Chemotherapy for primary central nervous system lymphoma

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Chemotherapy, with or without radiotherapy, is the mainstay of treatment for primary central nervous system lymphoma (PCNSL). High-dose methotrexate (MTX) is the most effective drug available to treat these lesions, and it is used in doses of 1 to 8 g/m², either as a single agent or in combination with other drugs such as corticosteroid agents, cytarabine, procarbazine, vincristine, carmustine, lomustine, thiotepe, cyclophosphamide, temozolomide, and rituximab. To date, an overwhelming number of different regimens in which high-dose MTX is used have been reported. Given the lack of randomized trials, however, the optimal treatment remains controversial. Varying methodology makes the comparison of available studies extremely difficult, yet some common themes can be found throughout the literature. Treatment paradigms vary considerably according to the patient’s age. Most studies support the use of chemotherapy-only treatments for elderly patients (>60 years), given the high risks of neurotoxicity associated with radiotherapy. Nevertheless, the prognosis remains poor regardless of the chemotherapy chosen, and less toxic regimens might be preferable for such elderly patients. Conversely, in younger patients (<60 years), there is growing evidence that commonly used chemotherapy-only regimens are associated with increased relapse rates that may not justify deferral of radiotherapy. Thus, a significant focus of research has been the development of intensified chemotherapy regimens that could replace radiotherapy. In this article, the authors discuss the principles guiding the use of chemotherapy for PCNSL, and critically review the available literature, including the most recent trials.

KEY WORDS • primary central nervous system lymphoma • brain neoplasm • methotrexate • chemotherapy • radiotherapy

Primary CNS lymphoma is a non-Hodgkin lymphoma that arises within the brain, eyes, leptomeninges, or spinal cord in the absence of systemic disease. Histological analysis discloses a B-cell lymphoma in more than 90% of patients, and the lesion usually has large cell or immunoblastic features. Despite being a relatively rare tumor, its incidence has been increasing among immunocompetent patients over the past several decades.

The first attempts to treat PCNSL were based on WBRT and corticosteroid drugs. This approach achieved limited results, with a median OS duration of 10 to 18 months, and 5-year survival rates of less than 5%. Subsequently, it was demonstrated in numerous reports that adding certain chemotherapy regimens to WBRT could decrease relapse rates and improve survival. The majority of active regimens include the use of high-dose MTX, which has become a standard component in the treatment of PCNSL. Nevertheless, the recognition of delayed neurotoxicity as a devastating and relatively frequent complication of combined chemotherapy and radiotherapy prompted investigators to explore the possibility of deferring radiotherapy and treating patients with chemotherapy alone.

Unfortunately, in most trials researchers have suggested that such an approach may compromise PFS, although some patients can be successfully treated with salvage therapy. This fact has introduced significant controversy in the field, which is divided on the question of what constitutes an acceptable risk of radiotherapy-related dementia when attempting to achieve prolonged disease-free survival. Such controversy, aggravated by the lack of randomized trials defining the standard of care, has created a situation in which any regimen including high-dose MTX may be considered acceptable, whether or not it is combined with radiotherapy or other drugs (Table 1). When confronted with the available literature, physicians and patients are overwhelmed by the wide range of different treatment approaches, and it is difficult to make an informed treatment decision. In this article, we discuss the principles guiding chemotherapy for PCNSL and critically review the available literature; our aim is to provide the necessary elements for better informed clinical decisions.

Abbreviations used in this paper: ASCT = autologous stem cell transplantation; BBB = blood–brain barrier; BCNU = 1,3-bis(2-chloroethyl)-1-nitrosourea (carmustine); CCNU = 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine); CNS = central nervous system; EFS = event-free survival; HDC = high-dose chemotherapy; KPS = Karnofsky Performance Scale; MPV-A = methotrexate, procarbazine, vincristine, and cytarabine; MTX = methotrexate; OS = overall survival; PCNSL = primary CNS lymphoma; PFS = progression-free survival; WBRT = whole-brain radiation therapy.
TABLE 1

