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Consolidation Therapy in Primary CNS Lymphoma: Current Evidence and Emerging Approaches

Chelsea Peterson DO[1] and Yazan Samhouri MD[1]

[1] Division of Hematology and Cellular Therapy, Allegheny Health Network Cancer Institute, Pittsburgh PA

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ABSTRACT

Primary Central Nervous System (PCNS) Lymphoma is an aggressive subtype of Large B-Cell Lymphoma (LBCL) present solely in the central nervous system and is identified as its own entity as of the 2017 WHO Classification of Lymphoid Tumors. The disease has a predilection for immunosuppressed individuals, but has also been seen in immunocompetent individuals with no identifiable risk factors. The treatment strategy for PCNSL is continuously evolving and is entirely different from systemic LBCL. This is especially true for consolidation, with conventional methods including high dose chemotherapy followed by autologous stem cell transplant (HDC-ASCT), whole brain radiation therapy (WBRT), or non-myeloablative chemoimmunotherapy (NMC). We aim to summarize the available literature supporting different consolidation strategies for primary CNS lymphoma. We performed a literature search using PubMed and the current clinical guidelines including ESMO and ASCO as a reference. The primary objectives and results of the trials as well as trial design are summarized per method of consolidation. The results generally favor either ASCT or WBRT as opposed to NMC for consolidation given proven OS and PFS benefits compared to chemotherapy alone. There does not appear to be a significant survival difference between ASCT and WBRT. The caveat is that selection criteria for transplant tend to exclude a portion of patients due to age and comorbidities. When compared with stem cell therapy and chemotherapy, WBRT has been shown multiple times to result in increased neurotoxicity. In conclusion, the ideal consolidation strategy remains controversial owing to the unique toxicities, benefits, and selection criteria associated with each strategy. Ongoing studies will provide insight into potential new consolidation methods.

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Introduction

Primary CNS lymphoma (PCNSL) is a type of non-Hodgkin's lymphoma which is strictly extranodal and presents only within the brain, spinal cord, leptomeninges, or eyes[1]. It accounts for 4-6% of all extranodal lymphomas, with a predilection for males and increasing incidence with age. Although the disease often arises in the setting of immunodeficiency (HIV, organ transplant recipients on immunosuppression), the disease can also arise in immunocompetent hosts and often portends a better prognosis in these cases. The median age of diagnosis in immunocompetent hosts is 68 years. Typical presentation for PCNSL varies and includes alterations in neurologic function as well as neuropsychiatric symptoms. B symptoms are rare in the presentation of PCNSL. The disease is often multifocal, making it even more difficult to treat. Histopathologically, the majority of primary CNS lymphomas are of the large B-cell type with over 90% being activated-B cell subtype[1]. The lesions are often infiltrative in nature and may involve the leptomeninges in up to 30% of cases, ocular involvement in 10-20% of cases, and rarely the spinal cord.

Induction strategies for PCNSL have been previously established and take into account the patient's baseline performance status, organ function, and age in order to determine which regimen to use. These regimens differ from those used in systemic DLBCL due to the poor blood brain barrier (BBB) penetration of the CHOP or CHOP-like regimens. High-dose methotrexate (HD-MTX) at a dose of at least $3g/m^2$ is recommended to be incorporated given its ability to penetrate the BBB and attain therapeutic levels in the CSF[2]. Based on this finding, HD-MTX combinations have now become standard of care for induction[3–5]. Despite improving response rates with HD-MTX combination regimens, with complete response rate (CRR) up to 46% as well as 3-year overall survival (OS) of 46% with the MATRix regimen, these patients still face about a 50% chance of relapse in the first two years[6]. The median time to relapse is 10-18 months with 10-15% of patients being primary refractory to high dose methotrexate induction. Unfortunately, prognosis of relapsed/refractory disease is poor with estimated OS of only 3.7 months for relapsed disease[7].

Beyond induction therapy, consolidation is now standard of care to reduce the risk of recurrence as well as treat any residual disease not seen on imaging[2]. A French oculo-cerebral lymphoma network (LOC) database study was published in 2020 and identified >1000 patients newly diagnosed with PCNSL from 2011-2016 to assess the trends in treatment and outcomes associated. They found that of the study population only 21% received consolidation therapy (6% HDC-ASCT, 15% WBRT) which was associated with an improvement in ORR from 59% following induction to 92% in those receiving consolidation[8]. Most of the patients who received consolidation were <60 years old. Patients who received consolidation experienced a significant improvement in PFS ($p<0.001$) and OS ($p=0.004$). Consolidation can be achieved by means of whole brain radiotherapy (WBRT), non-myeloablative chemoimmunotherapy (NMC), or high dose chemotherapy and autologous stem cell transplant (HDC-ASCT). Unfortunately, there have not been many large, randomized trials to determine the ideal consolidation strategy leaving the oncologist and the patient to weigh the risks and benefits of the available options without strong evidence. The aim of this article is to gather the most recent and relevant data regarding consolidation strategies alone and in comparison, with each other, and review the potential risks and benefits of each option.

