



HHS Public Access

Author manuscript

Ann Lymphoma. Author manuscript; available in PMC 2022 January 31.

Published in final edited form as:

Ann Lymphoma. 2021 September ; 5: . doi:10.21037/aol-20-43.

Primary central nervous system lymphoma in older adults and the rationale for maintenance strategies: a narrative review

Mazie Tsang¹, James L. Rubenstein^{1,2}, Elisa Jacobsen Pulczynski³

¹Division of Hematology and Oncology, University of California San Francisco (UCSF), San Francisco, CA, USA

²Helen Diller Family Comprehensive Cancer Center, UCSF, San Francisco, CA, USA

³Nordic and Danish Lymphoma Group, Holstebro Region Hospital, Holstebro, Denmark

Abstract

Objective: To provide a summary and analysis of the evidence for various agents applied as maintenance therapy and highlight ongoing trials or trials in development that evaluate the efficacy of maintenance therapy strategies in older patients with primary central nervous system lymphoma (PCNSL).

Background: PCNSL are rare neoplasms that can have an aggressive course with short-lived remissions when compared to systemic diffuse large B-cell lymphoma (DLBCL). There is currently a paucity of evidence on treatment in older adults with PCNSL, who may be unfit to tolerate effective therapies for PCNSL. Those who can tolerate these therapies and survive PCNSL are at increased risk from developing treatment-related toxicity, functional decline, and debilitating neurotoxicity. While there is no clearly defined role for maintenance therapy after treatment of systemic DLBCL, it should be considered in PCNSL because central nervous system (CNS) recurrence often has a devastating and irreversible impact on neurologic function. Therefore, at

This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

Correspondence to: Mazie Tsang, MD, MS. Division of Hematology and Oncology, Department of Medicine, University of California San Francisco, 505 Parnassus Avenue, Room M1286, Mailbox 1270, San Francisco, CA 94143-1270, USA. mazie.tsang@ucsf.edu.

Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/aol-20-43>). The series “Central Nervous System Lymphomas” was commissioned by the editorial office without any funding or sponsorship. MT is on a National Institute of Health/National Institute on Aging T32 training grant, which supports her salary. Dr. MT also received \$1,000 from Curio Science for participating in two workshops on oncology topics and recently purchased individual pharmaceutical stocks from AVEO and Poseida. JLR, MD, PhD receives research funding from and serves on advisory board for Kymera, received payments per lecture on Lymphoma 2019, and has a patent for anti-resistance lymphoma gene MONOCLONAL ANTIBODY. EJP received research funding from Roche. The authors have no other conflicts of interest to declare.

Provenance and Peer Review: This article was commissioned by the Guest Editors (Andrés J. M. Ferreri, Maurilio Ponzoni) for the series “Central Nervous System Lymphomas” published in *Annals of Lymphoma*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at <https://dx.doi.org/10.21037/aol-20-43>

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

least theoretically, use of effective maintenance therapy in older adults with PCNSL, either in lieu of consolidation or after consolidation therapy, may be better tolerated and help delay tumor progression, resulting in an improved overall global neurologic function and quality of life.

Methods: We systematically searched MEDLINE (via PubMed) for all studies of drug treatments for maintenance therapy in PCNSL and also relied on expert opinion. We provide a summary and analysis of the evidence for various maintenance therapy agents, including methotrexate, rituximab, lenalidomide, temozolomide, ibrutinib, and procarbazine. We also highlight ongoing trials or trials in development that evaluate the efficacy of maintenance therapy in PCNSL.

Conclusions: Prospective clinical studies focusing on PCNSL patients who are not candidates for intensive post-induction therapy are scarce. To date, there are no studies that clarify whether maintenance therapy can be used in lieu of consolidation therapy with autologous stem cell transplant or radiation. Prospective studies may provide critical data regarding the identification of optimal agents, whether consolidation therapy could be replaced by maintenance therapy, and the overall role of maintenance therapy as a means to potentially improve survival and preserve quality of life and function in a vulnerable, older patient population.

Keywords

Primary central nervous system lymphoma (PCNSL); maintenance therapy; older adults; review

Introduction

Evidence for improvements in survival in primary central nervous system lymphoma (PCNSL) that have been achieved during recent decades appears to be restricted to younger patients. At least 50–68% of patients with newly-diagnosed PCNSL, however, are aged 60 or older; the incidence of PCNSL continues to rise in this older age group (1–3). The median overall survival (OS) for PCNSL patients aged 70 years has not improved in over 40 years: OS was 6 months in the 1970's vs. 7 months in the 2010's (4). While older patients tolerate and benefit from high-dose methotrexate (HD-MTX)-based induction chemotherapy, dose-intensive chemotherapy consolidation is not an option for many older patients. Moreover, whole-brain radiotherapy (WBRT) is strongly associated with radiation-induced encephalopathy syndrome in patients age older than 60, characterized by progressive memory loss, apathy, gait impairment and incontinence (5). Outcomes in older PCNSL treated with methotrexate-based induction without consolidation are suboptimal, with median OS of approximately 14–30 months (6). Defining a consolidation regimen for this vulnerable patient group is of significant importance.