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Regimen</th>
<th>No. of Patients</th>
<th>ORR (%)</th>
<th>Median EFS/ PFS (mos)</th>
<th>Median OS (mos)</th>
<th>2-Yr OS (%)</th>
<th>Neurotoxicity (%)</th>
<th>Deaths Due to Toxicity (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrey, et al., 2000</td>
<td>MTX 3.5 g/m²; procarbazine, vincristine + IT MTX &amp; Ara-C ± WBRT</td>
<td>52</td>
<td>90</td>
<td>NR</td>
<td>51</td>
<td>65</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>O’Brien, et al., 2000</td>
<td>MTX 1 g/m² ± IT Ara-C + WBRT</td>
<td>46</td>
<td>90‡</td>
<td>17</td>
<td>33</td>
<td>62</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Ferreri, et al., 2006</td>
<td>MTX 3.5 g/m²; CCNU, procarbazine, prednisone ± IT MTX &amp; Ara-C ± WBRT or HDC &amp; ASCT for pts w/ less than complete response</td>
<td>64</td>
<td>90</td>
<td>13</td>
<td>NR (≥54)</td>
<td>87</td>
<td>9</td>
<td>3</td>
</tr>
</tbody>
</table>

* Ara-C = cytarabine. FU = follow up; IT = intrathecal; NA = not available; NR = not reached; ORR = objective response rate (partial + complete response) to chemotherapy; pts = patients.
† Acute toxic deaths unrelated to neurotoxicity.
‡ Response rates achieved after radiotherapy.
§ Patients younger than 60 years of age.

Interpreting the Literature on PCNSL

In the absence of Phase III trials, interpreting results of retrospective studies, patient series, pilot studies, and Phase II trials becomes essential for making evidence-based treatment decisions. However, such studies are frequently small, and large confidence intervals are observed around the reported outcome measures. Commonly reported end points such as response rates and survival are not adequate measures of efficacy in PCNSL. Response rates are frequently reported because they are easy to compare and can also be assessed in regimens that subsequently use WBRT. However, most regimens for PCNSL achieve similarly high response rates to chemotherapy and steroid agents, and therefore do not discriminate between various modalities. Moreover, if responses are not durable, the timing of the response assessment may significantly influence results. Shorter treatments may overestimate response rates in comparison with longer treatments because response assessment and confirmatory scans are obtained earlier in the course of the disease, when transient responses may still be seen. Likewise, when combined chemo- and radiotherapy regimens are used, response rates to chemotherapy obtained prior to WBRT are overestimated and cannot be confirmed, because final response rates assessed after WBRT are confounded by the activity of radiotherapy.

The OS is another frequently reported measure of efficacy that is reliable and easy to compare. However, this measure may be significantly influenced by salvage treatments, which are often effective in PCNSL, particularly after chemotherapy-only regimens; thus, considerable attention must be given to which salvage strategies were used when interpreting survival data. Because of the limitations in interpretation of response rates and OS, intent-to-treat EFS, time to treatment failure, or PFS are more adequate measures of efficacy in PCNSL and allow more reliable and appropriate comparisons among different regimens.

The risk of neurotoxicity is another important aspect to be considered. Various definitions of neurotoxicity have been used, ranging from subtle changes in the results of neuropsychological evaluation to severe and incapacitating dementia. Therefore, it is difficult to compare different studies for risk of neurotoxicity. Moreover, delayed neurotoxicity is a time-dependent variable because the incidence increases over time and is cumulative. Thus, variability in the extent of follow up among reported studies may render a comparison of data on neurotoxicity impossible. As a time-dependent variable, Kaplan–Meier analy-
sis with competing risk estimates would be the optimal way to overcome differences in follow-up duration, but using such methodology is difficult in the absence of a reproducible and standardized definition of neurotoxicity. However, comparison with other drugs in a variety of regimens. Limited experience with the use of such drugs as single agents in the treatment of PCNSL is available; therefore, direct evidence of activity is lacking. However, indirect evidence supports the use of a combination of drugs over single-agent high-dose MTX. A multidrug combination has been used in the vast majority of successful regimens for systemic non-Hodgkin lymphoma. Moreover, experience with single-agent MTX in doses of 8 g/m² has achieved less than optimal results when compared with regimens combining several drugs. Additional evidence of the activity of drugs other than MTX was provided by a study in which investigators reported on a combination of MTX, thiopeta, and procarbazine followed by WBRT. Results were compared with a previous same-institution study in which similar doses of single-agent MTX were used prior to WBRT, followed by cytarabine given after completion of WBRT. Response rates following induction chemotherapy and prior to WBRT were significantly higher (76%)

