates and median survival comparable to prior radiation therapy based studies. This protocol achieved an ORR of 100% (65% complete responses [CR], 35% partial responses [PR]). Median PFS was 17 months, and the median OS was 30 months. Most importantly, the regimen was well tolerated with an acceptable rate of myelosuppression and reversible renal insufficiency. This study also documented preservation of cognitive and memory skills in addition to an overall improvement in the KPS (median 90 versus 40 at diagnosis).

Two subsequent multicenter studies repeated similar MTX regimens using 8 g/m^2 but failed to reproduce these favorable results; both studies reported minimal side effects but the response rates were lower (CR 65% in the Guha-Thakurta *et al.* study versus 30% in the Herrlinger *et al.* study and 52% in the Batchelor *et al*. report) [Batchelor *et al.* 2003a; Herrlinger *et al.* 2002].

One multicenter trial closed with only 37 of 105 patients enrolled after an interim analysis demonstrated a low CR rate of 30% [Herrlinger *et al.* 2002]. The other study delivered MTX in induction, maintenance and consolidation phases over the course of 12 months. Of 23 evaluable patients 52% achieved CR [Batchelor *et al.* 2003a] (Table 1).

These results appear to be superior to historical series treated with WBRT alone [Nelson *et al.* 1992] but appear to be inferior to some studies of combination chemotherapy or chemotherapy combined with WBRT [Pels *et al.* 2003; Abrey *et al.* 2000; Sandor *et al.* 1998; DeAngelis *et al.* 1992]. Despite a better a side-effect profile (see below) it may be necessary to add additional agents to high-dose MTX in order to improve response and survival rates [Batchelor *et al.* 2003a].

Several differences between these three trials highlight questions related to the use of chemotherapy for patients with PCNSL. Despite a strikingly low baseline KPS (median 40) in the Guha-Thakurta *et al.* study, outcomes compared favorably to the trials of Herrlinger *et al.* and Batchelor *et al.* demonstrating a significant benefit of single-agent MTX for severely ill patients. A difference between the studies is the duration of treatment. In the Guha-Thakurta *et al.* and Batchelor *et al.* studies patients received MTX until CR or no further improvement was demonstrated while those in the Herrlinger *et al.* trial who did not achieve a CR had MTX stopped

after six cycles. This difference appears to be important, since patients in the Guha-Thakurta *et al.* trial required a median of six cycles to achieve a CR. Consistent with this observation, Herrlinger *et al.* reported that relapses occurred only in patients whose treatment was stopped prematurely, suggesting that maintenance therapy may have an important role [Batchelor *et al.* 2003a; Herrlinger *et al.* 2002; Guha-Thakurta *et al.* 1999].

Among these studies, Batchelor *et al.* reported details on acute and long-term toxicities of the treatment; which were described as modest in this report [Batchelor *et al.* 2003b]. Almost half of the patients had no grade 3 or 4 toxicity. MMSE testing was performed but not all patients returned for their follow-up testing. Of the 19 patients that had at least one follow-up MMSE score, only one declined from baseline (from 29 to 27). The cognitive evaluation in this study was very basic (MMSE) and was likely biased against patients with worse neurocognitive function, as those patients may not have been able to complete the follow-up evaluations. However, when compared to results from prior reports, which included radiation therapy, these findings were encouraging.

Neurotoxicity was more common and severe in the report by Herrlinger and colleagues, although evaluated in a different way [Herrlinger *et al.* 2005]. Of the 27 patients who survived at least 12 months, 20 were evaluated by magnetic resonance imaging (MRI) for evidence of neurotoxicity. Therapy was associated with significant increase in leukoencephalopathy load in seven of those patients, two of which had received chemotherapy alone without salvage WBRT. This study estimated 34% of patients will develop significant leukoencephalopathy 4 years after therapy. Although the rate of chemotherapy alone associated leukoencephalopathy was estimated as high as 10%, it still compared favorably to the 58% in the group that received WBRT [Herrlinger *et al.* 2005]. MMSE scores increased in all patients, however, neuropsychologic test batteries revealed some cognitive impairment, pointing out to the insensitivity of MMSE to assess cognitive aspects thoroughly [Herrlinger *et al.* 2005].

A recent study from South Korea readdressed the issue of high-dose MTX monotherapy and deferred WBRT [Yang *et al.* 2009]. This single-institution report describes 16 patients in a younger cohort (median age 52) with performance scores (median KPS 90) higher than those in prior studies (see Table 1). Patients received MTX 8 g/m^2 for three cycles as induction followed by maintenance at a dose of 3.5 g/m^2. Despite the relatively favorable patient selection, the response rates were not superior to prior studies with eight CRs (50%) and one PR (7%) (ORR 56%). In contrast, the response durations were long and the survival rates high. The median OS of all patients was 50 months, but the median survival of the patients with CR had not been reached at the time of publication [Yang *et al.* 2009]. Another recent retrospective study of elderly (median age 74 years) used MTX monotherapy. Despite the need for dose reduction in many patients (71% of the population), the response rate was very high; ORR was 97% (60% CR and 37% PR) with CRs achieved after a median of only four cycles. Most of the toxicities were reversible and overall, it was felt that high-dose MTX was tolerated well in this population and associated with good outcome [Zhu *et al.* 2009].