Increased attention has recently been drawn to the maintenance treatment strategies in older adults with PCNSL, especially in those who cannot tolerate consolidation therapy. Maintenance treatment is defined as treatment that is designed to prolong the response achieved through induction and to prevent relapse. Agents used as maintenance treatment in recent studies include HD-MTX, rituximab, temozolomide (TMZ), procarbazine, lenalidomide, and ibrutinib. In some of these studies, the maintenance agent was applied in the induction therapy as well (7–12), whereas in other studies an agent not previously used was chosen as the maintenance drug (13,14).

There is no clearly defined role for maintenance therapy after standard induction treatment of systemic diffuse large B-cell lymphoma (DLBCL) or PCNSL. While agents such as lenalidomide and rituximab may delay progression after standard therapy when used as maintenance, these agents do not enhance OS in advanced stage DLBCL. An important distinction between PCNSL and systemic DLBCL, however, is that central nervous system (CNS) recurrence often has devastating and irreversible effects on neurologic function, resulting in a deleterious impact on quality of life (QOL). Thus, at least theoretically, effective maintenance therapy in older PCNSL that delays tumor progression is likely to be associated with overall enhanced global neurologic function and QOL compared to the absence of maintenance strategies. To date, however, this hypothesis has not been formally tested in a randomized trial.

In this review, we provide an overview and discuss the available evidence for various maintenance strategies for PCNSL in older adults (Table 1). We systematically searched MEDLINE (via PubMed) for all studies of drug treatments for maintenance therapy for PCNSL and also relied on expert opinion. A key component of the drugs that have been studied for maintenance therapy for PCNSL is that they must efficiently cross the blood brain barrier. In addition, since maintenance therapy is used over an extended duration and is non-curative in intent, the drugs used for maintenance ideally would improve QOL, be cost-effective and convenient, and prolong progression-free survival (PFS) and OS. We present the following article in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/aol-20-43>).

Agents and strategies

Maintenance HD-MTX—Maintenance HD-MTX has long been studied as a method of consolidation in PCNSL, in lieu of radiation therapy, and is the first agent to be considered for maintenance therapy in PCNSL. Cher and colleagues were early pioneers in the use of high-dose intravenous methotrexate monotherapy for PCNSL without irradiation (15). The group published a retrospective/prospective study in 19 CNS-lymphoma patients treated with HD-MTX-based induction chemotherapy. Those who had a complete response (CR) received HD-MTX every 4 weeks for three cycles, then every 3 months until recurrence. Median age in the retrospective (8 patients) and the prospective (11 patients) group was 63.5 years (range, 27–78 years) and 60.5 years (range 46–84 years), respectively. Performance status was not reported. Response rate for the entire cohort was 90%. Survival in those patients who achieved CR after induction ranged from 8 to 122 months. Toxicities were manageable with no treatment-related deaths. One patient, retreated due to recurrence, progressed during maintenance therapy. Based on these data, HD-MTX was a well-tolerated regimen. A remaining question was whether the persistent responses were due to the induction therapy or HD-MTX maintenance.

Two retrospective studies showed that methotrexate was as effective as other regimens and had an overall favorable toxicity profile, although it remained unclear whether there was a survival benefit from HD-MTX methotrexate. Zhu *et al.* (16) published a retrospective study in 31 older PCNSL patients (median age 74 years; range, 70–85 years) treated with HD-MTX maintenance (3.5–8 g/m²) in a total of 11 cycles every 4 weeks after

HD-MTX monotherapy induction. Four patients continued to receive MTX (8 g/m^2) every 3 months following the maintenance phase. The overall response rate (ORR) at completion of induction was 96.7%. Eighteen patients achieved CR (60%), 11 partial response (PR) (36.7%), one progressive disease (PD) (3.3%). Median PFS and OS was 7.1 months and 37 months, respectively. Although the majority of the toxicities were mild and reversible, 87.9% of the HD-MTX cycles required dose reduction due to impaired creatinine clearance. However, the dose reduction did not appear to limit the efficacy of MTX. Treatment related deaths during maintenance treatment were not reported. Omuro *et al.* published the results of a retrospective study in 23 PCNSL patients aged 60–79 years (median age 68) treated with HD-MTX + TMZ induction in responding patients (18 patients) followed by a maintenance phase consisting of monthly cycles of HD-MTX 3 g/m^2 and TMZ 100 mg/m^2 days 1–5. Median OS for the entire cohort was 35 months, and median event-free survival (EFS) was 8 months with a 2-year EFS of 22%. One treatment-related death during induction was recorded (7). While outcomes cannot be compared across studies, the response rates were similar across both retrospective studies.

