Thiotepa-based autograft for primary central nervous system lymphoma

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TITLE	Results of intensive chemotherapy followed by hematopoietic stem-cell rescue in 22 patients with refractory or recurrent primary CNS lymphoma or intraocular lymphoma.
AUTHORS	Soussain C, Suzan F, Hoang-Xuan K, et al.
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Historically, whole-brain radiotherapy was the mainstay of treatment for primary central nervous system lymphoma (PCNSL). However, long-term remission rates were poor, with a median overall survival of approximately 12 months. Combination chemo-radiotherapy with high-dose methotrexate improved survival outcomes, but at the cost of high rates of delayed and often fatal neurotoxicity.

Carole Soussain and colleagues were the first to describe the use of thiotepa-based autografting (TT-ASCT) as a consolidation strategy in PCNSL, in a single-center series of patients with relapsed or refractory disease.[1] In their landmark 2001 publication in the *Journal of Clinical Oncology*, Soussain *et al.* reported on 15 patients with relapsed or refractory PCNSL who were systematically treated with salvage high-dose cytarabine and etoposide (CYVE) followed by thiotepa, busulfan and cyclophosphamide (TBC)-conditioned autografting, in addition to seven patients with isolated intraocular lymphoma who were treated with upfront TT-ASCT without CYVE. The group had previously reported encouraging data using TBC autografts for a small number of patients with relapsed intraocular lymphoma in a 1996 publication.[2]

The treatment was remarkable for its efficacy in the relapsed-refractory setting, with a 3-year estimated overall survival of 64% at a median follow-up of 41.5 months. However, the toxicity of the approach was also significant. Seven patients (32%) experienced neurotoxicity, with two fatalities. This rate is significantly higher than that occurring with the modern experience with TT-ASCT, and it is notable that ten patients in the series had previously received radiation doses ≥30 Gy to the whole brain. The TBC conditioning regimen has also been associated with a higher treatment-related mortality, especially in patients >60 years.[3]

Despite being a small study, the strategy adopted by Soussain *et al.* would underpin several subsequent publications further exploring the utility of autografts in PCNSL. More than a decade later, the results of the European phase II cooperative-group PRECIS and IELSG32 trials would be published, in which patients with newly diagnosed disease were randomized to receive consolidative TT-ASCT or whole-brain radiotherapy. These studies demonstrated equivalent overall survival outcomes but improved neurocognitive function in recipients of TT-ASCT. An event-free survival benefit for TT-ASCT was also demonstrated in the PRECIS trial.[3,4] Compared to further chemotherapy without autografting, TT-ASCT would also be shown to produce superior progression-free and overall survival in the phase III randomized IESLG43 study in patients treated with MATRix induction (methotrexate, cytarabine, thiotepa and rituximab).[3] Finally, the recently published MARTA trial demonstrates the feasibility of TT-ASCT following abbreviated high-dose methotrexate-based therapy in a selected population of older adults, up to 80 years old.[5]

While TT-ASCT is now widely accepted as a standard-of-care for transplant-eligible patients and has supplanted whole-brain radiotherapy in the frontline management of PCNSL, controversies and regional differences in practice remain. The optimum induction strategy for PCNSL remains unclear; excellent outcomes have been described with both MATRix as well as other high-dose methotrexate-based induction strategies.[3] Similarly, both TBC and other thiotepa-based ASCT conditioning regimens have been shown to be efficacious, but randomized comparisons are lacking. In contrast, outcomes in elderly, unfit patients and relapsed-refractory PCNSL remain poor. Nonetheless, the success of TT-ASCT consolidation, beginning with the