Randomized clinical trials

STEM CELL TRANSPLANT VS. WHOLE BRAIN RADIATION THERAPY

The PRECIS trial was published in 2022 and compared ASCT to WBRT for immunocompetent patients <60yrs old with newly diagnosed CNS lymphoma. Between 2008 and 2014, patients were randomized to receive either 40Gy whole brain radiation or high dose chemotherapy followed by ASCT following completion of induction chemotherapy. The high dose chemotherapy regimen used in this trial consisted of thiotepa, busulfan, and cyclophosphamide[9]. A total of 53 patients completed the prespecified WBRT treatment, and 44 completed the HDC-ASCT treatment. At a median follow-up of 8 years the authors found a significantly lower risk of relapse in the ASCT arm (HR 0.13, $P<0.001$), as well as a higher 8-year EFS of 67% in the ASCT arm (95% CI 55-83) compared to 39% in the WBRT arm (95%CI 27-57) with a p-value of 0.03. There was no overall survival difference between the two groups at the 8-year follow-up. With regards to adverse events, there was a significant decline in neurocognitive function in the WBRT group compared to the ASCT group. There were two secondary malignancies that arose within the ASCT group (colon adenocarcinoma, lung cancer in a heavy smoker).

The IELSG32 Trial was a multicenter randomized phase 2 trial with two randomizations: once at induction and again for consolidation[4]. The induction arm aimed to assess the safety and efficacy of the MATRix regimen (high dose methotrexate, cytarabine, thiotepa, rituximab) by randomizing patients to receive methotrexate/cytarabine,methotrexate/cytarabine/rituximab,or methotrexate/cytarabine/thiotepa/rituximab for induction treatment. Patients with disease response or stable disease were then randomized to receive either WBRT or HDC-ASCT for consolidation. Patients with underlying immunosuppression, history of organ transplant, or HIV were excluded from this trial. There were 118 patients included in the second randomization, with 59 in each group. Patients in the HDC-ASCT group received carmustine and thiotepa prior to stem cell infusion. Patients in the WBRT arm received 36Gy whole brain radiation with a 9Gy boost to the tumor bed for those with partial response. The PFS was found to be similar in both consolidation groups with a 7-year PFS of 55% in the WBRT arm vs 50% in the ASCT arm (HR 1.15; 95% CI 0.78-1.68; $p=0.46$). Seven-year OS was also similar between consolidation arms at 63% for the WBRT arm and 57% for the ASCT arm (HR 1.25; 95% CI 0.84-1.88; $p=0.26$).

STEM CELL THERAPY VS. NON-MYELOABLATIVE CHEMOTHERAPY

An initial report on the IELSG43 trial published in 2022 compared myeloablative consolidation followed by ASCT versus nonmyeloablative chemoimmunotherapy consolidation with a primary endpoint of PFS. All patients received 4 cycles of MATRix chemoimmunotherapy induction, then if PR was achieved, they were randomized to either receive 2 cycles of rituximab, dexamethasone, etoposide, ifosfamide, carboplatin (R-DeVIC) or to HDC consisting of carmustine and thiotepa followed by ASCT. The 3-year interim analysis revealed comparable toxicity between both arms, however, a significant difference in PFS was observed with a 79% (95% CI 71-86) PFS after ASCT vs 53% (95% CI 43-62) in the R-DeVIC arm (HR 0.42, p=0.0003). 3-year OS was also significantly higher in the ASCT arm at 86% (95% CI 78-91) vs 71% (95% CI 61-78) in the R-DeVIC arm (HR 0.47; p=0.01)[10].