In a prospective phase 2 clinical trial, HD-MTX maintenance therapy showed that HD-MTX therapy can treat residual disease after induction therapy. Chamberlain *et al.* conducted a prospective phase II study in 40 PCNSL patients at a median age of 61.5 years (range, 18–93 years) treated with HD-MTX maintenance 8 g/m^2 every 4 weeks for 4 cycles after HD-MTX plus rituximab—induction delivered biweekly for 4–6 cycles (8). The response rate at completion of induction was CR 60%, PR 20% and PD 20%. Thirty-two patients went on to the maintenance phase. Four of them progressed while on maintenance treatment. Interestingly, 6 of the 12 patients in PR after induction achieved CR during maintenance. The median OS was 29 months for the entire cohort and 33.5 months for the 28 patients who completed maintenance therapy (8). The toxicity was manageable with no treatment-related deaths.

The results of these studies highlight that HD-MTX maintenance therapy can allow for a period of disease-free survival and possible eradication of residual disease with overall minimal toxicity. Limitations of these studies, however, are that they evaluated a small number of patients and that the induction therapy protocol differs from what is currently used. Important additional considerations to using HD-MTX as maintenance therapy include that some PCNSL are refractory to methotrexate, and it can be time-intensive for patients to undergo monthly administrations of HD-MTX. Consequently, other agents have been studied for maintenance.

Maintenance rituximab/anti-CD20 antibody—Rituximab maintenance has been evaluated in retrospective studies as an option for CNS lymphoma patients at a high-risk for relapse or who were considered unable to tolerate consolidation therapy (17). In a small study of 9 patients [5 PCNSL, 1 post-transplant central nervous system lymphoma (CNSL), 3 secondary CNSL (SCNSL)] with a median age of 59 years (range, 40–76 years), maintenance rituximab 750 mg/m^2 every 4 or 6 weeks was found to be well-tolerated. Unfortunately, 4 patients relapsed while on maintenance rituximab and 3 patients developed hypogammaglobulinaemia, with one patient requiring intravenous immune globulin (IVIG) (17). In a larger single-institution retrospective study of 66 patients with newly diagnosed

PCNSL, 20 patients received maintenance therapy with rituximab 375 mg/m² every 1–2 months for 3 months and then every 3 months until progression (median number of infusions was 11, range, 1–25) after induction with HDMTX with a blood brain barrier disruption regimen (18). The median age of those treated with maintenance rituximab was 60.3 years (20.5–86.5 years). Median PFS and OS were prolonged in the maintenance group (20 patients) were 51.7 months and not reached, respectively vs. median PFS of 30.8 and 49.5 months, respectively in the non-maintenance group (46 patients). While the difference in duration of CR was not statistically significant (P=0.113), univariate analysis suggested a statistically significant increase in OS (P=0.012) (18). Relapses while on maintenance or toxicity during the maintenance treatment was not reported. Based on this data, the authors suggested that maintenance rituximab could be associated with prolonged survival, although there are no clinical trials that confirm this. Prospective, randomized clinical trials may help further elucidate the role of maintenance therapy using rituximab for patients with PCNSL.

Maintenance TMZ—TMZ is an oral alkylating agent that crosses the blood brain barrier and also has immunomodulatory properties that make it an active agent in the treatment of various brain tumors (19). The first prospective cooperative group study on TMZ maintenance was in 2016 in which TMZ was administered in conjunction with rituximab, followed by WBRT and TMZ maintenance (10). In this study, maintenance treatment with TMZ was assessed in 13 patients (phase I) and 53 patients (phase II). Median age was 57 years (range, 24–73 years). The induction treatment consisted of rituximab, HD-MTX and TMZ; the postinduction consolidation was hyperfractionated WBRT for a total dose of 36 Gy. TMZ maintenance at 200 mg/m² daily for 5 days was delivered at an interval of 4 weeks for a total of 10 cycles. The median follow-up time for eligible living patients was 3.6 years. Two-year OS and PFS for the entire cohort were 80.8% and 63.6%, respectively. The estimated median PFS was 5.4 years. Treatment was well-tolerated with no treatment-related deaths. Interestingly, QOL assessed by Spitzer QOL scores improved from 6 at baseline to 10 at 3 years. An increase in MMSE score at 3 years was more pronounced in patients aged 60 years. These encouraging results suggested that TMZ maintenance could prolong PFS and improve QOL and cognition.

