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REVIEW ARTICLE

Primary central nervous system lymphoma: how to treat younger patients?

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Abstract

Primary central nervous system lymphoma (PCNSL) is a rare subtype of extranodal lymphoma which is associated with a relatively poor prognosis compared to other diffuse large B-cell lymphomas.

Population-based cancer registry data demonstrates that there has been a significant improvement in the survival of patients with PCNSL over the past two decades. This improvement likely reflects the introduction of high-intensity chemotherapy based on an induction regimen with high-dose methotrexate, and consolidation strategy including autologous stem cell transplantation. As a result, the improvement has been mainly observed in younger patients. New approaches such as Bruton tyrosine kinase inhibitor, immunomodulatory agents, immune checkpoint inhibition, and chimeric antigen receptor T-cell therapy are under investigation for PCNSL. In addition, trials combining novel agents in front-line induction treatment are ongoing.

Key words: primary central nervous system lymphoma, PCNSL, HD-MTX, methotrexate

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Introduction

Great progress has been made over the last 20 years in optimizing therapeutic platforms in primary central nervous system lymphoma (PCNSL), particularly in younger patients who can undergo optimal therapy based on an induction regimen and consolidation treatment.

In the context of optimal combination therapy, younger patients are usually defined as <65 years of age. In clinical practice, age, performance status (PS) and comorbidities are of fundamental importance for prognosis, as they all determine the possibilities of adequate therapy. Optimal induction treatment is possible in patients with PS 0–2/3, without significant age restrictions, but with adequate renal function (creatine clearance >50 mL/min) and heart ejection fraction, which will allow the administration of high-dose methotrexate (HD-MTX) and the use of adequate hydration (minimum 4–5 liters of infusion fluids per day).

The prognosis of younger patients with a worse general condition, which results directly from the presence of lymphoma, without significant disease burden (also those with a borderline creatine clearance, but ≥40 ml/min) should be carefully assessed, because the administration of HD-MTX can sometimes dramatically improve the patient's condition and kidney function. In this case, treatment can be started with lower doses of MTX and escalated in subsequent cycles of chemotherapy. Regardless of age, special attention should be paid to diabetic patients, in whom large fluctuations in glycemia can be expected and the risk of discovering renal failure is high. Performing optimal consolidation treatment is much more related to age, as high-dose chemotherapy with autologous stem cell transplantation (HD-ASCT) is usually proposed as safe for patients <60–65, while it is recommended to avoid radiotherapy in consolidation in patients >60 due to the risk of significant neurotoxicity [1–4].

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Induction treatment

The established standard in the treatment of PCNSL are multiagent regimens of chemotherapy based on the combination of HD-MTX with rituximab (an anti-CD20 monoclonal antibody). The optimal dose is MTX ≥3.5 g/m^2 in a rapid, 2–4-hour infusion, every 2–3 weeks (optimally every two weeks), repeated 4–8 times (optimally at least six cycles) [1, 2]. HD-MTX at a dose ≥3.5 g/m^2 achieves the therapeutic concentration in the cerebrospinal fluid (CSF), and therefore does not require additional drug administration by lumbar puncture. Methotrexate in lower doses, but >1 g/m^2, also penetrates the blood brain barrier (BBB), but does not reach the appropriate concentration in the CSF. In this case, additional intrathecal administration (12–15 mg it.) is recommended. HD-MTX is usually associated with rituximab (day 1 of the cycle) [1, 2]. It has been suggested to optimally use rituximab by administering the drug once a week, at the beginning of treatment (the first 6–8 weeks) i.e. in the period of the greatest damage to the BBB, which may favor better penetration for a large molecule such as anti-CD20 [5]. Rituximab (R) is currently included in most induction programs of chemotherapy, although there is still controversy about its role in the treatment of PCNSL [6–8]. The choice of other drugs in the regimens comes down to individual preferences and does not result from a direct comparison of regimens.

