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Mini Review

Autologous stem cell transplantation in Primary Central Nervous System Lymphoma: A Systematic Review

Sara Steffanoni*

Department of Medicine, Division of Hematology, Valduce Hospital, 22100 Como, Italy

Consolidation therapy demonstrated to improve the outcome of naïve patients affected by Primary Central Nervous System Lymphoma (PCNSL). In the past, Whole Brain Radiotherapy (WBRT) represented the standard consolidation approach for PCNSL in response after high dose methotrexate-based induction chemotherapy [1,2]. Initially, high-dose chemotherapy followed by rescue with autologous stem cell transplantation (HDC/ASCT) was applied in relapsed/refractory PCNSL patients. However, the poor performance status of PCNSL patients at the replace/progression moment and low response rate after salvage chemotherapy limited the feasibility of HDC/ASCT. PCNSL survivors treated with WBRT consolidation experienced devastating neurotoxic adverse effects secondary to radiotherapy, with an incidence rate ranging from 12 to 65% at 5 years and which represented even more important issue for clinicians. In the last decades, HDC/ASCT has represented an undiscussable alternative consolidation strategy to WBRT, becoming a part of first line treatment [3]. By randomized studies HDC/ASCT has demonstrated to achieve:

- Similar or better outcome than those obtained with WBRT both in terms of progression free survival (PFS) and overall survival (OS): PFS of 50% in HDC/ASCT arm vs 55% in WBRT arm among patients enrolled in IELSG 34 trial and with a median follow up of 7 years; 2-year PFS of 87% in HDC/ASCT arm versus 69% in WBRT arm among patients enrolled in PRECIS trial
- A significant improvement/preservation in cognitive and executive functions [4,5].

***Corresponding author:** Sara Steffanoni, Department of Medicine, Division of Hematology, Valduce Hospital, 22100 Como, Italy, E-mail: sara.steffanoni@gmail.com

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Thus, the aim of a consolidation therapy is not only to maintain over time the results obtained by induction therapy but also to further eradicate any potential residual cancer cells, conditioning schedules containing drugs with high CNS penetrance, able to achieve CSF level of over 80% of plasma concentrations, have replaced the Melphalan-based regimens. Regimens containing Busulfan and Alkylating agents (such as BCNU and Thiotepa) were investigated achieving both long-term disease control and long-term survival in PCNSL patients with 2 years-PFS of 58-81% and 2years-OSof 61-87%) [2,6-10].

Non-myeloablative regimens containing agents with high CNS bio-availability and without cross mechanism of action with MTX (such as etoposide, cytarabine, ifosfamide) have demonstrated to be a safe and efficient consolidation strategy in PCNSL patients in response after induction chemotherapy [11,12]. Safety and efficacy of both non-radiation consolidation strategies (non-myeloablative chemotherapy and HDC/ASCT) were compared in recent randomized studies [13,14]. Patients randomized in non-myeloablative arm had a shorter PFS in both studies and a lower OS in IELSG 43 study (3-year OS 71% vs 86%, HR 0.47; p=0.01).Based on these results, HDC with highly CNS-penetrating agents followed by ASCT rescue represents, to date, the best choice among the available consolidation strategies for fit newly diagnosed PCNSL patients.Ninety-four per cent of patients with PCNSL who received ASCT as consolidative treatment experienced or maintained complete or partial responses, and 84% had improved responses after ASCT in the consolidation setting.

To date, it still has to be established which is the best thiotepa-basedcondictioning regimen (busulfan/thiotepa (Bu/TT) versus thiotepa/busulfan/cyclophosphamide (TBC) versus carmustine/thiotepa (BCNU/TT)) for PCNSL patients. Norandomised study had compared them head to head. However, by multivariate analysis, TBC regimen resulted to have a better outcome versus other regimens (2-yearPFS of 86% with TBC versus 67% with Bu/TT versus 64% with BCNU/TT and 2 years OS of90% with TBC versus 82% with Bu/TT versus 75% with BCNU/TT)but with higher therapy-related mortality rate (19% vs 3% vs 0% with BCNU/TT and Bu/TT), restricting its feasibilityto experienced clinical centers [6-8,15,16].

To optimize the management of PCNSL patients eligible for HDC/ASCT, some open questions need to be resolved.

- The past and worldwide concept that the biological age itself could determine the alone discriminating factor for distinguishing patients eligible for HDC/ASCT or not should be abandoned. For this reason, a prognostic scoring system including host features and disease prognostic factors, could be a useful tool to discriminate patients older than 70 years who could benefit from consolidation with HDC/ASCT
- The maintenance therapy after HDC/ASCT demonstrated in some lymphoproliferative diseases to confer an improved outcome, whether this may also apply to transplanted PCNSL patients, particularly in case of partial response, remains to be investigated.

- It is still unknown if the autograft cellular composition used as rescue after HDC could condition the outcome of transplanted PCNSL patients. The optimal thresholds and composition of infused cells need to be established.
- HDC/ASCT consolidation has a wide variety of short- and long-term complications, including mucositis, infections, prolongated cytopenia with risk of infection and need of transfusion support. Recent ongoing studies are moving to investigate a de-escalated induction treatment strategy to minimize the induction therapy-related toxicity and to improve the event-free survival. However, it is still unknown if patients, exposed to a lower dose dense chemotherapy before transplantation, can have a lower incidence of early and late transplant-related complications.

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