Results of the ALLIANCE 51101 Trial published in June 2024 compared a different chemoimmunotherapy consolidation technique to ASCT. In this phase II randomized trial, patients in both arms received induction therapy with rituximab, methotrexate, temozolomide, and cytarabine and then proceeded to consolidation with either HDC-ASCT using carmustine/thiotepa or etoposide plus cytarabine if they attained at least stable disease with induction. Median PFS was found to be 6 years in the myeloablative group compared to 2.4 years in the non-myeloablative group with an HR of 0.51 (95% CI, 0.29-0.90; P=0.02). Interestingly, prior to receiving consolidation in this trial 11% of patients in the myeloablative group and 28% in the nonmyeloablative group went off protocol for various reasons despite receiving the same induction regimen. For this reason, a secondary analysis was performed for patients who completed consolidation and revealed an estimated 2-year PFS rate of 86% (95% CI 69-94) in the myeloablative arm vs 71% (95% CI 52-83) in the nonmyeloablative arm, although not statistically significant (HR 0.58; 95% CI 0.25-1.36; P=0.21). At median follow-up of 4.1 years, there was no difference in OS between the two arms (HR 0.60; 95% CI 0.27-1.31; P=0.19). Toxicities were comparable between the two consolidation arms, with the most common grade ≥ 3 adverse events being hematologic (thrombocytopenia, neutropenia, anemia) occurring in 92% of the myeloablative patients and 94% of the nonmyeloablative patients[11].

Single modality studies, database reviews, and retrospective studies

HIGH DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANT

The role for high dose chemotherapy followed by autologous stem cell rescue has been well established for consolidation of CNS lymphoma. Historically regimens used for conditioning in non-Hodgkin's lymphoma were found to be ineffective. A few small, prospective single arm studies found significant PFS and OS benefits when thiotepa was incorporated into the conditioning regimen[5,12].

The MARTA trial, published in January 2024 was a single arm prospective study which investigated the use of HDC-ASCT in patients >65 years[13]. In this trial patients received two cycles of induction chemoimmunotherapy (HD-MTX, Ara-C, Rituximab) followed by high dose busulfan and thiotepa with stem cell rescue. The 12-month PFS was 58.5% (95% CI 44.1-70.9) with the most common adverse event being leukopenia. Three out of 54 patients died due to infectious complications. The median age was 71 years (68-75), demonstrating the feasibility of HDC-ASCT in select elderly patients with PCNSL.

A database study published in 2022 assessed outcomes of patients who underwent either WBRT or ASCT for consolidation between the years of 2004-2015 using the National Cancer Database (NCDB). In this study 1620 patients were included in the analysis and at a median follow-up of 68.4 months the median OS was 91.4 months in the WBRT vs not reached in the ASCT group (p<0.001). Five-year OS was found to be significantly higher in the transplant group compared to the WBRT group with rates of 74.4% vs 58.7% respectively (HR 0.40, 95% CI 0.27-0.60; p<0.01). The authors also found a trend in increasing use of ASCT over time with an annual percentage change of 23%[14].

In another retrospective study published in December 2024 looking at trends of consolidation amongst patients with PCNSL, the most commonly used consolidation method was non-myeloablative chemotherapy. This was an institutional database study of patients diagnosed with PCNSL from 1983-2020, and of the 385 patients that underwent consolidation, 43% received NMC, followed by 21% receiving ASCT. This study, however, also revealed a changing pattern in consolidation methods with a decrease in the use of WBRT while ASCT and NMC use was increasing (p<0.001). Furthermore, when clinical outcomes were assessed based on consolidation method the authors found a significant increase in PFS in patients that received ASCT (HR 0.37; 95% CI 0.23-0.60; p<0.001) and reduced-dose WBRT (HR 0.52; 95% CI 0.35-0.79; p=0.002) compared to NMC. On multivariate analysis, there was no significant PFS associated with any specific mode of consolidation, but rather the receipt of consolidative therapy itself was associated with a PFS and OS benefit (p<0.001)[15].

WHOLE BRAIN RADIOTHERAPY

Initial data supporting the use of WBRT was published in 2010[16]. This was a German study designed to demonstrate non-inferiority of methotrexate based chemotherapy alone compared to methotrexate based chemotherapy followed by WBRT for consolidation with regards to overall survival. Patients in this trial received induction HD-MTX + ifosfamide followed by either 45Gy whole brain radiation divided into 30 fractions vs no radiation. Of note, patients that were allocated to the chemotherapy alone group did receive high dose cytarabine if they did not achieve a CR with induction. The German PCNSL Study Group found that their hypothesis could not be proven, and could not demonstrate non-inferiority with the omission of WBRT. Patients who underwent WBRT were found to have an OS of 32.4 months (95% CI 25.8-39.0) vs 37.1 months (95% CI 27.5-46.7) in those who did not undergo WBRT (HR 1.06; 95% CI 0.80-1.40; p=0.71). PFS with the inclusion of WBRT was found to be 18.3 months vs 11.9 months in the group that did not receive WBRT (p=0.14). There was

also a notable increase in neurotoxicity in patients who received whole brain radiation, with 49% of patients in the WBRT group experiencing neurotoxicity by clinical assessment compared to 26% in the patients that did not receive WBRT.