Currently, four induction regimens are considered to be equivalent: MATRix/IELSG-32 (R-HD-MTX, cytarabine, thiotepa) [9], R-MPV (R-HD-MTX, vincristine, procarbazine) [10, 11], MR-T (R-HD-MTX, temozolomide) [5] and R-MBVP (R-HD-MTX, etoposide, carmustine and prednisone) [12]. The expected remission rate (ORR) after induction treatment, as well as progression-free survival (PFS) and overall survival (OS) after consolidation, are in the range: 77–95% ORR, 2-year PFS 57–87% and 5-year OS 65–81% [5, 9–12]. The MATRix program was associated with a significant risk of grade 3 and 4 hematological toxicities. Based on real-world study data, the British Society of Hematology recommends for patients at higher risk (PS >2, age >65, significant comorbidities) a reduction of the cytarabine dose by 25% (with a possible 25% reduction in the dose of thiotepa), especially in the first cycle [13]. The R-MPV regimen is characterized by low toxicity and can be safely used in elderly patients or those in a worse general condition [10, 11]. The MT-R scheme with escalation of the MTX dose to 8 g/m^2/every two weeks, requires a dose reduction in 45% of cases [5].

In the opinion of most researchers, there are no rational grounds for escalating the MTX dose significantly >3.5 g/m^2. At the Department of Lymphoid Malignancies, Maria Skłodowska-Curie National Research Institute of Oncology in Warsaw, Poland, in cooperation with the Polish Adult Lymphoma Group (PALG), a program has been developed by the clinic team (R-MIV-AT), based on a combination of HD-MTX at dose of 3.5 g/m^2 every two weeks with ifosfamide at a dose of 1.5/0.8 g/m^2/days 3–5 (age-dependent dose) and vincristine 1.4 mg/m^2/day 1 (six cycles in total). Rituximab 375 mg/m^2 is administered once weekly at the initiation of therapy for a total of six administrations. The induction phase completes one cycle with cytarabine at a dose dependent on age, 2/1 g/m^2/bid/days 1–2 (four doses per cycle), in combination with thiotepa 30 mg/m^2/day 3. Then depending on risk groups, patients are qualified for the consolidation stage with HD-ASCT (thiotepa, BCNU, etoposide) or whole-brain radiation therapy (WBRT) at a dose of 36 Gy (partial remission or stable remission after induction) or 24 Gy (complete remission after induction).

Consolidation therapy

Consolidation is integral to optimal therapy. Despite the high effectiveness of induction treatment, it is unlikely that long-term remission will be maintained without consolidation treatment. The goal of consolidation is to significantly improve progression-free survival and delay the time to relapse through the eradication of minimal persistent disease (potential highly resistant cell clones). For this purpose, WBRT, HD-ASCT and non-myeloablative chemotherapy may be considered [4].

Radiotherapy

The role of radiotherapy is uncertain. Despite its high effectiveness, recurrences and progressions are very common and occur shortly after the end of therapy. A study to compare chemotherapy with consolidation of WBRT (45 Gy) to a chemotherapy-only arm (G-PCNSL-SG1 study) did not provide conclusive answers. The benefit of adding WBRT was only the effect on PFS, but not OS, while late neurotoxicity was observed in the WBRT arm [14–16]. Standard doses of radiation therapy (43–36 Gy) are associated with a significant risk of early neurotoxicity, including life-threatening leukoencephalopathy, but also of late-delayed neurotoxicity complications such as dementia, gait ataxia and urinary incontinence, which significantly impair patient quality of life. In a retrospective analysis of PCNSL patients treated with HD-MTX chemotherapy followed by WBRT (45–36 Gy), 24% developed symptoms of rapidly progressive subcortical dementia (RTOG 93–10 study) within five years of follow-up [17]. These observations are confirmed by a large meta-analysis [18], supporting the recommendation to avoid standard doses of WBRT in first-line treatment, especially in patients older than 60 [16–18]. The risk of significant neurotoxicity after WBRT has recently been confirmed by two large randomized trials, IELSG-32 (36 Gy) [9] and PRECIS (40 Gy) [12], in which WBRT vs. HD-ASCT were compared directly in the consolidation. The neurological

status of HD-ASCT patients was consistently improved, in contrast to WBRT patients who continued to develop and worsen neurotoxicity symptoms. Nevertheless, WBRT has been shown to be an effective method of consolidation and produces PFS and OS comparable to the ASCT arm (although significant relapse rates were observed in the PRECIS study in the WBRT arm) [9, 12].

Since the possibilities of safe HD-ASCT implementation concern a limited, selected group of patients, new ways of optimizing the use of WBRT are being investigated. One of these was hyperfractionated WBRT, but several years of observations confirmed that this technique did not reduce neurotoxicity, but only delayed its effect over time even in relatively young patients [19, 20].