Treatments for PCNSL

Single-Agent MTX

Methotrexate is an antimetabolite agent that inhibits the enzyme dihydrofolate reductase, resulting in intracellular depletion of folates, which are critical for cell function. The role of MTX in non-Hodgkin lymphoma is limited, but paradoxically, it has been found to be the most active drug for PCNSL, either as a single agent or in combination with other drugs. Despite the fact that MTX is a water-soluble agent, rapid infusion of high doses (1–8 g/m²) has been reported to cross the BBB and achieve therapeutic concentrations within the CNS. This may explain why high-dose MTX improves survival in this disease, whereas standard non-Hodgkin lymphoma regimens such as cyclophosphamide, hydroxydaunomycin/doxorubicin, Oncovin (vincristine), and prednisone do not. Infusions of high-dose MTX require vigorous hydration, urine alkalinization, and leucovorin rescue. Patients are hospitalized until MTX is cleared from circulation, which is achieved through renal metabolization. The main toxicities include renal failure, hematotoxicity, mucositis, liver enzyme elevation, interstitial pneumonitis, skin rash, photosensitivity, and acute or subacute neurotoxicity. Patients with delayed MTX elimination may be rescued with the use of glucarpidase, which is a recombinant carboxypeptidase G2 enzyme (Voraxaze, Protherics UK Ltd.). This drug is commercially available in Europe under special regulation, and through an orphan drug program in the US. A single infusion of glucarpidase immediately clears MTX from the circulation by hydrolysis of MTX to the inactive metabolites 4-deoxy-4-amino-N10-methylpteroyl acid and glutamate. Although glucarpidase may decrease the length of hospitalization, the extent to which such accelerated clearance prevents development of acute toxicities remains uncertain. It is also unknown whether the early use of glucarpidase (24–48 hours after MTX infusion) decreases the MTX area under the curve and potentially diminishes the efficacy of this agent.

The optimal dose of MTX has not been established. As a single agent, and when administered without WBRT, the most frequently used dose has been 8 g/m², with dose adjustments made according to creatinine clearance. Two chemotherapy-only Phase II trials using this regimen have been published (Table 1). The Neuro-Oncology Working Group of the German Cancer Society trial enrolled 37 patients. Accrual was terminated early because of low objective response rates (30%), with a median PFS of 10 months and a median OS of 25 months. Investigators in the New Approaches to Brain Tumor Therapy trial enrolled 25 patients and achieved a 74% response rate and a median OS of 55 months. The PFS time, however, was only 13 months. Both regimens were associated with low acute toxicity rates, although elderly patients with lower creatinine clearance rates received doses as low as 4 g/m².

Many patients in both trials underwent WBRT as salvage treatment. In a retrospective study reporting on the results of salvage WBRT after failure of single-agent MTX it was suggested that such an approach is effective in prolonging survival, with the advantage of decreased neurotoxicity compared with first-line WBRT. However, updated results of the German Cancer Society trial suggested that significant leukoencephalopathy developed in up to 58% of patients who underwent salvage WBRT, and many patients experienced overt dementia. Thus, that group of investigators does not recommend this treatment strategy. Further attempts to combine 8 g/m² doses of MTX with other drugs such as thiopeta have resulted in unacceptable toxicity.

Single-agent MTX at lower doses (1–3.5 g/m²) has been used in combination with WBRT, and has achieved a median OS of 20 to 41 months in older studies. There is growing evidence, however, that within this dose range a combination of MTX with other drugs may achieve superior results compared with single-agent MTX. In a study in which 3.5 g/m² single-agent MTX was used as induction chemotherapy prior to a myeloablative chemotherapy regimen, investigators found relatively low response rates (57%) after four cycles of MTX. Unlike doses of 8 g/m², MTX given at 1 to 3.5 g/m² can be safely combined with other drugs. Such combinations are discussed in the section that follows.

