Biol Blood Marrow Transplant 25 (2019) e141–e142

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

The Bottom Line

A Tale of Two Eras: The Story of Autologous Stem Cell Transplantation with and without Thiotepa for Primary Central Nervous System Lymphoma

Bei Hu*

Department of Hematologic Oncology and Blood Disorders, Levine Cancer Institute/Atrium Health, Charlotte, North Carolina

Article history:
Received 7 March 2019
Accepted 8 March 2019

Primary central nervous system lymphoma (PCNSL) is an aggressive and rare form of extranodal non-Hodgkin lymphoma that occurs in the brain, spinal cord, eyes, or cerebrospinal fluid [1], with highest incidence in patients over 65 [2]. Poor performance status at diagnosis often impedes enrollment in clinical trials. Thus, therapeutic recommendations are based on a few randomized trials, single-arm phase II trials, and retrospective studies. There is no uniform consensus on the optimal treatment strategy for PCNSL patients.

In general, experts in the field agree that treatment of PCNSL consists of induction and consolidation. Induction consists of high-dose methotrexate (HD MTX)-based chemotherapy regimens [3] because of high penetration of the blood–brain barrier at doses > 1.5 g/m^2 [4,5] Single-agent HD MTX resulted in overall response rates (ORR) of 35% to 74%, median progression-free survival (PFS) of 10 to 13 months, and median overall survival (OS) of 25 to 55 months [6–8]. Over time, various chemotherapy agents were combined with MTX. The IELSG32 trial randomized patients to HD MTX/cytarabine (arm A), HD MTX/cytarabine/rituximab (arm B), and HD MTX/cytarabine/rituximab/thiotepa (arm C) [9]. The addition of rituximab improved ORR to 73% from 53%, complete remission (CR) to 30% from 23%, and 2-year PFS to 46% from 36% [9]. Thiotepa further improved ORR to 86%, CR to 49%, and 2-year PFS to 61% [9].

Consolidation strategies mainly consists of whole brain radiation (WBRT) or high-dose chemotherapy (HDT) followed by autologous stem cell transplant (ASCT). When HD MTX was combined with WBRT, high response rates of 70% to 94% were observed with 5-year survival of 30% to 50% [10–15], but high rates of neurotoxicity were also observed [16,17]. A randomized trial of HD MTX with or without WBRT of 45 Gy demonstrated that although WBRT improved 2 year PFS to 43% (versus 31%), 49% (versus 26%) experienced neurotoxicity without differences noted in OS (32 versus 37 months) [18]. Thus, there has been a trend to omit WBRT.

An emerging consolidative approach is HDT-ASCT, especially in patients with chemosensitive disease who achieve a CR or partial remission. Several conditioning regimens have been studied, but small numbers of patients and variable use of radiation have produced various outcomes that can be difficult to interpret. Thus, no consensus exists as to which is the optimal conditioning regimen.

Although thiotepa containing regimens have always been believed to be superior in PCNSL, Japanese physicians encountered an obstacle when thiotepa became unavailable in Japan in 2011, prompting development of thiotepa-free regimens. Kondo et al. [19] demonstrated in their retrospective analysis of 102 PCNSL patients treated with HDT-ASCT either in the upfront or relapsed setting, HDT with thiotepa was an essential ingredient because it remained an independent prognostic factor for improved PFS (hazard ratio, .42; 95% confidence interval, .19 to .95). Additionally, 5-year PFS was 65.7% in thiotepa-based regimens versus 31.8% in those without.

Although there are no randomized trials comparing conditioning regimens for HDT-ASCT, nonthiotepa regimens have yielded disappointing results. Although most trials with BEAM contained WBRT and intrathecal chemotherapy, a radiotherapy-free phase II trial at Memorial Sloan Kettering yielded median event-free survival of 9 months and 57% of transplanted patients relapsing within 6 months [20]. These discouraging outcomes are likely due to low central nervous system penetration rates [21]. Equally disheartening results are seen with BUCYE (busulfan, cyclophosphamide, etoposide) used in 11 patients after HD MTX/cytarabine induction [22]. Although all patients achieved CR before HDT-ASCT, 6 of 8 patients relapsed after 1 year, and median event-free survival was 15 months [22]. Another small study of 13 patients with PCNSL underwent methotrexate/vincristine/procarbazine (MVP)/HD cytarabine induction with less than half proceeding to LEED HDT-ASCT (cyclophosphamide, etoposide, melphalan, dexamethasone) resulting in 3-year OS of 80% [23]. However, small numbers and use of WBRT in over half of the patients make results difficult to

* Correspondence and reprint requests: Bei Hu, MD, Levine Cancer Institute-Atrium Health, Department of Hematologic Oncology and Blood Disorders, 1021 Morehead Medical Drive, Suite 5300, Charlotte, NC 28204.
E-mail address: Bei.Hu@atriumhealth.org

https://doi.org/10.1016/j.bbmt.2019.03.014

interpret and may partly explain why the relapse rate was higher in the cohort seen in the study by Kondo et al. [19] than that by Miyao et al. [23].