More promising seems to be the possibility of using reduced doses of WBRT (rdWBRT). In a phase II study, after R-MPV induction treatment (5–7 cycles of chemotherapy), rdWBRT at a dose of 23.4 Gy (13 fractions at 180 cGy) was used as a consolidation, with impressive results: 2-year PFS of 77% and 5-year OS of 80%. At the same time, no increase in neurotoxicity was observed during the 4-year follow-up. These results represent some of the best results in terms of OS and safety, but apply to a very small group of PCNSL patients and should be treated with caution [11]. Results from RTOG 1114 are awaited and should answer the question of whether rdWBRT plays a significant role in the consolidation of R-MPV/cytarabine chemotherapy compared to the cytarabine-only consolidation arm. In other words, is it safe to eliminate the WBRT from first-line treatment?

In summary, it can be stated that the use of WBRT in consolidation gives a potential advantage over chemotherapy alone, but one must take into account significant neurotoxicity and, compared to HD-ASCT, worsening of PFS. Standard doses of WBRT are generally not recommended for first-line treatment, especially for those over 60. Currently, in consolidation for patients who are not candidates for HD-ASCT, WBRT 36 Gy (20 fractions) or preferred 23.4–24 Gy (180 or 200 cGy per fraction) may be considered.

High-dose chemotherapy with autologous stem cell transplantation

HD-ASCT is usually recommended for consideration as a consolidation for first-line treatment in all patients for whom it is potentially safe [1, 2, 4]. This indication is supported by the recent results of two large randomized trials comparing WBRT to HD-ASCT in consolidation treatment.

In the IELSG32 study, WBRT (36 Gy) was used in one of the arms, and in the other HD-ASCT (conditioning: thiotepa/TT and carmustine/BCNU). There was no difference between the arms in either progression-free survival (2-year PFS 80% vs. 69%, respectively) or overall survival (2-year OS 85% vs. 71%, respectively) [9]. However, a consequent improvement of neurological status observed in HD-ASCT as opposed to an increase in neurotoxicity in the WBRT arm, made HD-ASCT the first-choice method in consolidating PCNSL treatment for patients who qualify for this procedure [10].

In the similar PRECIS study (WBRT 40 Gy versus HDC-ASCT with TBC conditioning: thiotepa, busulfan, cyclophosphamide), a trend was observed in the HD-ASCT arm towards improvement of progression-free survival (2-year PFS 86.8% vs. 63.2%, respectively) without impact on overall survival (2-year OS 75% vs. 66%, respectively) [12]. It should be remembered that HD-ASCT is associated with a significant toxicity of treatment and may apply to a selected group of patients. Conditioning with TT-BCNU compared to TBC is associated with lower treatment-related toxicity (TRM 1–3% [9, 21] vs. 11% [10, 12], respectively), however the results of the meta-analysis indicate a higher efficiency of TBC conditioning, with the possibility of plateauing in long-term relapse-free survival (5-year PFS 81% vs. 46%, respectively) [22]. Although there is no strict age limit, patients <60 years are usually eligible for HD-ASCT, although the 60–70 age group may also benefit.

Non-myeloablative chemotherapy

Consolidation of non-myeloablative chemotherapy is usually considered in elderly patients who are not eligible for HD-ASCT and who want to avoid WBRT-related neurotoxicity, but also for younger unfit patients. HD-ASCT is likely superior to non-myeloablative chemotherapy, but no randomized studies are available. Two multicenter, randomized trials are currently underway to answer the question of whether non-myeloablative chemotherapy can be an effective alternative to HD-ASCT. In the CALGB 51101/NCT01511562 study, the EA scheme (etoposide 40 mg/kg/96 hour continuous infusion plus cytarabine 2 g/m^2/bid/4 days), and in the IELSG 43/NCT02531841 study, the R-DeVIC scheme (rituximab, dexamethasone, etoposide, ifosfamide and carboplatin) are being compared to TT-BCNU conditioning [1, 2, 4].

Recent advances in targeted therapy

The use of novel agents has so far been limited to patients with recurrent or refractory PCNSL. Agents targeting B-cell receptor (BCR) and Toll-like receptor (TLR), Bruton tyrosine kinase (BTK) inhibitors, PI3K/mTOR targeted agents, immunomodulatory drugs (IMiDs), checkpoint inhibitors, and CD19 CAR T-cells therapy, despite high response rates, have a relatively short duration of response. Two agents, ibrutinib (BTK inhibitor) and lenalidomide (IMiD), based on reliable data from several studies have been included in the NCCN Guidelines for consideration as salvage therapies. Better outcomes are expected as a result of incorporating new agents into combination therapy, including chemotherapy.