High-Dose MTX Combined With Other Chemotherapy Agents

High-dose MTX (1–5 g/m²) has been combined with other drugs in a variety of regimens. Limited experience with the use of such drugs as single agents in the treatment of PCNSL is available; therefore, direct evidence of activity is lacking. However, indirect evidence supports the use of a combination of drugs over single-agent high-dose MTX. A multidrug combination has been used in the vast majority of successful regimens for systemic non-Hodgkin lymphoma. Moreover, experience with single-agent MTX in doses of 8 g/m² has achieved less than optimal results when compared with regimens combining several drugs. Additional evidence of the activity of drugs other than MTX was provided by a study in which investigators reported on a combination of MTX, thiopeta, and procarbazine followed by WBRT. Results were compared with a previous same-institution study in which similar doses of single-agent MTX were used prior to WBRT, followed by cytarabine given after completion of WBRT. Response rates following induction chemotherapy and prior to WBRT were significantly higher (76%...
complete response and 12% partial response) with MTX/thiotepa/procarcabazine, compared with single-agent MTX (no complete response and 64% partial response). Moreover, because survival was similar in both studies, the addition of cytarabine after WBRT may have played an important role in prolonging survival in the patients initially treated with single-agent MTX. These findings support the suggestion that cytarabine, procarcabazine, and thiotepa are active drugs in PCNSL.

The choice of drugs for PCNSL regimens has been based on their activity in non-Hodgkin lymphoma and their ability to penetrate an intact BBB. Commonly used drugs include cytarabine, procarcabazine, vincristine, carmustine, lomustine, thiotepa, topotecan, cyclophosphamide, and corticosteroid agents. Several regimens combining these drugs have been proposed, and the most recent ones are listed in Table 1. Two regimens have achieved what appear to be superior results and merit further discussion.

Combination MPV-A and Intrathecal MTX

The combination of MPV-A with intrathecal MTX has been extensively studied.3 A report of a Phase II study performed at Memorial Sloan–Kettering Cancer Center is available, along with updated long-term results.3,18 In that study MPV-A was used (MTX dose 3.5 mg/m²), followed by WBRT, and 52 patients were enrolled. The median OS was 51 months, and the median PFS was not reached. However, neurotoxicity eventually developed in 30% of patients. Elderly patients (> 60 years old) were particularly at risk (75%), but in 26% of younger patients neurotoxicity also developed. A substantial proportion of elderly patients (22 individuals) refused WBRT, and 19% of them were alive at the last follow-up interval, with a good quality of life and no neurotoxicity. Another study of MPV-A was performed by investigators in the Radiation Therapy Oncology Group and enrolled 98 patients at several institutions.10 The dose of MTX was slightly lower (2.5 g/m²). Results were less favorable than the single-center study, with a median PFS of 24 months, a median OS of 37 months, and a 15% rate of neurotoxicity. Long-term outcomes are not available. Taken together, these studies indicate that MPV-A followed by WBRT is associated with prolonged PFS times and OS rates, but neurotoxicity remains a significant risk in all patients who undergo WBRT. Although elderly patients seem to benefit from deferral of WBRT, the efficacy of MPV-A without WBRT in younger patients remains unknown.

Some insight into this question was provided by another study in which a regimen with similar doses of MTX (3 g/m²) but a slightly different combination of drugs (MTX, procarcabazine, and lomustine) was used in patients younger than 60 years. In that study, WBRT was deferred in patients whose tumors responded (90%). Although extended survival (median OS > 54 months) was observed, such a treatment strategy was associated with a disappointingly low PFS time (median PFS 13 months), which is similar to results obtained with single-agent high-dose (8 g/m²) MTX and deferred WBRT.37 Taken together, studies of chemotherapy-only regimens with either single-agent MTX (8 g/m²) or MTX (2.5–3.5 g/m²) in combination with other drugs suggest that such a strategy is associated with lower PFS times compared with combined chemo- and radiotherapy, although a substantial proportion of patients may be rescued by salvage treatment.

