

Trials and tribulations in primary CNS lymphoma

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A minority of patients with primary central nervous system lymphoma achieve a complete response to therapy and most patients have a poor prognosis. A recent randomised phase II trial demonstrated that the addition of high-dose cytarabine to high-dose methotrexate increases the complete response rate and improves patient outcome.

Primarily central nervous system lymphoma (PCNSL) is an uncommon extranodal B-cell non-Hodgkin lymphoma confined to the central nervous system (CNS) that represents approximately 1% of all non-Hodgkin lymphomas. Although this disease has been observed in patients with immune deficiency, the incidence in immunocompetent patients has increased, particularly among elderly patients.¹

Due to the rarity of PCNSL, randomised studies have been very difficult to conduct. Patients with this disease have not benefitted from the progress made in systemic B-cell lymphoma, in that standard treatment

approaches such as cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) chemotherapy have not been effective in PCNSL because of poor drug penetration into the CNS.² The use of therapies that are considered effective – high-dose methotrexate, autologous stem-cell transplantation and whole-brain radiation therapy (WBRT) – has proved challenging because many patients are elderly and more susceptible to the toxic effects associated with these treatments.

The initial treatment for patients with PCNSL was to use WBRT. While PCNSL tumours are very radiosensitive, local disease relapses are frequent

and there are virtually no long-term survivors.³ Based on its ability to penetrate the CNS, methotrexate was subsequently used in clinical trials, and high doses with folinic acid rescue were found to improve patient outcome.⁴ While there is no consensus as to the exact dose that should be used, it is generally accepted that 'high-dose' methotrexate regimens utilise between 1 g/m² to 8 g/m² administered every two to three weeks. Other agents, including cytarabine, procarbazine, temozolomide and rituximab, have since been added to high-dose methotrexate and have produced higher response rates and potentially improved progression-free survival.⁵ However, a higher instance of

toxic effects have been seen in studies testing chemotherapy combinations, resulting in higher rates of treatment-related mortality compared with high-dose methotrexate alone.

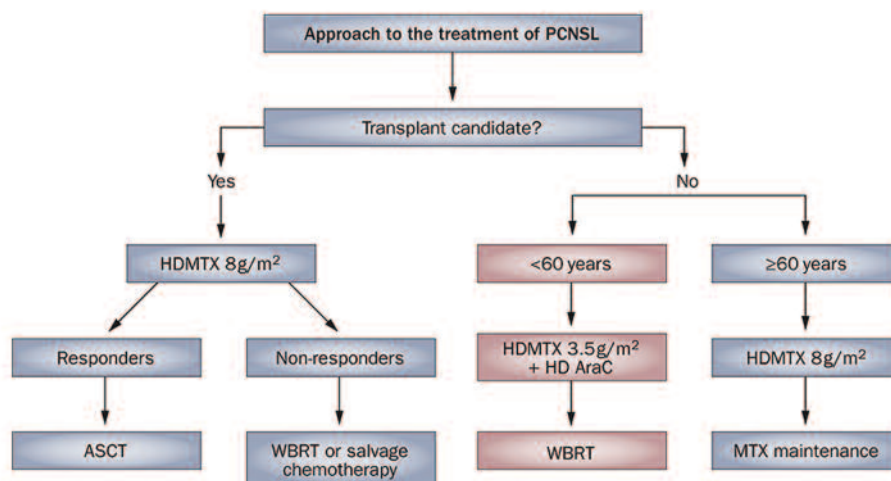
In most of these studies, chemotherapy formed part of a combined modality approach and WBRT was given as consolidation after induction therapy. A high incidence of neurotoxicity was seen, particularly in patients older than 60 years who received combined modality treatment.⁶ Recent studies have attempted to limit neurotoxicity, either by omitting radiation therapy⁷ and in some studies consolidating the response to initial therapy using autologous stem-cell transplantation,⁸ or by use of lower doses of radiation therapy.⁹ In studies in which autologous stem-cell transplantation was added and radiation therapy omitted, it was evident that patients who benefitted most were those who had a complete response to initial induction therapy. Similarly, lowering the dose of WBRT to diminish potential long-term neurotoxicity might only be feasible in patients who have a complete response to treatment. Therefore, to utilise these approaches we need to identify treatment regimens that result in high complete response rates.

High-dose methotrexate has become a standard approach for many groups treating patients with PCNSL, and doses of up to 8 g/m² are given every two weeks. A recent study by Ferreri et al.¹⁰ suggests that the addition of high-dose cytarabine to high-dose methotrexate results in a superior complete response rate and overall response rate when compared with methotrexate alone. In this randomised phase II trial, 79 patients were randomly assigned to receive methotrexate 3.5 g/m² alone or in combination with cytarabine 2 g/m² twice daily on two days for four cycles as primary therapy for CNS lym-

phoma. The primary endpoint of the study was complete response rate. In total, 46% of patients receiving both high-dose methotrexate and high-dose cytarabine had a complete response to treatment compared with 18% of patients receiving high-dose methotrexate alone. The overall response rate and subsequent outcomes of patients were improved with the addition of high-dose cytarabine to high-dose methotrexate. Although significant haematological toxic effects were seen, this was managed with growth factor administration and adverse effects were felt to be acceptable. These findings suggest that intensification of induction therapy as demonstrated by this study might improve long-term patient results.