Although many studies have tested either single agents or combination chemotherapeutic regimens, few studies directly compared MTX-only regimens with MTX-based combinations. A recent randomized multicenter phase II trial suggested benefit, including higher response rates, event free and OS with the addition of high-dose cytarabine to MTX. Chemotherapy in this study was followed by WBRT. The combination therapy included MTX 3.5 g/m^2 on day 1 followed by cytarabine 2 g/m^2 twice daily on days 2 and 3. The ORRs were 69% and 40% with the cytarabine combination and MTX alone, respectively. The 3-year failure-free survival was 38% and 21% in the combination and single-agent groups, respectively. In addition, the respective OS rates were 46% and 32% [Ferreri *et al.* 2009]. As expected, this study reported more hematologic and infective toxicities in the combination chemotherapy group and MTX dose reduction occurred more often in the group receiving combined chemotherapy than in the MTX alone group [Ferreri *et al.* 2009].

Another question in the treatment of PCNSL is the role for consolidation therapy after CR has been achieved. A retrospective study of 122 patients who were in CR after initial MTX-based chemotherapy failed to demonstrate a

survival benefit in patients who received consolidation therapy with high-dose cytarabine, WBRT or both [Ekenel *et al.* 2008]. Thus, many questions in the use of single agents and combinations remain open to investigation.

High-dose chemotherapy followed by autologous stem-cell rescue

High-dose chemotherapy followed by autologous stem-cell rescue (HDC/ASCR) has been an accepted treatment modality for aggressive systemic lymphoma, used mostly at the time of relapse or refractory disease [Wrench and Gribben, 2008; Smith *et al.* 2002a]. This approach has been used as a second-line treatment for PCNSL, and several studies have investigated the role of this treatment modality to consolidate remission after induction therapy. When used as first-line therapy for newly diagnosed patients with primary CNS lymphoma, results have been variable [Ferreri *et al*. 2008].

Abrey and colleagues reported outcomes of HDC/ASCR in patients with newly diagnosed PCNSL who had responded to induction chemotherapy [Abrey *et al.* 2003]. The induction therapy in this study was systemic MTX 3.5 g/m^2 and cytarabine and the regimen used prior to infusion of stem cells was BEAM (BCNU, etoposide, cytarabine and melphalan). Only 14 of the 28 patients in the study underwent autologous stem-cell transplantation (ASCT), 13 of whom relapsed within 7 months of transplant. Eight of these patients relapsed at a median of 2.3 months after transplant [Abrey *et al.* 2003]. Thus, the response rate to induction chemotherapy was poor (ORR 57%), and among those who underwent transplant, the rate of early relapse was very high.

In contrast to the Abrey *et al*. study, subsequent trials intensified their induction chemotherapy by adding other agents and/or increasing the dose of MTX up to 8 g/m^2. In addition, the pretransplant conditioning regimen was changed to a thiotepa-based chemotherapy in one study and post-transplant radiation therapy was added in all studies [Colombat *et al.* 2006; Illerhaus *et al.* 2006; Brevet *et al.* 2005]. Response rate in these studies improved to the range of 70–100%, but because these studies also added WBRT, comparison of other outcomes with chemotherapy-only studies is difficult. These studies concluded that HDC ASCT was feasible in younger patients with newly diagnosed PCNSL and carries an acceptable toxicity profile.

In order to limit neurotoxicity, more recent studies have investigated ASCT without radiation therapy. Montemurro and colleagues performed a study with tandem transplants using MTX and ASCR and allowed patients with no response to the conditioning regimen or less than a complete remission after the transplants to receive WBRT. The response rate was 83% but the median OS of 20 months was inferior to that of similar studies. This study also reported disappointingly high rates of severe neurotoxicity (3 of 9 patients who received WBRT) and was therefore closed prematurely [Montemurro *et al.* 2007].

Illerhaus and colleagues conducted a pilot study similar to their phase II report in 2006, where they dose-intensified chemotherapy (increased the number of chemotherapy cycles and the thiotepa dose within the conditioning regimen) and also restricted WBRT to patients who did not respond completely to chemotherapy [Illerhaus *et al.* 2008]. Thirteen patients enrolled in this study with a response rate of 62% to chemotherapy. Except for two patients with symptomatic disease progression after chemotherapy, all 11 other patients underwent HDC/ASCT, which resulted in seven CRs and four PRs. Overall, 5 of 13 patients received WBRT at some point through treatment due to disease progression or PR post-transplant [Illerhaus *et al.* 2008]. When compared with the data by Montemurro *et al.*, this study had better results and when compared with the prior study by Illerhaus et al., which included WBRT in the protocol, the 3-year OS was 77% in the study with deferred WBRT versus 5-year OS of 69% in ASCT followed by WBRT. It is important to note that the setting of the studies were different; the former study was a phase II multicenter study with 30 patients [Illerhaus *et al.* 2006] whereas the latter was a single-center pilot study with results reported based on 13 patients [Illerhaus *et al.* 2008]. This pilot study, however, did not report any neurotoxicity and the authors concluded that reserving WBRT as salvage therapy for non-responders or partial responders would improve toxicity profile and not compromise survival outcome [Illerhaus *et al.* 2006, 2008].

Although some of these results sound encouraging, it is important to remember most of the patients entered in trials of ASCT were younger and had better performance status than many other studies with chemotherapy-alone regimens, which makes interpretation of results and

comparison between trials more difficult. The best induction chemotherapy and preparative conditioning regimen has yet to be defined. It is also important to consider transplant-related morbidity (and mortality) when considering HDC/ASCT as a treatment choice. Among reports of HDC/ASCT, it appears that limiting radiation therapy to those who experience progressive disease has been associated with promising outcome in some studies and should be investigated further.

Challenge of the blood–brain barrier

Like other brain tumors, one of the major challenges in treatment with chemotherapeutic agents remains the delivery of therapeutic concentrations of drugs to the CNS. A study of blood–brain barrier (BBB) permeability in a rat brain tumor model demonstrated a large heterogeneity of microvascular leakage; the vasculature within and around the brain tumors has a wide range of permeabilities, from normal capillaries with no (BBB) leakage to a tumor vasculature that allows free entry of large molecules [Ewing *et al.* 2006].