Bonn Protocol

A different approach was proposed in a multicenter German study based on the use of an intensified chemotherapy-only regimen; results have been updated recently, and the sample increased.23,39 The regimen uses higher MTX doses (5 g/m²), along with a complex combination of drugs composed of vincristine, ifosfamide, dexamethasone, cyclophosphamide, vindesine, and intracerebral prednisolone, MTX, and cytarabine (the so-called Bonn protocol). High rates of acute toxicity were seen (including a 10% mortality rate due to toxicity), in addition to severe hematotoxicity, Ommaya reservoir infections, and encephalopathy. Several dose adjustments were necessary, and protocol violations occurred. However, excellent PFS and OS results were achieved. The expanded study included 88 patients, and investigators reported a median time to treatment failure of 20 months and a median OS of 55 months, which is comparable to combined chemo- and radiotherapy. Delayed neurotoxicity was minimal, and only developed in patients who underwent WBRT for salvage therapy. Results in elderly patients were significantly less favorable, however, with a time to treatment failure of 9 months and a median OS of 36 months. From such results we can infer that this regimen may be an attractive option as a chemotherapy-only treatment for patients younger than 60 years. For elderly patients, however, this regimen does not seem superior to other less toxic regimens such as MPV-A and MTX/temozolomide, which are discussed in the following section.

Chemotherapy for PCNSL in Elderly Patients

Patients older than 60 years of age account for 50% of those with PCNSL. Treating these patients is particularly difficult, not only because response rates and PFS times are less favorable, but also because of the increased risk of acute toxicity and late delayed neurotoxicity.24 In elderly patients, neurotoxicity following combined chemo- and radiotherapy may affect up to 90% of those undergoing treatment.3 Therefore, most practitioners favor deferring radiotherapy in this population, and there is currently a trend to conduct separate trials for patients younger and older than 60 years of age.

A single prospective study focusing on patients older than 60 years and using chemotherapy-only treatment is available (Table 2). In that Phase II study conducted by the European Organisation for Research and Treatment of Cancer, a regimen consisting of MTX at a dose of 1 g/m², lomustine, procarbazine, methyprednisolone, and intrathecal MTX was used. Among the 50 patients enrolled, responses were seen in 48% (complete response in 42% and partial response in 6%); disease was stable in 28%. The median OS was 14 months and the 1-year PFS was 40%. Toxicities were common, but considering the pre-morbid characteristics of the population, the regimen was relatively well tolerated.25

Outcomes in elderly patients in other studies are similar (Table 2). A study in which MPV-A was used included 22 patients older than 60 years who were treated with chemo-
Chemotherapy for primary CNS lymphoma

therapy only. The median PFS was 10 months and the median OS was 33 months. The regimen was relatively well tolerated and no toxicity-related death occurred, although significant toxicity was seen after administration of cytarabine. 3,18 Separate results in elderly patients with the use of the Bonn protocol have also been reported. The median time to treatment failure (9 months) and the median OS (34 months) were comparable to other regimens, but significant toxicity was observed. 27,39

More recently, results of a multicenter study performed by the French Association of Neuro-Oncology reporting on outcomes associated with the combination of MTX at a dose of 3 g/m² and temozolomide in 23 elderly patients were made available. 38 The treatment was well tolerated, with nephrotoxicity and hematotoxicity the main adverse events. Responses were seen in 55% of patients; the median time to treatment failure was 8 months and the median OS was 35 months. Although results need to be confirmed in larger series, that study supports the suggestion that a combination of MTX and temozolomide is as effective as the Bonn protocol and MPV-A, with the advantage of a more favorable toxicity profile and elimination of intrathecal chemotherapy.

It is difficult, however, to determine whether such favorable results reflect the effectiveness of temozolomide or are secondary to the use of an extended course of treatment, which encompassed 5 months of maintenance chemotherapy. Overall, studies on chemotherapy-only treatments for elderly patients with PCNSL support the suggestion that there is a subgroup of 50% of patients who respond well to high-dose MTX regimens independently of the combination used. Because this subgroup of responding patients seems to do well independently of the initial treatment, less toxic regimens such as MPV-A and MTX and temozolomide are appropriate for elderly individuals with PCNSL. A randomized Phase II trial for elderly patients comparing MPV-A with MTX and temozolomide is planned.

