Peer Review File
Article information: https://dx.doi.org/10.21037/tcr-22-2341

Reviewer A

Comment: Good and simple explanation of PCNSL as a condition and the treatments as well. No new knowledge in the first section but it set well written and gives an overview. Interesting section on the new therapies even though the studies mentioned are small and requires more investigation. But the explanation is good and useful for a person who is not well known in this field according to new therapies.
Reply: We thank the reviewer for the comment. We revised the error in our article and added the latest clinical trial of CAR-T therapy. Adding the discussion about the unclear role of Rituximab in PCNSL, thiotepa-based autologous stem cell transplantation therapy and temozolomide therapy in our manuscript.

Reviewer B

Comment 1: The chemotherapy section should be expanded to discuss the role of high dose cytarabine as well as thiotepa in combination with high dose methotrexate, based on the IELSG32 trial and PMID 19767089
Reply 1: We thank the reviewer for the comment. We searched the relevant literature and added its major contents to our manuscript
Changes in the text: In line 225-242. A randomised phase 2 clinical trial was undertaken in 24 centres in six countries by Ferreri AJ et al[91], 79 patients were enrolled, among them 40 patients treated with high-dose methotrexate alone, 39 patients treated with high-dose cytarabine plus high-dose methotrexate. Their results suggested that the addition of high-dose cytarabine to high-dose methotrexate provides improved outcome with acceptable toxicity compared with high-dose methotrexate alone. For the international randomised phase 2 International Extranodal Lymphoma Study Group-32 (IELSG32) trial[96], 227 eligible patients were recruited. patients treated with rituximab and thiotepa had a complete remission rate of 49% (95% CI 38-60), compared with 23% (14-31) of those treated with methotrexate-cytarabine alone (hazard ratio 0.46, 95% CI 0.28-0.74) and 30% (21-42) of those treated with methotrexate-cytarabine plus rituximab (0.61, 0.40-0.94). The IELSG32 trial provides a high level of evidence supporting the use of MATRix combination as the new standard chemoimmunotherapy for patients aged up to 70 years with newly diagnosed PCNSL. Importantly, MATRix and ASCT did not result in higher non-relapse mortality or second tumors incidence[115].

Comment 2: The role for rituximab is unclear and the conflicting results of the IELSG32 and HOVON 105/ALLG NHL24 trials should be discussed
Reply 2: We thank the reviewer for the comment. We consulted and learned the relevant literature and corrected this part of our manuscript.

Changes in the text: In line 289-298. One intergroup, multicentre, open-label, randomised phase 3 study was done at 23 centres(HOVON 105/ALLG NHL 24), they got similar results that no clear benefit of addition of rituximab to methotrexate, carmustine, teniposide, and prednisone chemotherapy in primary CNS lymphoma[58]. However, the result of IELSG32 trial showed that patients treated with rituximab plus high-dose methotrexate had a better complete remission rate than patients who treated with high-dose methotrexate along. The role of rituximab for PCNSL treatment is still unclear. Further research is needed to clarify the effect of rituximab on the prognosis of patients with PCNSL.

Comment 3: The authors state "there have been no reports of CAR-T treatment for PCNSL" but a phase I trial of CAR-T for PCNSL has been published: Blood (2022) 139 (15): 2306–2315.
Reply 3: We thank the reviewer for the comment and apology for our careless. We added the reference and modified our manuscript.
Changes in the text: In line 433-440. Recently, one phase 1/2 clinical trial of tisagenlecleucel was conducted by Frigault MJ et al[116]. 12 relapsed patients with PCNSL who were treated with tisagenlecleucel and followed for a median time of 12.2 months (range, 3.64-23.5). Seven of 12 patients (58.3%) demonstrated response, including a complete response in 6/12 patients (50%). There were no treatment-related deaths. Above data suggested that CAR-T therapy is safe and effective in this highly refractory PCNSL patients.