The TEDDi-R regimen was the first to combine a novel agent with chemotherapy in PCNSL, but with high frequency of treatment-related adverse events [23], However, a combination of ibrutinib with HD-MTX ±rituximab in another study proved to be effective and safe [24].

In addition, trials combining novel agents in front-line treatment are ongoing. The LOC-R01 study is of particular interest here. The objective of this randomized phase II study is to improve first-line induction chemotherapy by combining either ibrutinib or lenalidomide with a conventional immuno-chemotherapy of R-MPV (R-HD-MTX, procarbazine, vincristine) [NCT04446962].

Author's contributions

BO — sole author.

Conflict of interest

None.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

References

1. Graham MS, DeAngelis LM. Improving outcomes in primary CNS lymphoma. Best Pract Res Clin Haematol. 2018; 31(3): 262–269, doi: 10.1016/j.beha.2018.07.006, indexed in Pubmed: 30213395.
2. Holdhoff M, Mrugala MM, Grommes C, et al. Challenges in the treatment of newly diagnosed and recurrent primary central nervous system lymphoma. J Natl Compr Canc Netw. 2020; 18(11): 1571–1578, doi: 10.6004/jnccn.2020.7667, indexed in Pubmed: 33152700.
3. Abrey LE, Ben-Porat L, Panageas KS. Primary central nervous system lymphoma: the Memorial Sloan-Kettering Cancer Center prognostic model. J Clin Oncol. 2006; 24(36): 5711–5715, doi: 10.1200/JCO.2006.08.2941, indexed in Pubmed: 17116938.
4. Kim P, Omuro A. Consolidation therapy in primary central nervous system lymphoma. Curr Treat Options Oncol. 2020; 21(9): 74, doi: 10.1007/s11864-020-00758-4, indexed in Pubmed: 32725379.
5. Rubenstein JL, Hsi ED, Johnson JL, et al. Intensive chemotherapy and immunotherapy in patients with newly diagnosed primary CNS lymphoma: CALGB 50202 (Alliance 50202). J Clin Oncol. 2013; 31(25): 3061–3068, doi: 10.1200/JCO.2012.46.9957, indexed in Pubmed: 23569323.
6. Bromberg JEC, Issa S, Bakunina K, et al. Rituximab in patients with primary CNS lymphoma (HOVON 105/ALLG NHL 24): a randomised, open-label, phase 3 intergroup study. Lancet Oncol. 2019; 20(2): 216–228, doi: 10.1016/S1470-2045(18)30747-2, indexed in Pubmed: 30630772.
7. Schmitt AM, Herbrand AK, Fox CP, et al. Rituximab in primary central nervous system lymphoma — a systematic review and meta-analysis. Hematol Oncol. 2019; 37(5): 548–557, doi: 10.1002/hon.2666, indexed in Pubmed: 31418878.
8. Van Dijck R, Doorduijn JK, Bromberg JEC. The role of rituximab in the treatment of primary central nervous system lymphoma. Cancers (Basel). 2021; 13(8), doi: 10.3390/cancers13081920, indexed in Pubmed: 33923396.
9. Ferreri AJM, Cwynarski K, Pulczynski E, et al. International Extranodal Lymphoma Study Group (IELSG). Whole-brain radiotherapy or autologous stem-cell transplantation as consolidation strategies after high-dose methotrexate-based chemoimmunotherapy in patients with primary CNS lymphoma: results of the second randomisation of the International Extranodal Lymphoma Study Group-32 phase 2 trial. Lancet Haematol. 2017; 4(11): e510–e523, doi: 10.1016/S2352-3026(17)30174-6, indexed in Pubmed: 29054815.
10. Omuro A, Correa DD, DeAngelis LM, et al. R-MPV followed by high-dose chemotherapy with TBC and autologous stem-cell transplant for newly diagnosed primary CNS lymphoma. Blood. 2015; 125(9): 1403–1410, doi: 10.1182/blood-2014-10-604561, indexed in Pubmed: 25568347.
11. Morris PG, Correa DD, Yahalom J, et al. Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: final results and long-term outcome. J Clin Oncol. 2013; 31(31): 3971–3979, doi: 10.1200/JCO.2013.50.4910, indexed in Pubmed: 24101038.
12. Houillier C, Soussain C, Ghesquières H, et al. Intergroupe GOELAMS–ANOCEF and the LOC Network for CNS Lymphoma. Recurrent mutations of MYD88 and TBL1XR1 in primary central nervous system lymphomas. Clin Cancer Res. 2012; 18(19): 5203–5211, doi: 10.1158/1078-0432.CCR-12-0845, indexed in Pubmed: 22837180.
13. Fox CP, Phillips EH, Smith J, et al. British Society for Haematology. Guidelines for the diagnosis and management of primary central nervous system diffuse large B-cell lymphoma. Br J Haematol. 2019; 184(3): 348–363, doi: 10.1111/bjh.15661, indexed in Pubmed: 30467845.
14. Thiel E, Korfel A, Martus P, et al. High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial. Lancet Oncol. 2010; 11(11): 1036–1047, doi: 10.1016/S1470-2045(10)70229-1, indexed in Pubmed: 20970380.
15. Korfel A, Thiel E, Martus P, et al. Randomized phase III study of whole-brain radiotherapy for primary CNS lymphoma. Neurology. 2015; 84(12): 1242–1248, doi: 10.1212/wnl.0000000000001395.
16. Herrlinger U, Schäfer N, Fimmers R, et al. Early whole brain radiotherapy in primary CNS lymphoma: negative impact on quality of life in the randomized G-PCNSL-SG1 trial. J Cancer Res Clin Oncol. 2017; 143(9): 1815–1821, doi: 10.1007/s00432-017-2423-5, indexed in Pubmed: 28434043.
17. Omuro AMP, Ben-Porat LS, Panageas KS, et al. Delayed neurotoxicity in primary central nervous system lymphoma. Arch Neurol. 2005; 62(10): 1595–1600, doi: 10.1001/archneur.62.10.1595, indexed in Pubmed: 16216945.
18. Kasenda B, Ferreri AJM, Marturano E, et al. First-line treatment and outcome of elderly patients with primary central nervous system lymphoma (PCNSL) — a systematic review and individual patient data meta-analysis. Ann Oncol. 2015; 26(7): 1305–1313, doi: 10.1093/annonc/mdv076, indexed in Pubmed: 25701456.