Use of HDC and ASCT

The HDC and ASCT protocol has been an effective salvage treatment modality for refractory or recurrent systemic non-Hodgkin lymphoma. In patients with PCNSL, few studies have addressed the use of HDC and ASCT in both newly diagnosed and refractory disease (Table 3). Before the advent of HDC and ASCT, induction chemotherapy with agents known to have activity in PCNSL was usually used for selection of chemotherapy-sensitive patients and to allow stem cell harvesting. Because of toxicity risks, the HDC and ASCT modality is typically offered to younger patients with a good KPS status, and therefore the results of available studies must be interpreted within this context.

### TABLE 2
Literature review of results of chemotherapy-only regimens for elderly patients (> 60 years) with PCNSL

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Regimen</th>
<th>No. of Patients</th>
<th>ORR (%)</th>
<th>Median PFS (mos)</th>
<th>Median OS (mos)</th>
<th>2-Yr OS (%)</th>
<th>Neurotoxicity (%)</th>
<th>Deaths Due to Toxicity (%)</th>
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<tbody>
<tr>
<td>Abrey, et al., 2000 &amp; Gavrilovic, et al., 2005 (FU)</td>
<td>MTX 3.5 g/m², procarbazine, vincristine + IT MTX &amp; Ara-C ± WBRT</td>
<td>22</td>
<td>NA</td>
<td>10</td>
<td>33</td>
<td>NA</td>
<td>5</td>
<td>0</td>
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<tr>
<td>Hoang-Xuan, et al., 2003</td>
<td>MTX 1 g/m², CCNU, procarbazine, prednisone + IT MTX, Ara-C; no WBRT</td>
<td>50</td>
<td>48</td>
<td>10</td>
<td>14</td>
<td>48</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Pels, et al., 2003 &amp; Juergens, et al., 2006 (FU)</td>
<td>MTX 5 g/m², vincristine, ifosfamide, cyclophosphamide, vindesine, dexamethasone + IT MTX &amp; Ara-C; no WBRT</td>
<td>88†</td>
<td>68</td>
<td>9†</td>
<td>36†</td>
<td>NA</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Omuro, et al., 2006</td>
<td>MTX 3 g/m², temozolomide, prednisone, no WBRT</td>
<td>23</td>
<td>55</td>
<td>8</td>
<td>35</td>
<td>57</td>
<td>NA</td>
<td>4</td>
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</table>

* Acute toxic deaths unrelated to neurotoxicity.
† Updated partial results presented as abstracts.

### TABLE 3
Literature review of HDC and ASCT regimens for PCNSL

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>Induction Regimen</th>
<th>ORR to Induction</th>
<th>HDC &amp; ASCT Regimen</th>
<th>No. of Pts Receiving HDC &amp; ASCT (%)</th>
<th>ORR to HDC &amp; ASCT (%)</th>
<th>Median FU (mos)</th>
<th>2-Yr OS (%)</th>
<th>Neurotoxicity (%)</th>
<th>Deaths Due to Toxicity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrey, et al., 2003</td>
<td>28</td>
<td>MTX 3.5 g/m², Ara-C</td>
<td>57% (16 of 25)</td>
<td>BCNU, etoposide, cytarabine, melphalan (BEAM)</td>
<td>14 (50)</td>
<td>77</td>
<td>28</td>
<td>25</td>
<td>60</td>
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</tr>
<tr>
<td>Illerhaus, et al., 2006</td>
<td>30</td>
<td>MTX 8 g/m², Ara-C, thiotepa</td>
<td>80% (24 of 26)</td>
<td>BCNU, thiopepa (followed by WBRT)</td>
<td>23 (76)</td>
<td>100</td>
<td>63</td>
<td>79</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Soussain, et al., 2001</td>
<td>22</td>
<td>cytarabine, etoposide, vincristine</td>
<td>71% (10 of 14)</td>
<td>thiopepa, busulfan, cyclophosphamide</td>
<td>20 (90)</td>
<td>90</td>
<td>41</td>
<td>53</td>
<td>64</td>
<td></td>
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<tr>
<td>Cheng, et al., 2003</td>
<td>7</td>
<td>MTX 3.5–5 g/m² (± procarbazine), Ara-C</td>
<td>86% (6 of 7)</td>
<td>thiopepa, busulfan, cyclophosphamide</td>
<td>6 (86)</td>
<td>100</td>
<td>24</td>
<td>—</td>
<td>—</td>
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</table>