Binding of the chemotherapy agent to plasma protein (e.g. chlorambucil, etoposide, melphalan, vincristine and paclitaxel), high molecular weight drugs (e.g. vincristine, vinblastine, paclitaxel and etoposide) and drugs subjected to active efflux transport (e.g. paclitaxel, vincristine, vinblastine, doxorubicin and etoposide) are among the major factors that contribute to poor chemotherapeutic uptake across the BBB [Muldoon *et al.* 2007].

Although MTX crosses the BBB, far less is measurable in the brain tissue than in the serum. High-dose MTX ($>1\,g/m^2$) has been shown to be an independent factor correlating with survival [Blay *et al.* 1998]. Thus, MTX is administered in high doses, up to $8\,g/m^2$, in order to achieve therapeutic drug concentrations in the tumor and surrounding brain. Intravenous (IV) doses less than $1\,g/m^2$, similar to what has been used in the treatment of other malignancies outside the brain, reach CNS concentrations generally felt not to be cytotoxic [Morris and Abrey, 2009; Muldoon *et al.* 2007]. Thus, doses greater than $1\,g/m^2$ are considered necessary for adequate delivery to the CNS [Blay *et al.* 1998].

To overcome the obstacle of the BBB and to improve drug delivery into brain tumor tissue, multiple studies have attempted to enhance drug delivery by methods such as altered administration schedules (IV bolus versus IV infusion), intra-arterial (IA), and IA after osmotic BBB disruption (BBBD). In a rat glioma model, MTX reached a fivefold higher area under curve (AUC) when administered by bolus compared with 4-hour infusion [Dukic *et al.* 2000].

Reversible osmotic BBBD followed by IA chemotherapy (IA/BBBD) delivers substantially higher concentrations to the CNS when compared with IV administration. BBBD enhances the CNS penetration of systemically administered MTX by 50–100-fold in animal models [Neuwelt *et al.* 1980]. In human studies using contrast-enhanced neuroimaging, MTX delivery to the tumor and immediate surrounding brain increased after BBBD compared with IA delivery without BBBD. MTX persisted longer within brain tissue after BBBD [Neuwelt *et al.* 1981]. This delivery technique has been used across centers in the United States, Canada and Israel with acceptable morbidity and mortality [Angelov *et al.* 2009; McAllister *et al.* 2000; Dahlborg *et al.* 1996; Neuwelt *et al.* 1991]. A comprehensive review of IA/BBBD for PCNSL is beyond the scope of this manuscript, but this method of chemotherapy delivery has been reviewed elsewhere [Angelov *et al.* 2009; Jahnke *et al.* 2006a; Doolittle *et al.* 2000; McAllister *et al.* 2000].

A recent report summarized the multi-institutional experience of 149 newly diagnosed (with no prior WBRT) patients with PCNSL treated with IA/BBBD MTX from 1982 to 2005 [Angelov *et al.* 2009]. These patients received a median of 16 IA/BBBD treatments in 8-monthly courses. CRs occurred in 57% of patients with a 5-year PFS of 31%. The median OS was 3.1 years but 25% of patients lived at least 8 years. Low-risk patients (age <60 and KPS ≥ 70) had a median OS of approximately 14 years with a plateau after 8 years suggesting that some patients may have achieved cure. The most frequent complication was periprocedural focal seizures, not resulting in permanent neurological dysfunction or uncontrolled seizures. Strokes, however, occurred in 11 (7.4%) patients, 4 (2.7%) of whom were left with permanent neurologic deficits. The most important drawback of IA/BBBD has been the need for general anesthesia and the potential for neurovascular complications of the procedure. On the other hand, with the caveats of a retrospective analysis,

outcomes with IA/BBBD appear to be similar or better than those accomplished with combination chemotherapy and/or brain irradiation, but without the neurocognitive sequelae associated with brain irradiation.

Intrathecal drug delivery

Leptomeningeal involvement in PCNSL occurs in 37% of patients [DeAngelis *et al.* 1992], but pathological involvement in autopsies is seen in 100% of patients, probably due to the periventricular location of most PCNSL lesions [Schaumburg *et al.* 1972]. IT chemotherapy attempts to improve cerebrospinal fluid (CSF) drug delivery; thus, many studies of PCNSL included IT chemotherapy. This strategy allows for high drug concentration in the meninges and CSF with low total dose and minimal systemic side effects [DeAngelis *et al.* 1992; Balis and Poplack, 1989].

When given intravenously, the MTX concentration ratio between plasma and CSF is approximately 100:1 [Ettinger *et al.* 1982]. Although higher IV doses of MTX increase CSF concentrations, an increase in IV dose from 3.0 to 8.0 mg/m^2 yields only a modest increase in CSF concentration that is not statistically different [Borsi and Moe, 1987; Ettinger *et al.* 1982]. The serum half-life of MTX after a 24-hour infusion is 2.2–4.6 hours depending on the systemic dose [Borsi and Moe, 1987], while intra-Ommaya administration produces a CSF half-life of up to 48 hours [Shapiro *et al.* 1975].