19. Glass J, Won M, Schultz CJ, et al. Phase I and II study of induction chemotherapy with methotrexate, rituximab, and temozolomide, followed by whole-brain radiotherapy and postirradiation temozolomide for primary CNS lymphoma: NRG Oncology RTOG 0227. J Clin Oncol. 2016; 34(14): 1620–1625, doi: 10.1200/JCO.2015.64.8634, indexed in Pubmed: 27022122.
20. Fisher B, Seiferheld W, Schultz C, et al. 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. 2005; 74(2): 201–205, doi: 10.1007/s11060-004-6596-9, indexed in Pubmed: 16193393.
21. Illerhaus G, Kasenda B, Ihorst G, et al. High-dose chemotherapy with autologous haemopoietic stem cell transplantation for newly diagnosed primary CNS lymphoma: a prospective, single-arm, phase 2 trial. Lancet Haematol. 2016; 3(8): e388–e397, doi: 10.1016/S2352-3026(16)30050-3, indexed in Pubmed: 27476790.
22. Alnahhas I, Jawish M, Alsawas M, et al. Autologous stem-cell transplantation for primary central nervous system lymphoma: systematic review and meta-analysis. Clin Lymphoma Myeloma Leuk. 2019; 19(3): e129–e141, doi: 10.1016/j.clml.2018.11.018, indexed in Pubmed: 30584023.
23. Lionakis MS, Dunleavy K, Roschewski M, et al. Inhibition of B cell receptor signaling by ibrutinib in primary CNS lymphoma. Cancer Cell. 2017; 31(6): 833–843.e5, doi: 10.1016/j.ccell.2017.04.012, indexed in Pubmed: 28552327.
24. Grommes C, Tang SS, Wolfe J, et al. Phase 1b trial of an ibrutinib-based combination therapy in recurrent/refractory CNS lymphoma. Blood. 2019; 133(5): 436–445, doi: 10.1182/blood-2018-09-875732, indexed in Pubmed: 30567753.