* ITT = intent-to-treat analysis; — = not reported.
The feasibility and efficacy of HDC and ASCT was first assessed in a French study performed at Hôpital Pitie-Salpêtrière, in which 22 patients with recurrent/refractory PCNSL or isolated intraocular lymphoma were enrolled. Patients with refractory CNS involvement received the HDC and ASCT treatment only if they responded to induction chemotherapy in which high-dose cytarabine and etoposide were used. Overall, good response rates were seen (80% complete and 10% partial response), and the 3-year OS was 64%. Such results implied promising activity, although the interpretation of results was limited by the heterogeneity of patient characteristics in terms of CNS involvement, disease status at start of treatment, and previous treatments (including WBRT in several patients).\(^4\)

Notably, 32% of patients experienced acute or chronic neurotoxicity.

A confirmatory Phase II multicenter trial using the same regimen is ongoing. Preliminary results in 43 patients with recurrent or refractory PCNSL seem to confirm the efficacy of this strategy (Soussain, personal communication, 2006). Interestingly, 11 patients in whom the disease was refractory to induction treatment have received the HDC and ASCT component; 10 achieved a complete response, despite what was thought to be chemotherapy-resistant disease. If confirmed, this finding may support the suggestion that, in addition to intrinsic tumor cell properties, the mechanisms of resistance in recurrent PCNSL may include poor BBB penetration of potentially active drugs, which can be overcome by HDC and ASCT. Similarly encouraging results (100% response rate) were found in a separate, smaller study, in which induction of MTX, procarbazine, and cytarabine, followed by HDC and ASCT with thiopeta and busulfan, was used in seven patients with PCNSL who had unfavorable prognostic factors (KPS score < 50, age > 60 years, or relapse of disease).\(^9\)

In a group of newly diagnosed patients, 28 individuals received induction chemotherapy with MTX and cytarabine, followed by HDC and ASCT with high-dose BCNU, etoposide, cytarabine, and melphalan. Low response rates were seen after induction chemotherapy (57%), and only 14 patients eventually received HDC and ASCT. The median EFS duration was 9 months and the 3-year OS was 60%. No neurotoxicity developed. The investigators concluded that a better induction regimen was necessary to increase the number of patients who eventually receive HDC and ASCT, and that BCNU, etoposide, cytarabine, and melphalan was not an optimal choice for HDC because these drugs do not have good penetration in the CNS.\(^2\)

More recently, another study in which the HDC and ASCT modality was used in 30 newly diagnosed patients with PCsNL was reported. An intensive induction regimen (8 g/m² MTX, followed by cytarabine and thiopeta) was used. Twenty-three patients (76%) eventually proceeded with HDC and ASCT, with Carmustine and busulfan as the chemotherapy agents. This was followed by hyperfractionated WBRT for all 21 remaining patients (two had dropped out). All patients responded completely to HDC and ASCT. However, the relevance of the HDC and ASCT component of the regimen is difficult to assess because WBRT was used in all patients. The 3-year PFS (79%) was significantly superior to that observed in the previous HDC and ASCT study (25%), but the 3-year OS was similar (69% compared with 60%, respectively).

Neurotoxicity was observed in 17% of patients after a median follow-up duration of 63 months.\(^2\) Taken together, these two studies of first-line HDC and ASCT seem to validate the concept that chemotherapy-only strategies result in lower PFS, similar OS, and less neurotoxicity compared with chemotherapy combined with WBRT in younger patients with PCNSL.

Intrathecal Chemotherapy

The role of intrathecal chemotherapy in PCNSL is controversial. Most successful regimens have included the use of intrathecally delivered drugs such as MTX, cytarabine, and thiopeta. However, intrathecal chemotherapy is associated with significant morbidity, including arachnoiditis, infection, bleeding, leukoencephalopathy, and other complications specific to Ommaya reservoir placement or repeated lumbar punctures. Retrospective studies have failed to demonstrate a clear benefit of this practice, but prospective validation is lacking.\(^2\) Some authors reserve the use of intrathecally delivered chemotherapy for patients with positive results on cytological studies of cerebrospinal fluid or evidence of leptomeningeal disease on magnetic resonance imaging. However, the sensitivity of the cytological examination of the cerebrospinal fluid is low, and it may not be a reliable parameter for treatment decisions. It has been suggested that the importance of intrathecal chemotherapy may be regimen specific because it may depend on the MTX dose, efficacy, and BBB penetration properties of other drugs.