One of the early studies that included IT chemotherapy evaluated 46 patients for evidence of leptomeningeal lymphoma, 17 (37%) of whom had either meningeal infiltration on biopsy or positive CSF cytology [DeAngelis *et al.* 1992]. In the 31 patients who received preradiation chemotherapy, a relatively low dose of IV MTX (1 g/m^2) was used but all patients received six doses of intra-Ommaya MTX regardless of positive biopsy or cytology. Patients in this subgroup, when compared *post hoc* with those who received radiation therapy alone, had improved PFS and OS with fewer brain and meningeal relapses with no spinal cord relapses [DeAngelis *et al.* 1992]. It is difficult to conclude the role of IT chemotherapy from this trial. Two more recent trials, however, add some context to these earlier data [Batchelor *et al.* 2003b; Herrlinger *et al.* 2002]. Of note, the DeAngelis *et al.* trial was a single-center study while the two latter studies were multicenter trials. With these caveats, it appears that lower dose IV MTX with IT MTX in the DeAngelis *et al.* trial produced pre-irradiation response rates (64%) roughly in the range of those accomplished in the more recent trials of high-dose MTX alone (35% and 74% in Herrlinger *et al.* and Batchelor et al., respectively). When compared with the study by Batchelor *et al.*, the addition of IT chemotherapy does not seem to have added to response rates (64% after IV and IT MTX versus 74% after IV MTX alone) [Batchelor *et al.* 2003b]. These data suggest that as long as high-dose IV MTX is used, IT chemotherapy can be omitted, but if high levels cannot be administered due to patients' comorbidities, etc., IT chemotherapy may need to be included in the regimen.

Although no prospective studies have compared regimens with and without IT therapy, a relatively large retrospective multicenter study of 378 patients reported no additional survival benefit from IT chemotherapy in patients who have received high-dose MTX-based regimen [Ferreri *et al.* 2002b]. Two-year OS was 51% for the group of patients who received IT chemotherapy ($n = 81$) and 50% for the group which did not receive IT chemotherapy ($n = 79$, $p = 0.4$). Interestingly, further analysis of results did not show any correlation between dose of IV MTX (1–2.9 g/m^2/course versus $\geq$3 g/m^2/course) or positive CSF cytology and benefit from IT chemotherapy [Ferreri *et al.* 2002b].

Another retrospective study that attempted to answer this question was a single-institution case-controlled study comparing these two groups of patients both of whom had received high-dose MTX (3.5 g/m^2 or higher) [Khan *et al.* 2002]. IT MTX did not improve disease control or survival and the CSF relapse rate was similar in the two groups. In the group with no IT therapy, patients with leptomeningeal tumor at diagnosis had no leptomeningeal relapse, demonstrating effective treatment with systemic chemotherapy alone. All patients received a relatively high dose of MTX over short period of time (at least 3.5 g/m^2 delivered over 2 hours) [Khan *et al.* 2002]. CSF penetration of MTX is affected by the rate of drug delivery and slower infusions of MTX (e.g. 8 g/m^2 over 24 hours) may not achieve cytotoxic CSF levels [Morris and Abrey, 2009; Khan *et al.* 2002; Vassal *et al.* 1990]. Rapid infusion of MTX significantly increased concentrations of MTX in the CSF in a study comparing

3-hour infusion versus 6-hour infusion schedules ($p < 0.001$) and resulted in significant parenchymal tumor volume reduction [Hiraga *et al.* 1999]. These results suggest that the rapid infusion of systemic MTX used in the Khan *et al*. study achieved cytotoxic CSF concentrations thus explaining the lack of additional benefit from IT chemotherapy. Thus, treatment of CSF compartment may be achieved with HD-MTX alone provided it is given over a short infusion (e.g. 2–4 hours).

Further support for this hypothesis came from a study of combined systemic and intraventricular chemotherapy which attempted to reproduce results from a prior study [Pels *et al.* 2003, 2009]. The more recent study omitted intraventricular therapy because 19% of the patients in the earlier trial had suffered from Ommaya reservoir infections [Pels *et al.* 2003]. MTX was delivered at 5 g/m^2 over 24 hours in both trials. The results of the newer study without intraventricular therapy were clearly inferior to those of the study with intraventricular treatment. In fact, the study closed prematurely after an interim analysis revealed an unacceptably high number of relapses in both the brain and the leptomeninges. Although ORRs were comparable (interim analysis 76% without intraventricular therapy and 86% with intraventricular therapy in the age-matched group), the time to treatment failure (TTF) and the response duration appeared to be inferior in the study without intraventricular therapy (median TTF and maximum response duration [MRD] 8 and 10 months, respectively, compared with TTF and MRD not reached after median follow up of 26 months, $p < 0.01$) [Pels *et al.* 2009].

The results of this study favor IT/intraventricular therapy as part of the therapeutic regimen. Although more patients in later trial (without intraventricular therapy) appeared to have radiographic evidence of leptomeningeal involvement at relapse, this finding was not confirmed by CSF analysis [Pels *et al.* 2009]. When comparing the results of the 2003 study by Pels *et al*. with some studies using chemotherapy regimens without IT therapy, the results appear to be better in the study by Pels *et al*. [Illerhaus *et al.* 2009; Yang *et al.* 2009; Omuro *et al.* 2007; Batchelor *et al.* 2003a; Herrlinger *et al.* 2002]. However, some of those studies used a lower dose of MTX (3.0 g/m^2) and were designed for an older population with median age 68 and 70 years compared with the patient population in the 2003 study by Pels *et al*. (MTX 5 g/m^2 and median age 53 years), which could have adversely affected the outcomes in these studies [Illerhaus *et al.* 2009; Omuro *et al.* 2007]. It is also important to recall that the study by Omuro *et al*. was observational in contrast to the others which were prospective. The NABTT 96-07 study used a higher dose of MTX alone (8 g/m^2) and achieved an ORR similar to the study by Pels (74% without IT compared with ORR 71% with IT therapy) but PFS was inferior when IT therapy was omitted (PFS 13 versus 21 months). The median OS, however, was comparable in the two studies (OS 50 versus 55 months) [Gerstner *et al.* 2008; Pels *et al.* 2003].