Based on early favorable data, additional studies evaluated response to TMZ maintenance therapy. The Nordic Lymphoma Group's clinical phase II study in 39 patients aged 65 years or younger and 27 patients aged 66–75 years applied TMZ maintenance in the older subgroup only (9). Induction treatment was an age-adjusted multiagent immunochemotherapy regimen based on HD-MTX and high-dose cytarabine (AraC). In the older subgroup (median age 70 years; range, 66–75 years), the induction was deescalated by lowering the HD-MTX and high-dose AraC dose and replacing ifosfamide with TMZ. Radiotherapy was not part of the regimen. Eastern Cooperative Oncology Group (ECOG) performance was 3–4 in around 25% of the patients in both age groups. Induction treatment in responding older patients was followed by TMZ maintenance, 150 mg/m² daily for 5 days every fourth week for 1 year or until relapse/progression. The ORR was 73.8%: 69.9% in the younger subgroup and 80.8% in the older patients. At a median follow-up of 22 months, relapse after achieving CR occurred in 17 of 27 patients (63%) younger than 66 years and in 5 of 18 older patients (28%). Three older patients in PR at completion of

induction achieved CR during maintenance treatment (2 patients) or during follow-up (1 patient). Two-year OS in the younger and older subgroup was 60.7% and 55.6% respectively and the corresponding PFS was 33.1% and 44.4%. The maintenance chemotherapy was well tolerated with no treatment related deaths occurred during the maintenance treatment. Unfortunately, the induction was still too toxic in older patients, given that 3 of 4 treatment related-deaths occurred in the older subgroup, despite the fact that induction treatment was scaled-down.

A retrospective study showed that treatment with TMZ maintenance had variable responses. Faivre *et al.* described the results of a retrospective study in 10 PCNSL patients who were treated with TMZ maintenance after MPV (methotrexate, procarbazine and vincristine) induction (13). Median age was 67 years (range, 61–76 years). ECOG performance status was 1 in 8 of 10 patients. The TMZ dose was 150–200 mg/m² for 5 days at an interval of 28 days with a median number of 6 cycles of TMZ (range, 3–12 cycles). Two patients who were in near-CR after completion of induction achieved CR during maintenance treatment, whereas 2 patients progressed. With a median follow-up of 55 months, the OS at 2, 3, and 5 years was 88%, 75%, and 57%, respectively. The corresponding PFS was 67%, 56%, and 33%. TMZ was associated with moderate toxicity including grades 3–4 thrombocytopenia.

TMZ maintenance therapy was also studied in primary vitreoretinal lymphoma (PVRL), which is a rare subset of PCNSL with a high risk of relapse in the brain and/or eyes despite treatment. A retrospective study from France in 21 PVRL patients treated with TMZ across 16 centers in seven countries (20). The median age was 75 years (range, 35–90 years). Nineteen patients had received a heterogeneous array of 1–4 treatments previously, while two patients aged 85 and 90 years had never been treated before. The TMZ dose was 150–200 mg/m² for 5 days each month. Median duration of TMZ treatment was 5.2 months (range, 1–40 months). The ORR was 81%, which included CR in 15 patients (71%). The median PFS was 12 months with a 2-year PFS of 30%. Median OS was not reached at a median follow-up of 42 months (9–115 months). The treatment was overall well tolerated. The authors concluded that TMZ can be considered a good therapeutic option for older patients or relapsed/refractory (R/R) PVRL.

Based on these initial studies, TMZ appears to be a reasonable candidate for maintenance therapy in PCNSL and R/R primary vitreoretinal lymphoma. TMZ is well tolerated in older patients and can be used for a prolonged duration. There is an ongoing randomized phase III trial (NCT02313389) of rituximab-MTX-TMZ (R-MTX-TMZ) maintenance treatment *vs.* observation in patients >60 years in complete remission after rituximab-MPV-cytarabine (R-MPV-A) chemotherapy which can help clarify the role of TMZ maintenance.

Maintenance procarbazine—Procarbazine is an oral alkylating agent that has activity in lymphoid malignancies. There is currently limited evidence for use of procarbazine as a maintenance regimen. The PRIMAIN study investigated HD-MTX-rituximab-procarbazine-(lomustine) induction treatment followed by maintenance with procarbazine in 107 older patients (median age 73 years; range, 66–85 years), irrespective of clinical performance status (11). Median Karnofsky performance status was 70 (30–100). The procarbazine maintenance dosed at 100 mg for 5 days was administered every 4 weeks for a total of

6 cycles. A total of 53 patients were treated with maintenance procarbazine, of whom 34 (64.2%) patients completed all 6 planned cycles of maintenance therapy. Median follow-up was 33.7 months. Median OS and median PFS were 20.7 and 10.3 months, respectively. Two-year OS was 47% and 2-year PFS was 37%. During maintenance treatment, 2 patients died from treatment-related causes and 12 patients died due to PD (11). The authors could therefore only speculate that the procarbazine maintenance strategy, introduced to reduce the risk of relapse, had been of any success. To clarify the efficacy of procarbazine as maintenance therapy, a comparison of procarbazine vs. lenalidomide maintenance after induction with HD-MTX, rituximab, and procarbazine is being investigated in the ongoing randomized phase II IELSG45 trial (FIORELLA) in patients \geq 70 years with newly diagnosed PCNSL (NCT03495960). Patients not eligible for HD-MTX treatment can be enrolled in this study as well in a non-randomized fashion. Protocol schema includes radiotherapy (WBRT 23.3 Gy) combined with Rituximab and TMZ followed by TMZ maintenance.