In contrast to BEAM or BUCYE, thiotepa has excellent central nervous system penetration with cerebrospinal fluid levels greater than 80% [21] and has been combined with busulfan, cyclophosphamide, and carmustine in different conditioning regimens. BCNU-thiotepa has been shown to be active with 5-year OS of 87% in 1 German phase II study [24], and no patients died of toxicity. Additionally, CR increased to 85% after ASCT from 31% after induction, resulting in 3-year OS of 77% in another phase II study and suggesting high central nervous system penetration and activity of this combination [25]. Unlike the LEED trial, CR resulted in long remissions without the use of WBRT [25]. Other studies with busulfan and thiotepa have resulted in good PFS and OS of 81% at 41 months [26] and high response rates of 83% [27], but it has been associated with high treatment-related mortality of 10% to 24% [26,28–31].

The PRECIS study demonstrated that thiotepa containing HDT ASCT preserved or improved cognitive function when compared with radiation [31]. ASCT resulted in superior event-free survival at 87% (versus 69% for WBRT) but high treatment-related mortality at 11%. OS was similar in both groups: 64% and 66% at 4 years for WBRT and ASCT, respectively. This was a result of ASCT offered to a significant portion of patients in the WBRT arm and the high treatment-related mortality of ASCT. This highlights the need for future studies to find the optimal thiotepa conditioning regimen that balances efficacy with safety in transplant-eligible patients.