Overall, it is reasonable to consider IT MTX for those patients with a positive CSF cytology, or in regimens where lower doses of MTX are delivered over longer periods of time. It is probably reasonable to withhold IT chemotherapy in those patients who have no detectable subarachnoid disease and who can receive higher dose of MTX over shorter infusion periods.

Chemotherapy and the blood ocular barrier

Intraocular lymphoma (IOL) is a very rare disease and refers to infiltration of the vitreous humor, retina and optic nerve by malignant lymphocytes. It can be seen independently or in association with PCNSL (known as primary IOL [PIOL]) or in the setting of systemic lymphoma. PIOL can occur as the presenting picture in CNS lymphoma or as a site of relapse. This disease should be distinguished from orbital involvement in the context of systemic lymphoma, which mostly involves the choroid [Whitcup *et al.* 1993]. The diagnosis of IOL can be very difficult and is usually made by vitrectomy/choroidal/retinal biopsy or clinical ophthalmic examination [Grimm *et al.* 2007; Batchelor *et al.* 2003b].

Patients with PIOL often develop CNS involvement during course of their disease. The exact rate of CNS involvement and overlap between the two sites of disease is unknown. In up to half of the cases of ocular lymphoma, the eyes were the initial site of disease, and as many as 80% of patients will eventually develop brain disease [Grimm *et al.* 2007; Peterson *et al.* 1993; Char *et al.* 1988]. It appears that the natural history of patients with PCNSL with ocular dissemination is similar to that in patients with isolated parenchymal brain lymphoma, and survival

rates are not worse when there is ocular involvement at diagnosis [Grimm *et al.* 2007; Abrey *et al.* 2006; Ferreri *et al.* 2003].

Like the BBB, the blood–retinal barrier and the blood–aqueous barrier hinder diffusion of drugs from the blood into ocular tissues [Jahnke *et al.* 2007]. The retinal vessels and the retinal pigment epithelium appear to limit drug delivery into the intraocular space. Like PCNSL, it is believed that the blood–retinal barrier may limit the effect of chemotherapeutic agents at concentrations nontoxic to other organs. This has led to a number of studies investigating different treatment modalities including focal therapy.

Because the eye can serve as a reservoir of untreated disease that increases the risk of recurrence, the eradication of ocular lymphoma is critical in treatment this disease whether or not it presents in conjunction with parenchymal brain lymphoma. Treatment options for ocular lymphoma include high-dose systemic chemotherapy, IT chemotherapy, myeloablative chemotherapy with ASCT, intravitreous chemotherapy and radiation therapy [Itty *et al.* 2009; Soussain and Hoang-Xuan, 2009; Frenkel *et al.* 2008; Grimm *et al.* 2007; Gunduz *et al.* 2006; Isobe *et al.* 2006; Hormigo *et al.* 2004; Abrey *et al.* 2003; Batchelor *et al.* 2003b; Ferreri *et al.* 2002a; Valluri *et al.* 1995].

Focal radiotherapy is commonly used but is associated with high cerebral relapse rates and radiation-related side effects including optic neuropathy, retinopathy, glaucoma, dry eye syndrome, corneal defects and cataracts leading to visual loss in long-term survivors [Jahnke *et al.* 2007; Ferreri *et al.* 2002a; Buggage *et al.* 2001; Char *et al.* 1988]. In addition, for patients who later need whole brain radiation, the juxtaposition of the whole brain field with the previously irradiated ocular field can result in local overdosing if the fields overlap or underdosing if a gap exists between the fields.

Most of the reports on treatment of IOL with systemic chemotherapy have included parenchymal disease as well as IOL in their patient population. Although most of the regimens are MTX-based, others have included agents known to cross the blood–ocular barrier such as cytarabine, ifosfamide or trofosfamide [Jahnke *et al.* 2005a, 2005b, 2007; Strauchen *et al.* 1989; Baumann *et al.* 1986] or agents established in the treatment of systemic lymphoma, including thiotepa, vincristine, cyclophosphamide and rituximab [Hormigo *et al.* 2004; Ferreri *et al.* 2002a; Sandor *et al.* 1998].

Sustained cytotoxic concentrations of MTX and of cytarabine in the ocular compartment are achievable after IV administration of the drug [Batchelor *et al.* 2003b; de Smet *et al.* 1996; Baumann *et al.* 1986]. High-dose IV MTX ($8\,g/m^2$) has been studied in patients with ocular lymphoma. In one study, 7 of 7 patients with concurrent PCNSL and IOL had CRs of their brain disease but 3 of 7 relapsed in the eyes requiring orbital radiation, to which they responded. The ocular response was sustained in four of seven patients [Batchelor *et al.* 2003b].

Cytarabine has produced mixed results. High-dose IV cytarabine alone produced one CR in six patients but good ORRs (5/6) [Strauchen *et al.* 1989] leading to additional trials of combination regimens. Combination IT cytarabine/MTX-based regimens yielded response rates as high as 100% with no ocular relapses [Mason and Fischer, 2003; Sandor *et al.* 1998]. IV or IT cytarabine in combination with IV MTX and/or radiation produced varied response rates (68–100%) and relapse rates (0–60%) [Hormigo *et al.* 2004; Ferreri *et al.* 2002a; Valluri *et al.* 1995].