Maintenance lenalidomide—Lenalidomide is a second-generation immunomodulatory agent shown to be able to penetrate the blood barrier with significant activity in relapsed, refractory primary and SCNSL patients, as documented in a phase 1 study by Rubenstein *et al.* (21). The patient cohort included 6 patients with relapsed PCNSL and 8 relapsed SCNSL patients. Nine patients achieved better than PR with lenalidomide monotherapy, 6 maintained response \geq 9 months, and 4 maintained response \geq 18 months (21). Vu *et al.* reported encouraging outcomes of a subgroup analysis in 13 PCNSL patients \geq 70 years (median age 77 years; range, 70–86 years) who received maintenance lenalidomide therapy at 5–10 mg/day after HD-MTX, TMZ and rituximab induction therapy. After a median overall follow-up of 31.64 months, median PFS had not been reached (14). Using the European Organization of Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30), Tsang *et al.* described preliminary QOL data in older CNS lymphoma patients and provided evidence that low-dose lenalidomide maintenance has minimal impact on QOL and symptom burden (22). These findings suggest that low-dose lenalidomide at 5–10 mg/day on days 1–21 is a reasonable maintenance regimen, following HD-MTX-based induction therapy, for older adults with PCNSL with preserved QOL and low symptom burden.

While the results earlier described have been favorable for maintenance lenalidomide, Ghesquieres *et al.* had contradictory results in a phase II study. In this study, applying lenalidomide 10 mg/day as maintenance treatment after rituximab/lenalidomide induction in 45 assessable patients with R/R PCNSL (34 patients) or PVRL (11 patients) (23). The median age was 69 years (range, 46–86 years). ORR after induction was 35.6%. Eighteen patients including twelve patients in CR at completion of induction started the maintenance phase, which was completed in five patients of whom four remained in CR and one showed PD after completion of maintenance treatment (23). With a median follow-up of 19.2 months, the median PFS and OS were 7.8 months and 17.7 months, respectively. The authors concluded that the study showed a limited benefit of lenalidomide maintenance (23). Based on these results, it is possible that lenalidomide maintenance therapy was not as effective because of the lower ORR after induction therapy. Therefore, based on the

evidence, low-dose lenalidomide maintenance could be considered only after a HD-MTX-based regimen.

Additional studies on maintenance low-dose lenalidomide are underway to evaluate its efficacy. Lenalidomide maintenance is a component of a recently-developed multicenter Alliance study (A051901) that evaluates a novel induction regimen that combines HD-MTX plus lenalidomide, nivolumab, and rituximab as components of induction, followed by low-dose lenalidomide maintenance ([NCT04609046](#)). This trial is focused on a study population of patients that are not candidates for myeloablative or non-myeloablative chemotherapeutic consolidation. As above, lenalidomide is being compared to procarbazine maintenance in the FIORELLA study ([NCT03495960](#)). Lenalidomide is also being evaluated in combination with rituximab maintenance therapy as consolidation for patients with PCNSL who are ineligible for transplant ([NCT04627753](#)).

Maintenance ibrutinib—Ibrutinib, an inhibitor of Bruton's tyrosine kinase (BTK), has shown efficacy in R/R CNSL based on data from a dose escalation study in 13 PCNSL and 7 SCNSL patients treated with single-agent Ibrutinib until progression (24). Responses were short-lived with a median PFS of 4.6 months and OS of 15 months. The same group conducted a phase 1b clinical trial to evaluate an ibrutinib, HD-MTX and rituximab combination as induction followed by single-agent Ibrutinib as maintenance (24). Fifteen patients (8 recurrent PCNSL, 1 refractory PCNSL, 1 recurrent SCNSL, 2 refractory SCNSL, and 3 newly diagnosed SCNSL) at a median age of 62 years (23–74 years) were enrolled in a phase 1b clinical trial on ibrutinib (560 or 840 mg/day) in combination with HD-MTX and rituximab (12). Median ECOG performance status was 1 (range, 0–2). Eleven of the 15 patients received maintenance single-agent ibrutinib upon completion of 4 cycles of the ibrutinib/HD-MTX/rituximab combination (12). ORR for all patients was 80%: in R/R PCNSL 89% and SCNSL 67%. Best responses included 8 CRs, 4 PRs, 1 stable disease (SD), and 2 PD, with an ORR of 80%. Median PFS for all patients was 9.2 months, whereas the median PFS in the subset of PCNSL patients has not been reached. Two patients developed PD while on maintenance Ibrutinib. Based on this data, maintenance ibrutinib had no dose-limiting toxicities or treatment-related mortality (12).