Although the findings are persuasive, certain caveats need to be kept in mind when interpreting these results. First, as in most CNS tumours, radiographic assessment of response is not always easy, and has limitations as a surrogate for clinical benefit. This is further exacerbated in non-blinded studies. Second, although studies of combination chemotherapy and combined modality therapy in this disease have used varying doses of 'high-dose' methotrexate, the trials that use high-dose methotrexate as a single agent have employed a dose of 8 mg/m² every two weeks. This dose results in a high response rate, is well tolerated, and can be administered repeatedly until progression in most patients. The study by Ferreri et al.¹⁰

TREATMENT OF NEWLY DIAGNOSED PCNSL PATIENTS



Transplant-eligible patients receive high-dose chemotherapy followed by an autologous stem-cell transplant, in patients who respond to treatment. Elderly patients are treated with a chemotherapy-only approach to avoid neurological toxicity associated with WBRT. Younger patients who are not eligible for an autologous stem-cell transplant could be treated with high-dose chemotherapy followed by WBRT (as per the data from the clinical trial of Ferreri et al.¹⁰ (highlighted in the figure).

ASCT – autologous stem-cell transplantation; HD AraC – high-dose cytarabine; HDMTX – high-dose methotrexate; MTX – methotrexate; PCNSL – primary central nervous system lymphoma; WBRT – whole-brain radiation therapy

used a lower dose of methotrexate, 3.5 g/m² delivered every three weeks, which might account for a lower response rate than has been reported in other studies. Third, the vast majority of patients (77%) received WBRT as consolidation after the initial induction chemotherapy. Many groups favour consolidation with autologous stem-cell transplantation rather than administering WBRT, because of the increased neurotoxicity seen with WBRT. Finally, dose reductions were necessary in 44% of patients treated with the combination approach (compared with 3% of patients treated with methotrexate alone), suggesting that it might be easier to intensify therapy by increasing the dose of methotrexate than by adding a second drug, such as high-dose cytarabine.

The data presented by Ferreri et al.¹⁰ could be particularly relevant in patients or practices where high-dose therapy with autologous stem-cell transplantation is not employed. For many groups, the initial decision might be to define which patients are eligible for transplantation. In eligible patients, high-dose methotrexate at a dose of 8 g/m² could be considered with autologous stem-cell transplantation performed in patients who respond to this therapy.

Nonresponders are commonly managed with salvage chemotherapy including temozolomide, rituximab and other treatment approaches, or alternatively receive WBRT (see algorithm). In patients where an autologous transplant is not considered or at centres which do not employ this approach, the data presented by Ferreri et al. could be of value. In view of the fact that patients aged over 60

years receiving WBRT might have significant neurotoxicity, these patients could be managed with chemotherapy alone and could receive methotrexate with or without other chemotherapy agents. Alternatively, younger patients might benefit from the results presented by Ferreri et al.¹⁰ and these patients could be treated with high-dose methotrexate in combination with high-dose cytarabine and then receive consolidation treatment with WBRT.

Primary CNS lymphoma remains a challenging disease and further trials are needed to provide information to further optimise the care of patients with this devastating illness. The use of drugs that penetrate the blood–brain barrier at increased doses seems to be the best approach. Patients responding to this therapy might further benefit from consolidation approaches, including autologous stem-cell transplantation or lower dose WBRT.

References

1. JE Olson et al. (2002) The continuing increase in the incidence of primary central nervous system non-Hodgkin lymphoma: a surveillance, epidemiology, and end results analysis. *Cancer* 95:1504–1510
2. GM Mead et al. (2000) A medical research council randomized trial in patients with primary cerebral non-Hodgkin lymphoma: cerebral radiotherapy with and without cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy. *Cancer* 89:1359–1370
3. DF Nelson et al. (1992) Non-Hodgkin's lymphoma of the brain: can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG): RTOG 8315. *Int J Radiat Oncol Biol Phys* 23:9–17
4. T Batchelor et al. (2003) Treatment of primary CNS lymphoma with methotrexate and deferred radiotherapy: a report of NABTT 96–07. *JCO* 21:1044–1049
5. GD Shah et al. (2007) Combined immunochemotherapy with reduced whole-brain radiotherapy for newly diagnosed primary CNS lymphoma. *JCO* 25:4730–4735
6. LE Abrey, LM DeAngelis, J Yahalom (1998) Long-term survival in primary CNS lymphoma. *JCO* 16:859–863
7. IT Gavrilovic, A Hormigo, J Yahalom et al. (2006) Long-term follow-up of high-dose methotrexate-based therapy with and without whole brain irradiation for newly diagnosed primary CNS lymphoma. *JCO* 24:4570–4574
8. LE Abrey et al. (2003) Intensive methotrexate and cytarabine followed by high-dose chemotherapy with autologous stem-cell rescue in patients with newly diagnosed primary CNS lymphoma: an intent-to-treat analysis. *JCO* 21:4151–4156
9. B Fisher et al. (2005) Secondary analysis of Radiation Therapy Oncology Group study (RTOG) 9310: an intergroup phase II combined modality treatment of primary central nervous system lymphoma. *J Neurooncol* 74:201–205
10. AJ Ferreri et al. (2009) High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial. *Lancet* 374:1512–1520

Practice point

The use of high-dose cytarabine in combination with high-dose methotrexate followed by whole-brain radiation therapy could be effective in younger patients with primary central nervous system lymphoma for whom autologous stem-cell transplantation is not planned.