Systemic chemotherapy alone or in combination with ocular +/− WBRT has also been studied with response rates as high as 100% in mixed populations of PCNSL and ocular lymphoma. Some studies have shown better survival and lower ocular failure rates in patients treated with chemotherapy plus ocular irradiation when compared with chemotherapy alone [Ferreri *et al.* 2002a], but ocular radiation can lead to serious side effects such as dry eye syndrome, cataracts, glaucoma, optic neuropathy and retinopathy, leading in some cases to permanent visual loss [Jahnke *et al.* 2007]. Unfortunately, most of the data on treatment of ocular lymphoma comes from patients treated on larger PCNSL trials rather than on studies specifically for patients with ocular lymphoma. Therefore, interpretation and application of results to this subpopulation is difficult.

HDC/ASCR has been studied in few trials which have included small numbers of patients with ocular disease. These studies have addressed newly diagnosed patients [Abrey *et al.* 2003]

and patients with refractory or recurrent disease [Soussain *et al.* 2001, 2008]. Ocular response rates are generally good, but relapse rates including ocular relapses remain high. This approach has had some promising results but because of comorbidities and other risks associated with HDC/ASCT, stem-cell transplant remains experimental.

Owing to the toxicities of radiation and systemic chemotherapy, and questions regarding therapeutic concentrations of certain systemic chemotherapeutic agents in the eye, some studies have addressed the benefit of intraocular therapy for the treatment of ocular lymphoma. de Smet *et al*. reported cytological clearance of the tumor achieved by intravitreal injections of MTX and thiotepa in addition to systemic and IT chemotherapy a patient who had recurrent intraocular lymphoma after radiotherapy and IT chemotherapy [de Smet *et al.* 1999]. Intravitreal MTX levels were measured and tumoricidal concentrations were documented 5 days after injection, which is longer than that achieved following systemic drug delivery [de Smet *et al.* 1999].

There is no consensus on best intraocular regimen and duration of treatment. Two recent studies have used intravitreal injections of MTX in induction, consolidation and maintenance phases (biweekly injections followed by weekly followed by monthly injections over a year) [Frenkel *et al.* 2008; Smith *et al.* 2002b].

In a small study of four patients with ocular lymphoma, intraocular MTX in addition to systemic therapy with IA chemotherapy and BBBD resulted in complete remission of all patients with no relapse during the follow-up period (up to 19 months) [Fishburne *et al.* 1997]. Another study of intraocular MTX with systemic and IA chemotherapy reported complete remission in all 16 patients. Three patients experienced ocular relapse but achieved second remissions with further intraocular MTX [Smith *et al.* 2002b].

Frankel *et al*. published a 10-year experience of 26 ocular lymphoma patients treated with intravitreal MTX [Frenkel *et al.* 2008]. They reported no intraocular recurrences and no serious adverse effects. The population in this study also included patients with a history of parenchymal PCNSL and patients in remission from prior systemic lymphoma. Fourteen patients (53%) died of their CNS or systemic lymphoma within a median of 17 months from the time of their ocular diagnosis. Twelve patients (46%) survived for median of 2 years from the time of ocular diagnosis. Eight patients (30%) have survived for over 3 years after the last injection with a median of 63 months. No patients had an ocular recurrence. Interestingly, 24 of 26 patients were clear of ocular lymphoma at the end of the second month of the treatment. The procedure can be considered feasible; 17 (39%) patients' eyes completed the treatment protocol, which consisted of total of 25 injections, and 23 patients' eyes (52%) did not complete the entire treatment protocol but all were cleared clinically of malignant cells.

Complications from intraocular chemotherapy with MTX appear to be mostly transient, and unlike focal radiation therapy to eye, less likely lead to permanent visual loss. Complications include keratopathy, maculopathy, cataract (acceleration of existing cataract), neovascular glaucoma, vitreous hemorrhage, optic atrophy and sterile endophthalmitis [Frenkel *et al.* 2008; Smith *et al.* 2002b]. Intraocular rituximab has also recently been tried successfully without significant short-term toxicity and multiple injections appear to be well tolerated [Itty *et al.* 2009; Kitzmann *et al.* 2007]. However, further studies using combination chemotherapy agents such as MTX and rituximab are needed.

The relative impact of different treatment modalities on outcome of patients with PCNSL and ocular disease has not been studied extensively. One retrospective multicenter study of 22 patients reported improvements in PFS (12 versus 5.5 months) and cerebral relapse rates following systemic chemotherapy compared with focal therapy. Most of the patients who received focal therapy in this study received radiation therapy, and only three patients had received intraocular chemotherapy [Jahnke *et al.* 2006b]. More recently, a large retrospective study in seven countries reported on two groups of patients: those with brain lymphoma and ocular dissemination [Grimm *et al.* 2008], and those with isolated ocular lymphoma (PIOL) [Grimm *et al.* 2007].

In the later report by Grimm et al., some of the patients with lymphoma involving the eyes and brain parenchyma at diagnosis had received dedicated ocular therapy in addition to systemic therapy for their brain disease. The dedicated

ocular therapy included ocular radiotherapy, intraocular MTX or both. Although the PFS appeared slightly better with the addition of dedicated ocular therapy it did not impact OS. Risk of progression and pattern of failure was not affected by the initial therapeutic approach suggesting that the addition of dedicated ocular therapy did not add to the efficacy of systemic therapy alone [Grimm *et al.* 2008].

In the report by Grimm *et al.* on patients with PIOL, some patients received focal therapy alone (intraocular MTX, ocular radiotherapy) and some received extensive therapy (systemic chemotherapy, WBRT). Of those patients who relapsed, 47% relapsed in brain but focal therapy alone did not increase risk of brain relapse. Treatment did not affect PFS or OS either, suggesting that focal therapy alone did not compromise outcomes in PIOL [Grimm *et al.* 2007].