Additional analysis of the expanded Bonn protocol may provide some insight into this issue.\(^27\) In the expanded study, intrathecally delivered chemotherapy was eliminated in 18 patients younger than 60 years of age, but the remainder of the treatment remained unchanged. In comparison with the original patients younger than 60 years of age who received intrathecal chemotherapy (30 patients), response rates were similar (78% compared with 84%), but the PFS was significantly longer in patients who received intrathecal chemotherapy. This difference was observed despite the very high intravenous dose of MTX (5 g/m²) used in both treatment versions, suggesting that high doses of MTX cannot compensate for the lack of intrathecal treatment.

Salvage Regimens

Available options for refractory or recurrent PCNSL include WBRT, HDC, and ASCT, repeated challenge with MTX-based chemotherapy, and chemotherapy regimens without MTX. The type of first-line treatment used provides important prognostic implications in relapsing PCNSL. There is growing evidence that patients whose disease relapses after a chemotherapy-only initial treatment may respond to salvage therapy, whereas relapses that occur after combined chemotherapy and WBRT are associated with an unfavorable prognosis.\(^2,26\) The WBRT modality remains one of the most effective treatments for patients who did not receive such treatment initially, with the caveat of an increased risk of neurotoxicity, particularly in the elderly.\(^31\) Likewise, combined HDC and ASCT seems to be another attractive option for salvage treatment, but it is limited to younger patients with good KPS status. Patients with late relapses may be candidates for repeated challenge with MTX, although the efficacy of such a practice remains poorly defined.\(^40\) Chemistry
Chemotherapy for primary CNS lymphoma

regimens without MTX remain the sole option for patients whose disease progresses while they are receiving or shortly after treatment with MTX and who are not candidates for WBRT or HDC and ASCT.

Few studies reporting outcomes in patients with recurrent or refractory PCNSL treated with non-MTX regimens are available (Table 4). Most are small series of patients who received various prior treatments, and it is thus difficult to assess regimen efficacy. Variable response rates (26–86%), PFS (1-year PFS of 13–53%), and OS (1-year OS of 25–57%) have been reported. Many regimens are fairly aggressive and poorly tolerated in this heavily pretreated population. Examples include high-dose cytarabine (as a single agent or combined with etoposide and/or ifosfamide), idarubicin/ifosfamide, and procarbazine/CCNU/vincristine. Other regimens seem to be better tolerated, such as single-agent topotecan and temozolomide as a single agent or combined with rituximab.

Some patients experience multiple relapses but respond to various salvage treatments, from which it may be inferred that there is a subgroup of patients with less aggressive tumors that remain sensitive to chemotherapy throughout the course of disease. These patients may benefit from less toxic regimens.

Conclusions

Despite the limitations and heterogeneity of available data, a few general conclusions can be drawn. Elderly patients have a worse prognosis overall, but these individuals clearly benefit from chemotherapy, and the risk associated with WBRT is not acceptable. Available studies of this group support the use of high-dose MTX in the range of 3 to 3.5 g/m² in combination with other drugs. In younger patients, the goal is to increase the chance of cure while preserving cognitive function and quality of life. Chemotherapy-only regimens are associated with a short PFS time and a decreased potential for cure. Therefore, the available data support the use of WBRT for young patients treated with MTX-based regimens. The Bonn protocol may represent an attractive alternative to a chemotherapy-only approach in younger patients, but the mortality rate from toxicity is unacceptable. However, the Bonn study validates the concept that “more is better” for this young population. This provides a rationale for exploring the role of intensified first-line treatments such as HDC and ASCT as a replacement for WBRT. Planned or ongoing studies are also investigating the role of other approaches such as BBB disruption, immunotherapy, very high doses of MTX with subsequent glucarpidase rescue, and alternative drugs such as temozolomide and rituximab.

Disclosure

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