EUROPEAN HEMATOLOGY ASSOCIATION

Rare hematological malignancies - Section 3

Primary central nervous system lymphoma

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Modern treatment of primary central nervous system lymphoma (PCNSL) includes induction and consolidation phases.[1] Usually, induction consists of polychemotherapy containing high-dose methotrexate (HDMTX; ≥1 g/m^2) as main drug. Different HDMTX-based combinations have been tested in single-arm phase II studies, mostly with addition of alkylating agents and/or high-dose cytarabine (HDARAC), with or without rituximab. However, these combinations are currently used in limited geographical areas, and their routine use is not supported by a randomized trial. As exception, the IELSG20 randomized trial has demonstrated that a HDMTX-HDARAC combination is associated with significantly better outcome than HDMTX alone.[2] Recently, preliminary results of the last IELSG randomized trial, named IELSG #32, were reported.[3] This trial consists of a factorial double randomization comparing three different induction combinations and two major consolidation strategies. The analysis of the first randomization showed that the addition of rituximab and thiotepa to conventional HDMTX-HDARAC combination (called MATRix regimen) was associated with significantly improved outcome and acceptable toxicity. Results of the second randomization are pending.

In the past, whole-brain irradiation (WBRT) was the most commonly used consolidation therapy, but concerns on postactinic neurotoxicity led some authorities to investigate alternative approaches. No significant survival improvement with consolidative WBRT was found in a randomized phase III trial in patients treated with HDMTX-based chemotherapy;[4] however, reported results are inconclusive since this study is compromised by several flaws in design and undertaking, and failed to prove its primary hypothesis.[5] Recently reported single-arm phase II studies showed that reduced-dose WBRT[6] and consolidative non-myeloablative chemotherapy[7] are associated with a 2-year PFS of ~60%, and that consolidative HD-chemotherapy supported by autologous stem cell transplantation is feasible and could replace WBRT, especially if a thiotepa-based conditioning is used.[8-10] Hopefully, these intensified options will significantly improve survival among young and fit patients. Conversely, results remain poor in elderly patients who should be assessed in ad hoc trials. A recent randomized trial suggests that a combination of HDMTX, procarbazine and vincristine is equally active to MTX-temozolomide combination,[11] whereas encouraging results with temozolomide maintenance were recently reported.[12] De-escalated approaches like consolidation by non-cross resistant conventional chemotherapy or maintenance chemotherapy are being also investigated both in young and elderly patients.

The most important ongoing randomized trials are aimed to establish the most effective and better tolerated consolidative therapy after induction chemoimmunotherapy.[13] Additionally, new molecules are being assessed in patients with relapsed/refractory PCNSL enrolled in phase II studies. Both strategies will delineate the new treatment options for PCNSL patients. International cooperation and multidisciplinary approach will be mandatory to achieve further progress in this field.

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