Although large studies dedicated to PIOL are lacking, review of the literature suggests that the best initial therapy in patients with PIOL is focal intraocular chemotherapy. Intraocular chemotherapy appears to be feasible, safe, with few long-term side effects, and offers survival rates and relapse patterns similar to that of more extensive therapy [Grimm *et al.* 2007]. Among patients with concomitant parenchymal brain and ocular involvement, the addition of intraocular chemotherapy to systemic therapy can improve PFS without significant additional side effects, but the addition of this therapy will not improve survival rates or impact local relapse.

Neurocognitive toxicity of therapy

Current treatment for PCNSL often involves high-dose MTX-based chemotherapy with or without WBRT. Although this treatment prolongs survival, neurotoxicity, especially in the delayed form, poses a substantial and feared complication [Correa *et al.* 2004, 2009; Harder *et al.* 2004; DeAngelis *et al.* 1992]. MTX and WBRT each may cause CNS damage, but there appears to be synergistic toxicity when these two modalities are combined [Correa *et al.* 2004; Crossen *et al.* 1994]. Cognitive disturbances are critically important when choosing a treatment modality for more vulnerable subgroups of patients. Some older studies have used MMSE to evaluate for cognitive disturbances but this test was not developed for brain tumor patients or for assessment of treatment-related morbidity [Correa *et al.* 2004; Weitzner and Meyers, 1997]. MMSE has a low sensitivity for detecting cognitive impairment in brain tumor patients, and it is very important that comprehensive neurocognitive evaluations are incorporated into outcome studies of CNS lymphoma patients.

Cognitive outcome: chemotherapy with WBRT

One of the early studies on late-onset treatment-related neurotoxicity reported that approximately one-third of patients treated with combined modality therapy developed neurotoxicity [Abrey *et al.* 1998]. The main symptoms were dementia, gait imbalance, urinary incontinence and worsening performance status, which developed after a median time of 13 months from diagnosis. Importantly, there was a significant association between older age group patients (age >60 years) and development of these side effects [Abrey *et al.* 1998].

Correa evaluated PCNSL survivors and compared results between patients who had received WBRT +/− chemotherapy with patients who received chemotherapy alone [Correa *et al.* 2004]. The group that had received WBRT was younger than the chemotherapy-alone group and had longer follow up. All patients in the chemotherapy-alone group were 60 years of age or older. Unfortunately, the details of their therapy were not outlined in the report. The baseline cognitive assessment was performed post-treatment and a subgroup of these patients was followed again after 8 months. Patients who received chemotherapy alone had significantly better scores in some cognitive domains than did patients treated with WBRT +/− chemotherapy. Older patients who received chemotherapy alone were cognitively significantly less impaired than older patients who received WBRT as part of their treatment. Interestingly, patients treated with chemotherapy only (all 60 years and older) were also significantly less impaired in memory than patients younger than 60 years of age who received WBRT. In patients treated with WBRT +/− chemotherapy, there were no significant differences in memory performance between younger patients and older patients [Correa *et al.* 2004]. This study documented the occurrence of WBRT-related neurotoxicity regardless of age.

A multicenter European study evaluated patients who received MBVP chemotherapy (methylprednisolone, MTX, teniposide, BCNU) in addition to IT MTX, IT cytarabine and hydrocortisone followed by WBRT [Harder *et al.* 2004].

Extensive neuropsychological and quality-of-life assessments were performed. This study had a young group of patients (median age 44 years). All had a complete tumor response without evidence of tumor activity and were at least 6 months post-treatment. The results were compared with matched control subjects with systemic hematological malignancies treated with systemic chemotherapy or non-CNS radiotherapy. Cognitive impairment was significantly higher in the PCNSL group despite a complete tumor response, suggesting that cognitive disturbances resulted from treatment rather than tumor. The authors argued that combined modality treatment for PCNSL is associated with cognitive impairment even in patients younger than 60 years of age [Harder *et al.* 2004].

A large study of combined modality therapy followed by WBRT in elderly patients demonstrated no acute high-dose MTX-related neurotoxicity was observed. Nineteen percent of patients had MRI evidence of leukoencephalopathy, and 7% demonstrated clinical evidence of late neurotoxicity. The results, however, were not segregated according to whether the patients received WBRT or not [Jahnke *et al*, 2005a].

A recently study reported prospective neuropsychologic evaluation in patients with PCNSL who received induction chemotherapy followed by reduced dose WBRT and consolidation chemotherapy [Correa *et al.* 2009]. These patients received rituximab, MTX, procarbazine and vincristine (R-MPV) as induction therapy. All patients had a CR after R-MPV and received 23.4 Gy of WBRT. After completion of WBRT, all but one patient received two cycles of high-dose cytarabine (ARA-C) consolidation chemotherapy. After induction therapy scores improved and during the follow-up period, cognitive performance and self-reported quality of life remained relatively stable suggesting that treatment with R-MVP and reduced-dose WBRT was not associated with significant cognitive decline, at least within the follow-up period of 2 years. However, there was a trend towards decline in verbal memory during the first year of follow up. This decline did not continue through the second year. Overall, there was no significant cognitive decline up to 24 months postchemotherapy. Although there were no significant correlations between treatment related white matter changes and cognitive test performance, there was a mild decline in some aspects of cognitive function (memory and executive function) in patients with more severe white matter changes (Fazekas grade 2–3 white matter changes) [Correa *et al.* 2009; Fazekas *et al.* 1987]. There was also a mild increase in treatment-related white-matter disease following treatment, seen mainly in older patients (age >60 years).These findings are consistent with prior evidence of delayed treatment-related neurotoxicity in older patients [Correa *et al.* 2004; Harder *et al.* 2004].