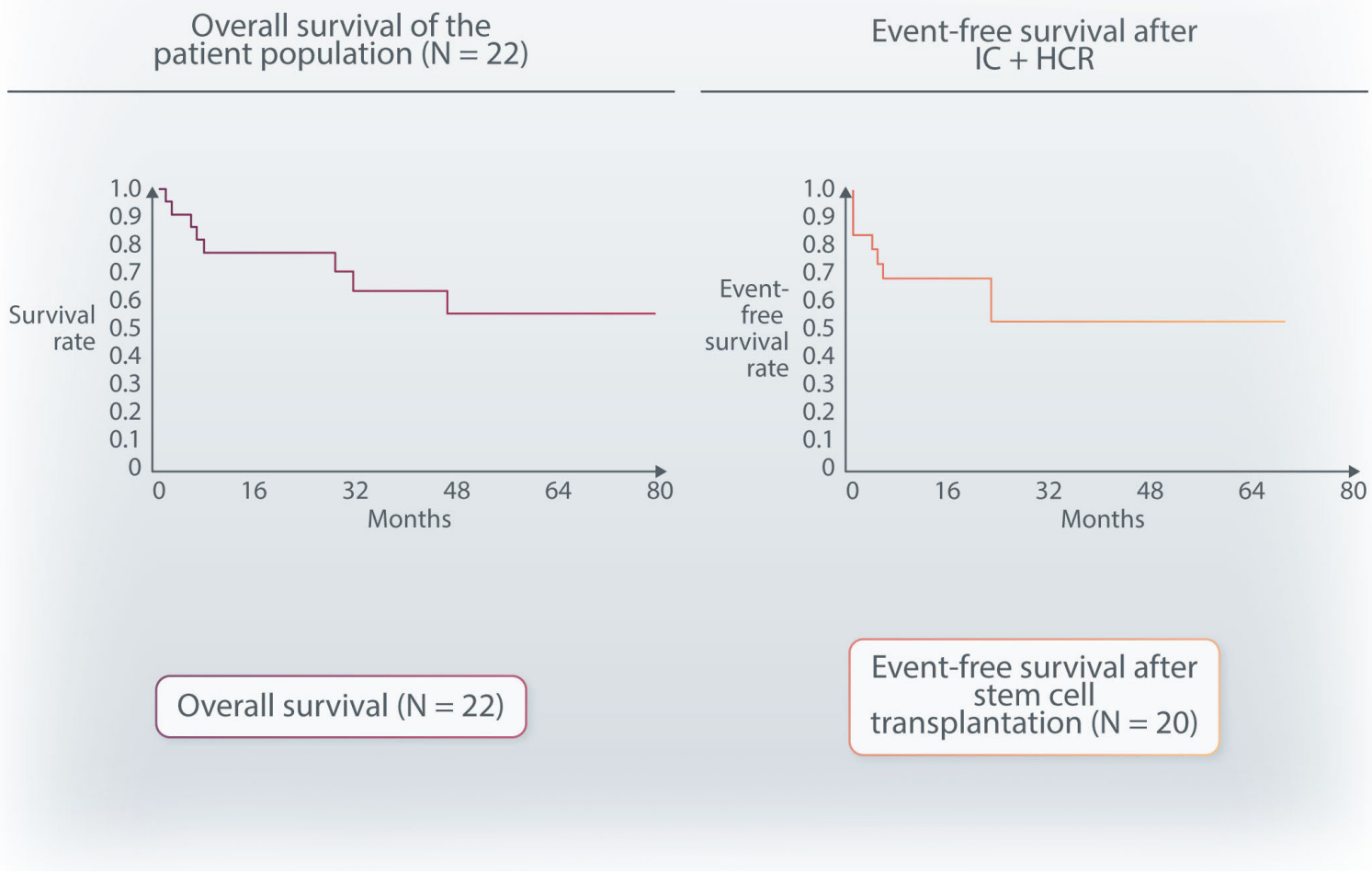

Figure 1. Survival outcomes of patients with primary central nervous system lymphoma or intraocular lymphoma. Left. Estimated 3-year overall survival in 22 patients with relapsed/refractory central nervous system or intraocular lymphoma, 64%. Right. Estimated 3-year event-free survival in 20 patients who received stem-cell transplantation, 53%. IC + HCR: intensive chemotherapy and hematopoietic cell rescue. *Figure adapted with permission from Soussain et al.*[1]

innovative single-center experience published by Carole Soussain and colleagues and subsequently proven in multiple inter-group randomized trials, provides a roadmap for advancing the care of patients with PCNSL in the current era of novel therapies.

Disclosures

No conflicts of interest to disclose.

Contributions

DB and KC contributed equally to this work.

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