Comment 4: It would be helpful to discuss the approach to patients with older age, comorbidities and poor performance status who may not be candidates for HD-MTX
Reply 4: We thank the reviewer for the comment. We added the related content in our manuscript.
Changes in the text: In line 253-258. Wang A et al[49] conducted a retrospective study which showed that HD-MTX dosed at 3-5 g/m2 demonstrated similar efficacy and lower toxicity compared to higher doses in PCNSL patients. Reducing the initial HD-MTX dose may help ensure tolerability and completion of induction therapy, especially in patients with co-morbidities or older age who have poorer outcomes.

Comment 5: A review of PCNSL is not complete without a discussion of the role for thiotepa based autologous stem cell transplantation, which is missing from this manuscript
Reply 5: We thank the reviewer for the comment and apology for the loss of important content. We added the related content in our manuscript.
Changes in the text: In line 299-325. **Thiotepa based autologous stem cell transplantation**
Thiotepa based autologous hematopoietic cell transplant (AHCT) is an accepted and effective consolidation strategy for PCNSL. Scordo M et al[60] conducted a observational cohort study. 603 patients who underwent AHCT were enrolled. Patients received 1 of 3 conditioning regimens: thiotepa/busulfan/cyclophosphamide (TBC, n=263), thiotepa/carmustine (TT-BCNU, n=275), and carmustine/etoposide/cytarabine/melphalan (BEAM, n=65). In this cohort study, progression-free survival rates were higher in the TBC cohort (75%) and TT-BCNU cohort (76%) compared with the BEAM cohort (58%) (P = .03). Lee JY et al[61] conducted a retrospective study. 22 patients with newly diagnosed PCNSL received high-dose

chemotherapy with thiotepa-based and autologous stem cell transplantation. With a median follow-up of 19.6 months (range, 7.5–56.5 mo), the 2-year progression-free survival and overall survival estimates were 84% and 88%, respectively. A European retrospective study[62] involved 52 patients who all underwent thiotepa-based HDT-ASCT from 11 centres. With a median follow-up of 22 months after HDT-ASCT, median PFS and OS were reached after 51.1 and 122.3 months, respectively. The 2-year PFS and OS rates were 62.0% and 70.8%, respectively. Alnahhas et al[63] conducted a systematic review and meta-analysis on ASCT for PCNSL, Subgroup analysis showed that the use of carmustine and thiotepa as a conditioning regimen carried the lowest risk of transplant-related mortality. The thiotepa, busulfan, and cyclophosphamide regimen, on the other hand, showed numerically superior OS and PFS rates. In summary, thiotepa based autologous stem cell transplantation therapy bring encouraging results on PCNSL.

Comment 6: Temozolomide is another promising agent for PCNSL which should be discussed

Reply 6: We thank the reviewer for the comment. We added the related content in our manuscript.

Changes in the text: In line 326-348.Temozolomide is an oral alkylating agent approved by the FDA for the use in the firstline treatment of glioblastom[64]. With the development of the function of temozolomide on brain tumor. Enting RH et al[65] used a combination of rituximab and temozolomide as salvage therapy for progressive PCNSL. Fifteen patients with a median age of 69 years had a 53% objective response rate with acceptable toxicity. This combination provides a reasonable therapeutic alternative for older patients with progressive PCNSL. One retrospective series explores temozolomide monotherapy in elderly patients with primary CNS lymphoma (PCNSL) and severe comorbidities[66]. In 17 patients (62-90 years old), the complete response rate was 47%, median progression-free survival was 5 months, and median overall survival was 21 months. Five of 17 patients (29.4%) had prolonged responses for at least 12 months and survived for more than 24 months. Temozolomide monotherapy appears to be effective in a subgroup of elderly PCNSL patients. One cohort study was conducted by Makino K et al[67] for salvage treatment with temozolomide in 17 refractory or relapsed PCNSL patients. Temozolomide resulted in a complete response (CR) in 29% and was well tolerated without any major toxicity. So temozolomide is well-tolerated and of moderate toxicity, it may be a good candidate agent for induction, consolidation, and maintenance therapy for patients with PCNSL and for salvage treatment.