Cognitive outcome: chemotherapy without WBRT

One of the early reports on cognitive outcome of chemotherapy for PCNSL evaluated patients who received MTX-based chemotherapy. Seven of the 14 patients had formal neurocognitive assessments, two of whom, the oldest in the group, experienced severe neurologic deterioration. One of these patients had had a stroke and had white-matter changes consistent with multiple infarcts prior to therapy. Similar to studies of radiation-induced neurotoxicity, age appeared to be the most significant predictor of neurocognitive outcome in this report [Sandor *et al.* 1998].

Later, a group in Germany reported stable cognitive function in their patients and have not identified particular worsening in cognitive performance among elderly patients [Fliessbach *et al.* 2003; Pels *et al.* 2003]. Pels and colleagues reported serious neurocognitive decline only in two patients, one that was attributed to tumor relapse and the second to residual tumor. However, they performed detailed neuropsychological evaluation in 22 of 65 patients in a trial of systemic and intraventricular chemotherapy and reported no cognitive decline in these patients. Some patients developed therapy induced white-matter changes on MRI, but these did not correlate with their neuropsychological scores. Interestingly, patients older than 60 years had lower scores at diagnosis, but their cognitive performance did not decline more than their younger counterparts [Pels *et al.* 2003].

Some authors argue that because cognitive disturbances are one of the known symptoms of PCNSL, post-treatment scores in patients in remission, rather than pretreatment measures should serve as baseline. In order to evaluate for long-term post-treatment side effects, follow-up evaluations should be compared with

the post-treatment baseline scores [Fliessbach *et al.* 2005]. An update of the German study described 23 patients who were in complete remission for at least 12 months. Ninety five percent of patients showed improved or stable cognitive function suggesting that combination chemotherapy with high-dose MTX does not negatively impact cognitive function long term and in fact may improve performance in many patients [Fliessbach *et al.* 2005]. For a sizeable fraction of patients, however, cognitive deficits noted at baseline persisted [Fliessbach *et al.* 2005].

Another study that confirms prior findings is an update of the report by Herrlinger and colleagues, which describes long-term outcome of treatment with regard to neurotoxicity and quality of life [Herrlinger *et al.* 2005]. Patients in this study received high-dose MTX initially, and at the time of relapse received either WBRT or other salvage chemotherapy. Like the prior study by Pels and colleagues, although 10% of patients who received chemotherapy alone (without salvage radiation) developed severe leukoencephalopathy, there was no meaningful correlation between white-matter changes and cognitive deficits. Six of 10 long-term survivors who had remained tumor free for at least 48 months were evaluated with a battery of neuropsychological tests; 5 of these patients had received chemotherapy alone and 1 had received WBRT at the time of relapse. All patients showed mild-to-moderate cognitive disturbance, which suggests late neurotoxicity should be considered as a possible side effect of chemotherapy-alone regimens. The authors concluded that polychemotherapy regimens cause less-severe neurotoxicity than traditional WBRT. Interestingly, for reasons not completely clear, this study also reports higher acute toxicities and worse response rates when compared with similar studies, which at the time resulted in early closure of the study [Batchelor *et al.* 2003b; Herrlinger *et al.* 2002, 2005; Guha-Thakurta *et al.* 1999].

IA/BBBD

Long-term cognitive outcomes were reported separately in a subset of patients treated with IA chemotherapy-based BBBD [Angelov *et al.* 2009]. Neuropsychologic assessments included a comprehensive battery of tests to evaluate different cognitive domains [Neuwelt *et al.* 2005; McAllister *et al.* 2000; Dahlborg *et al.* 1996; Crossen *et al.* 1992]. The authors argued that by assessment of cognitive abilities in patients with relapsed or progressive disease one could not distinguish treatment related from disease-related cognitive toxicity, and thus limited their report to patients who achieved long-term CR. Results were reported in separate reports and overall, most of these patients, and notably older population (age over 60), appeared to have cognitive improvement or preservation of their cognitive function relative to pretreatment status at follow up between 1 to 7 years after achieving CR [McAllister *et al.* 2000; Dahlborg *et al.* 1996].

These studies, with recognition of their pitfalls, suggest there is delayed neurotoxicity associated with WBRT, which impacts not only older patients (age above 60 years), but also significantly impairs outcomes in younger patients [Harder *et al.* 2004]. Lowering the dose of WBRT may cause less long-term neurocognitive toxicity [Correa *et al.* 2009], but this remains to be proven in older patients and for longer follow-up periods. Interestingly, one of the few modalities to show preserved and improved cognitive function in older population (age over 60) was IA chemotherapy with BBBD [Angelov *et al.* 2009; Neuwelt *et al.* 2005; McAllister *et al.* 2000; Dahlborg *et al.* 1996; Crossen *et al.* 1992].

Conclusion

Although chemotherapy as a single modality has an established role in the management of newly diagnosed PCNSL, much room for improvement exists. Clinical judgment will need to augment the data from relatively small clinical trials as the low incidence of this disease precludes adequately powered randomized trials. It appears that single-agent high-dose MTX can work well provided that it is given over a short infusion. While combination chemotherapy has good oncologic rationale and has proven effective, careful patient selection is required for its safe use. Radiation therapy has been avoided in most patients given the neurocognitive toxicity associated with traditional fraction sizes and total doses. Lower doses and twice-daily dosing designed to minimize toxicity, however, are currently in clinical trials and deserve consideration. More intensive approaches using HDC/ASCR or IA/BBBD need further study although involve considerable invasiveness. The role of focal therapy to address ocular and CSF involvement continues to evolve. Small series of intravitreal and IT regimens using rituximab have been reported

but need formal testing in clinical trials. As therapeutic regimens are refined the quality of life and neurocognitive function of patients with PCNSL will hopefully improve.

Conflict of interest statement

The authors declare they have no conflicts of interest.

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