REFERENCES

1. Ferreri AJ, Abrey LE, Blay JY, et al. Summary statement on primary central nervous system lymphomas from the Eighth International Conference on Malignant Lymphoma, Lugano, Switzerland, June 12 to 15, 2002. *J Clin Oncol*. 2003;21:2407–2414.
2. Villano JL, Koshy M, Shaikh H, Dolecek TA, McCarthy BJ. Age, gender, and racial differences in incidence and survival in primary CNS lymphoma. *Br J Cancer*. 2011;105:1414–1418.
3. Ferreri AJ. How I treat primary CNS lymphoma. *Blood*. 2011;118:510–522.
4. Shapiro WR, Young DF, Mehta BM. Methotrexate: distribution in cerebrospinal fluid after intravenous, ventricular and lumbar injections. *N Engl J Med*. 1975;293:161–166.
5. Borsi JD, Moe PJ. A comparative study on the pharmacokinetics of methotrexate in a dose range of 0.5 g to 33.6 g/m2 in children with acute lymphoblastic leukemia. *Cancer*. 1987;60:5–13.
6. Batchelor T, Carson K, O'Neill A, et al. Treatment of primary CNS lymphoma with methotrexate and deferred radiotherapy: a report of NABTT 96-07. *J Clin Oncol*. 2003;21:1044–1049.
7. Gerstner ER, Carson KA, Grossman SA, Batchelor TT. Long-term outcome in PCNSL patients treated with high-dose methotrexate and deferred radiation. *Neurology*. 2008;70:401–402.
8. Herrlinger U, Kuker W, Uhl M, et al. NOA-03 trial of high-dose methotrexate in primary central nervous system lymphoma: final report. *Ann Neurol*. 2005;57:843–847.
9. Ferreri AJ, Cwynarski K, Pulczynski E, et al. Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial. *Lancet Haematol*. 2016;3:e217–e227.
10. DeAngelis LM, Yahalom J, Thaler HT, Kher U. Combined modality therapy for primary CNS lymphoma. *J Clin Oncol*. 1992;10:635–643.
11. Glass J, Gruber ML, Cher L, Hochberg FH. Preirradiation methotrexate chemotherapy of primary central nervous system lymphoma: long-term outcome. *J Neurosurg*. 1994;81:188–195.
12. O'Brien P, Roos D, Pratt G, et al. Phase II multicenter study of brief single-agent methotrexate followed by irradiation in primary CNS lymphoma. *J Clin Oncol*. 2000;18:519–526.
13. Ferreri AJ, Reni M, Dell'Oro S, et al. Combined treatment with high-dose methotrexate, vincristine and procarbazine, without intrathecal chemotherapy, followed by consolidation radiotherapy for primary central nervous system lymphoma in immunocompetent patients. *Oncology*. 2001;60:134–140.
14. DeAngelis LM, Seiferheld W, Schold SC, Fisher B, Schultz CJ. Radiation Therapy Oncology Group S. Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group Study 93-10. *J Clin Oncol*. 2002;20:4643–4648.
15. Poortmans PM, Kluin-Nelemans HC, Haaxma-Reiche H, et al. High-dose methotrexate-based chemotherapy followed by consolidating radiotherapy in non-AIDS-related primary central nervous system lymphoma: European Organization for Research and Treatment of Cancer Lymphoma Group Phase II Trial 20962. *J Clin Oncol*. 2003;21:4483–4488.
16. Gavrilovic IT, Hormigo A, Yahalom J, DeAngelis LM, Abrey LE. Long-term follow-up of high-dose methotrexate-based therapy with and without whole brain irradiation for newly diagnosed primary CNS lymphoma. *J Clin Oncol*. 2006;24:4570–4574.
17. Omuro AM, Ben-Porat LS, Panageas KS, et al. Delayed neurotoxicity in primary central nervous system lymphoma. *Arch Neurol*. 2005;62:1595–1600.
18. 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;11:1036–1047.
19. Kondo E, Ikeda T, Izutsu K, et al. High-dose chemotherapy with autologous stem cell transplantation in primary central nervous system lymphoma: data from the Japan Society for Hematopoietic Cell Transplantation Registry. *Biol Blood Marrow Transplant*. 2019;25:899–905.
20. Abrey LE, Moskowitz CH, Mason WP, et al. Intensive methotrexate and cytarabine followed by high-dose chemotherapy with autologous stem-cell rescue in patients with newly diagnosed primary CNS lymphoma: an intent-to-treat analysis. *J Clin Oncol*. 2003;21:4151–4156.
21. Wiebe VJ, Smith BR, DeGregorio MW, Rappeport JM. Pharmacology of agents used in bone marrow transplant conditioning regimens. *Crit Rev Oncol Hematol*. 1992;13:241–270.
22. Yoon DH, Lee DH, Choi DR, et al. Feasibility of BU, CY and etoposide (BUCYE), and auto-SCT in patients with newly diagnosed primary CNS lymphoma: a single-center experience. *Bone Marrow Transplant*. 2011;46:105–109.
23. Miyao K, Sakemura R, Imai K, et al. Upfront autologous stem-cell transplantation with melphalan, cyclophosphamide, etoposide, and dexamethasone (LEED) in patients with newly diagnosed primary central nervous system lymphoma. *Int J Hematol*. 2014;100:152–158.
24. Illerhaus G, Marks R, Ihorst G, et al. High-dose chemotherapy with autologous stem-cell transplantation and hyperfractionated radiotherapy as first-line treatment of primary CNS lymphoma. *J Clin Oncol*. 2006;24:3865–3870.
25. Illerhaus G, Muller F, Feuerhake F, Schafer AO, Ostertag C, Finke J. High-dose chemotherapy and autologous stem-cell transplantation without consolidating radiotherapy as first-line treatment for primary lymphoma of the central nervous system. *Haematologica*. 2008;93:147–148.
26. 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;125:1403–1410.
27. Montemurro M, Kiefer T, Schuler F, et al. Primary central nervous system lymphoma treated with high-dose methotrexate, high-dose busulfan/thiotepa, autologous stem-cell transplantation and response-adapted whole-brain radiotherapy: results of the multicenter Ostdeutsche Studiengruppe Hamato-Onkologie OSHO-53 phase II study. *Ann Oncol*. 2007;18:665–671.
28. Soussain C, Hoang-Xuan K, Levy V. [Results of intensive chemotherapy followed by hematopoietic stem-cell rescue in 22 patients with refractory or recurrent primary CNS lymphoma or intraocular lymphoma]. *Bull Cancer*. 2004;91:189–192.
29. Cheng T, Forsyth P, Chaudhry A, et al. High-dose thiotepa, busulfan, cyclophosphamide and ASCT without whole-brain radiotherapy for poor prognosis primary CNS lymphoma. *Bone Marrow Transplant*. 2003;31:679–685.
30. Cote GM, Hochberg EP, Muzikansky A, et al. Autologous stem cell transplantation with thiotepa, busulfan, and cyclophosphamide (TBC) conditioning in patients with CNS involvement by non-Hodgkin lymphoma. *Biol Blood Marrow Transplant*. 2012;18:76–83.
31. Houillier C, Taillandier L, Dureau S, et al. Radiotherapy or autologous stem-cell transplantation for primary CNS lymphoma in patients 60 years of age and younger: results of the intergroup ANOCEF-GOELAMS randomized phase II PRECIS study. *J Clin Oncol*. 2019;37:823–833.