This noted increase in neurotoxicity with the aforementioned dosing of WBRT led to the RTOG1114 trial which compared the use of low dose WBRT vs no WBRT following induction chemotherapy. This study differed in that the chemotherapy regimen used was HD-MTX, procarbazine, vincristine, and cytarabine (R-MVP-A). Additionally, the dose of radiation used was much lower at 23.4Gy over 13 fractions. Preliminary data from this trial presented at the ASCO 2020 Annual Meeting revealed that at a median follow-up of 55 months PFS was improved in patients who received WBRT compared to those who did not (not reached vs 25 months; HR 0.51, 95% CI 0.27-0.95; p=0.015). Median OS had not yet been reached in either arm at the time of initial analysis, with no available updates as of the writing of this manuscript. Interestingly, neurotoxicity was not significantly different between the two arms (11.4% chemo vs 14% chemoRT; p=0.75)[17].

A prospective observational cohort study published in 2016 aimed to assess the benefit of adding gamma knife radiosurgery (GKRS) after completion of HDMTX induction. Patients in this study received single agent methotrexate at a dose of 8g/m2. The investigators identified 128 patients from 2007-2012 that were treated with chemotherapy alone (N=73) or chemotherapy plus GKRS (N=55). The median GKRS dose was 11Gy (11-16Gy). Median overall survival was significantly higher in the chemotherapy plus GKRS group at 47.6 months vs 26.8 months in the chemotherapy alone group (p=0.0034). There were only minimal side effects reported in the patients who received GKRS[18].

NON-MYELOABLATIVE CHEMOTHERAPY

In a phase II trial published in 2013, consolidative chemotherapy after induction chemoimmunotherapy was studied to evaluate the feasibility of high-dose consolidation chemotherapy as well to determine the PFS. In this study, 44 patients with newly diagnosed primary CNS lymphoma were treated initially with a regimen of high dose methotrexate, temozolomide, and rituximab. If they achieved a CR, they then proceeded to consolidation with etoposide and high dose cytarabine. Results from this trial revealed a CR rate of 66% with the MT-R regimen, and a 2-year PFS of 0.77 for those who then went on to receive the consolidation regimen as well. Median PFS was 2.4 years with a median OS that had not yet been reached at time of publication. The median TTP in the study population was 4 years. The main toxicities patients experienced included grade 4 neutropenia in 50% of patients with 81% of those events occurring during consolidation and one episode of death due to sepsis in a patient receiving consolidation[19].

Future Directions:

ONGOING STUDIES

The CREMA trial, taking place in Korea (NCT03569995) is set to complete in June 2025 and is evaluating the use of rituximab plus HDMTX followed by rituximab plus high dose cytarabine for elderly patients with PCNSL. Patients in this trial have to be >age 60 years and unfit for ASCT. Another trial currently undergoing at Wake Forest University (NCT04022980) is evaluating nivolumab consolidation for patients ≥65 years after receiving HDMTX based induction therapy.

With the expanding use and application of adoptive cell therapies this may also become of clinical significance in the treatment of PCNSL. A report from the French LOC published in *Blood* in 2022 reviews a retrospectively identified cohort of patients with relapsed/refractory (median prior lines of therapy=3) PCNSL who received either axicabtagene ciloleucel or tisagenlecleucel. Nine patients were identified in their study (7=tisa-cel; 2=axi-cel), with a median PFS of 122 days. Six month OS was 89% and 6-month PFS was 44%. Seven out of 9 patients (78%) experienced any-grade CRS, with only one grade 3 event. Five out of 9 patients (56%) experienced any-grade ICANS with one grade 3 and one grade 4. This data supports the use of commercial CD19 CAR T-cells in relapsed/refractory PCNSL with an acceptable toxicity profile, however, further studies with large numbers of patients are needed to verify this practice[21].

A trial recently completed at Massachusetts General Hospital (NCT04134117) enrolled 6 patients to receive tisagenlecleucel for the treatment of PCNSL. The inclusion criteria for this trial were patients ≥60 years old who were either unable to tolerate HDMTX induction, or failed to achieve a CR after two cycles of induction. A separate cohort included patients ≥18 years of age who had relapsed/refractory PCNSL after at least one line of prior therapy. The results of this trial have not yet been published. Another phase I study (NCT05625594) is beginning to investigate the safety and efficacy of intraventricularly administered CD19 directed CAR-T cells. To be eligible for this study, patients have to have failed/not tolerated HDMTX or high dose cytarabine.