In a phase 2 open-label study, ibrutinib has been investigated as maintenance therapy at a dose of 560 mg/day in adults with PCNSL ages 60–85 years (25). Of the 12 patients who were enrolled, the median PFS was 22.5 months (12–31.5 months). Three patients who had PR after induction therapy had improved to CR/unconfirmed CR (Cru) during maintenance therapy. Adverse effects included mostly grade 1–2 events with rare grade 3–4 events with no invasive fungal infections. One patient stopped treatment due to skin rash at 4.5 months, whereas two patients relapsed on maintenance after 4 and 15 months of treatment (25). Based on these favorable preliminary results, ibrutinib maintenance therapy could be considered in further studies as a safe and effective option for maintenance therapy in older adults with PCNSL. Ibrutinib is currently under investigation as maintenance therapy in newly-diagnosed PCNSL aged 60–85 years in an ongoing phase II trial ([NCT02623010](#)).

Conclusions

Prospective clinical studies focusing on PCNSL patients who are not candidates for intensive post-induction therapy are scarce. Maintenance therapy in PCNSL is of particular importance in older patients who can tolerate neither dose-intensive chemotherapy consolidation nor whole-brain irradiation. Agents used as maintenance drugs should have the properties of blood brain barrier penetration, ease of administration, and a favorable toxicity profile. There are several agents that may have a role as maintenance treatment in PCNSL, e.g., procarbazine, TMZ, lenalidomide and ibrutinib, but their overall effectiveness awaits prospective evaluation. While not having overt blood-brain barrier penetration, maintenance therapy with the anti-CD20 monoclonal antibody obinutuzumab has recently been studied in primary CNS lymphoma, however the study closed early because of slow accrual (26). One consideration from the studies that we reviewed is that a small percentage of patients progress while on maintenance therapy with various agents. This remains a question for future studies as there is currently no prospective data to help guide oncologists on how to manage patients who progress on maintenance therapy.

While our discussion on maintenance therapy is limited to older adults, who often are unable to tolerate consolidation therapy or whole-brain radiation, maintenance therapy can also be considered for younger adults with PCNSL. This can be especially relevant for younger patients with CNS lymphoma that is refractory to multiple lines of therapy. Use of maintenance therapies in this setting can help achieve a prolonged PFS and improve overall QOL.

To date, there are no studies that clarify whether maintenance therapy can be used in lieu of consolidation therapy with autologous stem cell transplant or radiation. Prospective studies may provide critical data regarding the identification of optimal agents, whether consolidation therapy could be omitted with maintenance therapy, and the overall role of maintenance therapy as a means to potentially improve survival and preserve QOL and function in a vulnerable, older patient population.

Acknowledgments

Funding: This work was supported by the Leukemia & Lymphoma Society, National Institute of Health (NIH) R01CA139-83-01A1 and R01CA239462 (JLR), and National Institute on Aging (NIA) T32-AG000212 (MT). This content is the responsibility of the authors and does not necessarily represent the views of the Leukemia & Lymphoma Society, NIH, or NIA.

References

1. Villano JL, Koshy M, Shaikh H, et al. Age, gender, and racial differences in incidence and survival in primary CNS lymphoma. *Br J Cancer* 2011;105:1414–8. [PubMed: 21915121]
2. Fallah J, Qunaj L, Olszewski AJ. Therapy and outcomes of primary central nervous system lymphoma in the United States: analysis of the National Cancer Database. *Blood Adv* 2016;1:112–21. [PubMed: 29296804]
3. Houillier C, Soussain C, Ghesquière H, et al. Management and outcome of primary CNS lymphoma in the modern era: An LOC network study. *Neurology* 2020;94:e1027–39. [PubMed: 31907289]

4. Mendez JS, Ostrom QT, Gittleman H, et al. The elderly left behind—changes in survival trends of primary central nervous system lymphoma over the past 4 decades. *Neuro Oncol* 2018;20:687–94. [PubMed: 29036697]
5. Abrey LE, DeAngelis LM, Yahalom J. Long-term survival in primary CNS lymphoma. *J Clin Oncol* 1998;16:859–63. [PubMed: 9508166]
6. Omuro A, Chinot O, Taillandier L, et al. Methotrexate and temozolomide versus methotrexate, procarbazine, vincristine, and cytarabine for primary CNS lymphoma in an elderly population: an intergroup ANOCEF-GOELAMS randomised phase 2 trial. *Lancet Haematol* 2015;2:e251–9. [PubMed: 26688235]
7. Omuro AM, Taillandier L, Chinot O, et al. Temozolomide and methotrexate for primary central nervous system lymphoma in the elderly. *J Neurooncol* 2007;85:207–11. [PubMed: 17896079]
8. Chamberlain MC, Johnston SK. High-dose methotrexate and rituximab with deferred radiotherapy for newly diagnosed primary B-cell CNS lymphoma. *Neuro Oncol* 2010;12:736–44. [PubMed: 20511181]
9. Pulczynski EJ, Kuittinen O, Erlanson M, et al. Successful change of treatment strategy in elderly patients with primary central nervous system lymphoma by de-escalating induction and introducing temozolomide maintenance: results from a phase II study by the Nordic Lymphoma Group. *Haematologica* 2015;100:534–40. [PubMed: 25480497]
10. 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;34:1620–5. [PubMed: 27022122]
11. Fritsch K, Kasenda B, Schorb E, et al. High-dose methotrexate-based immuno-chemotherapy for elderly primary CNS lymphoma patients (PRIMAIN study). *Leukemia* 2017;31:846–52. [PubMed: 27843136]
12. Grommes C, Tang SS, Wolfe J, et al. Phase 1b trial of an ibrutinib-based combination therapy in recurrent/ refractory CNS lymphoma. *Blood* 2019;133:436–45. [PubMed: 30567753]
13. Faivre G, Butler MJ, Le I, et al. Temozolomide as a Single Agent Maintenance Therapy in Elderly Patients With Primary CNS Lymphoma. *Clin Lymphoma Myeloma Leuk* 2019;19:665–9. [PubMed: 31351990]
14. Vu K, Mannis G, Hwang J, et al. Low-dose lenalidomide maintenance after induction therapy in older patients with primary central nervous system lymphoma. *Br J Haematol* 2019;186:180–3. [PubMed: 30714128]
15. Cher L, Glass J, Harsh GR, et al. Therapy of primary CNS lymphoma with methotrexate-based chemotherapy and deferred radiotherapy: preliminary results. *Neurology* 1996;46:1757–9. [PubMed: 8649588]
16. Zhu JJ, Gerstner ER, Engler DA, et al. High-dose methotrexate for elderly patients with primary CNS lymphoma. *Neuro Oncol* 2009;11:211–5. [PubMed: 18757775]
17. Ney DE, Abrey LE. Maintenance therapy for central nervous system lymphoma with rituximab. *Leuk Lymphoma* 2009;50:1548–51. [PubMed: 19637086]
18. Ambady P, Fu R, Szidonya L, et al. Impact of maintenance rituximab on duration of response in primary central nervous system lymphoma. *J Neurooncol* 2020;147:171–6. [PubMed: 32026432]
19. Zhang J, Stevens MF, Bradshaw TD. Temozolomide: mechanisms of action, repair and resistance. *Curr Mol Pharmacol* 2012;5:102–14. [PubMed: 22122467]
20. Baron M, Belin L, Cassoux N, et al. Temozolomide is effective and well tolerated in patients with primary vitreoretinal lymphoma. *Blood* 2020;135:1811–5. [PubMed: 32125361]
21. Rubenstein JL, Geng H, Fraser EJ, et al. Phase 1 investigation of lenalidomide/rituximab plus outcomes of lenalidomide maintenance in relapsed CNS lymphoma. *Blood Adv* 2018;2:1595–607. [PubMed: 29986852]
22. Tsang M, Cleveland J, Cerejo MC, et al. Survival and Patient-Reported Outcomes of Older Adults with Primary Central Nervous System Lymphoma on Low-Dose Lenalidomide. *Blood* 2020;136:21–2.
23. Ghesquieres H, Chevrier M, Laadhari M, et al. Lenalidomide in combination with intravenous rituximab (REVRI) in relapsed/refractory primary CNS lymphoma or primary intraocular

lymphoma: a multicenter prospective ‘proof of concept’ phase II study of the French Oculo-Cerebral lymphoma (LOC) Network and the Lymphoma Study Association (LYSA)†. *Ann Oncol* 2019;30:621–8. [PubMed: 30698644]

24. Grommes C, Pastore A, Palaskas N, et al. Ibrutinib Unmasks Critical Role of Bruton Tyrosine Kinase in Primary CNS Lymphoma. *Cancer Discov* 2017;7:1018–29. [PubMed: 28619981]
25. Bairey O, Amiel A, Yust-Katz S, et al. P05.04 Phase 2 open-label study of maintenance treatment with ibrutinib following first line methotrexate-based immuno-chemotherapy in elderly patients with primary CNS lymphoma (PCNSL). *Neuro Oncol* 2019;21:iii34.
26. Doolittle ND, Ambady P, Peereboom DM, et al. Safety Profile of Maintenance Obinutuzumab in Patients with Primary CNS Lymphoma in Complete Response. *Blood* 2020;136:12.