MAINTENANCE THERAPY

Given that the rising incidence of PCNSL is particularly relevant to the elderly population, with a median age of diagnosis at 68 years, some clinicians have even adopted a maintenance strategy. The BLOCAGE-01 trial and the FIORELLA trial are ongoing clinical trials looking at maintenance strategies in elderly patients with PCNSL. The BLOCAGE-01 (NCT02313389) trial is evaluating the outcomes of elderly patients treated with rituximab, HD-MTX, and temozolomide maintenance compared to observation in patients that achieve a CR with HD-MTX based induction. The FIORELLA trial (NCT03495960) will compare maintenance procarbazine vs lenalidomide in elderly patients with response to induction chemoimmunotherapy. An ongoing phase II trial (NCT06175000) is randomizing patients of all ages with CR or PR after induction therapy to either receive maintenance obinutuzumab vs observation.

Conclusion

Overall, the management of PCNSL post-induction remains a field of active investigation with multiple acceptable approaches. Although WBRT historically was

widely used for consolidation, it appears that this approach is falling out of favor particularly for patients suitable for HDC-ASCT. This is likely due to the decreased long-term neurotoxicity since there has not been a proven OS benefit with one approach or the other. Non-myeloablative chemotherapy has been studied with mixed results when compared to myeloablative HDC-ASCT but data shows it is the least efficient approach. There are ongoing studies looking into different methods of consolidation including immunotherapy, chemoimmunotherapy, and even CAR-T cell therapy.

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Table 1: Summary of Clinical Trials and Studies for Consolidation of PCNSL

Author	Date Published	Comparison Arm? Y/N	Study Arms	Outcome	Notes
Thiel et al[16]	2010	Y	WBRT 45Gy vs no-WBRT	OS 32.4 months vs 37.1 months (HR 1.06; 95% CI 0.8-1.4; p=0.71)	Increased neurotoxicity with WBRT
Rubenstein et al[19]	2013	N	Etoposide + high dose cytarabine	2-year PFS 0.77 (0.56-0.89); median TTP 4 years	
Ferreri et al[4]	2016	Y	WBRT 36Gy ±9Gy boost vs HDC-ASCT	7-year PFS 55% vs 50% (HR 1.15; 95% CI 0.78-1.68;p=0.46)	
Omuro et al[17]	2020	Y	Low dose WBRT 23.4Gy vs no-WBRT	PFS NR vs 25 months (HR 0.51; 95% CI 0.27-0.95; p=0.015)	No significant increase in neurotoxicity
Houillier et al[9]	2022	Y	WBRT 40Gy vs HDC-ASCT	EFS 39% vs 67% (p=0.03)	
Samhouri et al[14]	2022	Y	WBRT vs ASCT	5-year OS 58.7% vs 74.4% (HR 0.4; 95% CI 0.27-0.6; p<0.01)	NCDB database study
Illerhaus et al[10]	2022	Y	R-DeVIC vs HDC-ASCT	PFS 53% vs 79% (HR 0.42; p=0.0003) OS 71% vs 86% (HR 0.47; p=0.01)	
Alcantara et al[21]	2022	N	CD19 CAR-T	Median PFS 122 days; 6-month OS 89%, 6-month PFS 44%	
Schorb et al[13]	2024	N	HDC-ASCT	12-month PFS 58.5% (95% CI 44.1-70.9)	Median age 71 years
Batchelor et al[11]	2024	Y	HDC-ASCT vs etoposide + cytarabine	2-year PFS 86% vs 71% (HR 0.58; 95% CI 0.25-1.36; p=0.21)	
Tringale et al[15]	2024	N	HDC-ASCT, WBRT, NMC	No PFS benefit with one mode of consolidation over others	Retrospective review
Kim et al	Ongoing	N	Rituximab + high dose cytarabine	—-	NCT03569995
Park et al	Ongoing	N	Nivolumab	—-	NCT04022980
Frigault et al	Ongoing	N	Tisagenlecleucel	—-	NCT04134117
Siddiqi et al	Ongoing	N	Intraventricular CD19 CAR-T	—-	NCT05625594

Table 1 summarizes the data discussed in this paper. Maintenance therapy is now coming into question for patients not eligible for consolidation especially with the availability of targeted therapies which are typically well tolerated for extended periods of time. Further studies are needed to determine what role- if any- maintenance therapy will play in the treatment of PCNSL compared to a more definitive consolidation approach or even post consolidation.

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