Table 1

Summary of studies on maintenance therapy for PCNSL

Reference	Design	No of pts	Median age in years [range]	Performance status [range]	Patients on MT (n)	Induction	Maintenance agent	FU (mo)	Median PFS (mo)	Median OS (mo)	TRM during MT (n)
Omuro <i>et al.</i> 2007	Retrospective	23	68 [60–79]	KPS 60 [40–90]	18	HD-MTX, TMZ	HD-MTX, TMZ	26	2-yr PFS: 22%	35; 2-yr OS 38%	None
Chamberlain <i>et al.</i> 2010	Phase II	40	61.5 [18–93]	KPS 80 [50–100]	32	HD-MTX, rituximab	HD-MTX	–	21	29 (entire cohort); 33.5 (after completion of MTX)	None
Pulczynski <i>et al.</i> 2015	Phase II	66: age <66 yr, 39 pts; age 66–75 yr: 27 pts	64 [40–75]; 55 [40–65]; 70 [66–75]	ECOG 1 [0–4]	0; 15	Rituximab, HD-MTX, HD-AraC, ifosfamide, cyclophosphamide*, vincristine**, videsine, dexamethasone, Intraspinal AraC, TMZ***	TMZ***	22	2-yr PFS of entire cohort 37.8%; age <66 yr, 33.1%; age >65 yr, 44.4%	2-yr OS of entire cohort: 58.7%; age <66 yr, 60.7%; age >65 yr, 55.6%	None
Glass <i>et al.</i> 2016	Phase I/II	53	57 [24–73]	Zubrod 1 [0–2]	45	HD-MTX, rituximab, TMZ (RT consolidation)	TMZ	43.2	2-yr PFS: 63.6%	90; 2-yr OS: 80.8	None
Fritsch <i>et al.</i> 2017	Phase II	107 total: 69 R-MPL (rituximab, HDMTX, procarbazine, lomustine); 38 R-MP (rituximab, HD-MTX, procarbazine)	73 [66–85]	KPS 70 [30–100]	53	R-MPL; R-MP	Procarbazine	33.7	2-yr PFS: 37.3%	2-yr OS: 47%	2
Grommes <i>et al.</i> 2019	Phase I	15 (including 9 PCNSL, 6 SCNL)	62 [23–74]	ECOG 1 [0–2]	12	HD-MTX, rituximab, ibrutinib	Ibrutinib	19.7	9.2 (all patients)	NR; 1-yr OS 71.1%	None
Favre <i>et al.</i> 2019	Retrospective	10	67 [61–76]	ECOG 1 [0–2]	10	R-MPV, IT MTX	TMZ	55	57; 2-yr PFS, 67%; 3-yr PFS, 56%; 5-yr PFS, 33%	63; 2-yr OS, 88%; 3-yr OS, 75%; 5-yr OS, 57%	None
Vu <i>et al.</i> 2019	Retrospective	13	77 [70–86]	KPS 60 [50–80]	13	HD-MTX, TMZ, rituximab	Lenalidomide	31.6	NR	NR	None

Reference	Design	No of pts	Median age in years [range]	Performance status [range]	Patients on MT (n)	Induction	Maintenance agent	FU (mo)	Median PFS (mo)	Median OS (mo)	TRM during MT (n)
Ney <i>et al.</i> 2009	Retrospective	9 (including 6 PCNSL, 3 SCNSL)	59 [40–76]	KPS 80 [70–90]	9	Not specified	Rituximab	33.9 (rituximab maintenance)	26.7 (entire cohort)	–	None
Ambady <i>et al.</i> 2020	Retrospective	66 (46 no MT; 20 MT)	MT group 60.3 [20.5–86.5]	KPS 70	20	R-HD-MTX with BBBB regimen	Rituximab	41	30.8 (no maintenance); 51.7 (maintenance)	49.5 (no maintenance); NR (maintenance)	None
Rubenstein <i>et al.</i> 2018	Phase 1	14 (including 6 relapsed PCNSL; 8 relapsed SCNSL)	66 [47–79]	ECOG 2 [1–4]	12	Lenalidomide, rituximab	Lenalidomide	12.5	6 (lenalidomide, rituximab group)	45	None
	Retrospective	10 (relapsed PCNSL)	61.5 [45–81]		10	Methotrexate-based					

* ,in patients aged over 65, cyclophosphamide was replaced by TMZ in the 2nd and 5th chemotherapy cycle;

** ,vincristine was not part of the study treatment for patients aged over 65;

*** ,maintenance TMZ was added to responding patients aged over 65 in whom induction intensity was reduced. BBBB, blood brain barrier disruption; ECOG, Eastern Cooperative Oncology Group; FU, follow-up; HD-AraC, high-dose cytarabine; HD-MTX, high-dose methotrexate; KPS, Karnofsky performance scale; mo, month; MT, maintenance treatment; NR, not reached; OS, overall survival; PFS, progression-free survival; pts, patients; R, rituximab; RT, radiation therapy; TMZ, temozolomide; TRM, treatment-related mortality; yr, year.