ASBMT American Society for Blood and Marrow Transplantation

Primary CNS Lymphoma—Radiation-Free Salvage Therapy by Second Autologous Stem Cell Transplantation

Primary central nervous system lymphoma (PCNSL) is a rare aggressive extranodal non-Hodgkin lymphoma mostly of B-cell origin confined to the CNS compartment. High-dose methotrexate (HD-MTX) plus cytarabine (AraC) is considered as standard first-line therapy, but despite high response rates, the majority of patients still relapse [1,2], and because there is no consensus treatment for relapse, reported strategies vary strongly. High-dose chemotherapy plus autologous stem cell transplantation (HDC-ASCT) has been shown to be feasible and effective as initial therapy [3,4]. Were herein report the treatment strategies of 3 immuncompetent patients with recurrent PCNSL after first-line HDC-ASCT. Systemic lymphoma manifestation at time of diagnosis and relapse was ruled out by CT total body scans, bone marrow biopsy aspirate, and positron emission tomography (PET). Staging was carried out by contrast-enhanced magnetic resonance imaging (MRI) scans. Epstein-Barr association was ruled out a time of diagnosis. Our patients gave written informed consent for institutional-initiated research studies.

PATIENT 1

A 27-year-old man was diagnosed with multifocal anaplastic large-cell T cell lymphoma (Figure 1A). First-line therapy: 4 applications of HD-MTX and 2 cycles of AraC/thiotepa (TT) followed by ASCT ($CD34^+$ count 12.38×10^6/kg) after conditioning chemotherapy with BCNU and TT [3]. One month after therapy complete remission (CR) was confirmed (Figure 1B). After 2 years, MRI revealed multifocal relapse at the spinal cord expressed by weakness and pain in the right leg (Figure 1C and D). Salvage treatment: 2 cycles consisting of HD-MTX (3.5 mg/m^2 over 4 hours, day 1), AraC (2×2 g/m^2/day, days 2-3), and TT (30 mg/m^2, day 4). After the second cycle partial remission (PR) of the spinal lesions and ongoing CR in the brain were confirmed. Because of the very good clinical condition we decided for a second HDC-ASCT. Conditioning chemotherapy consisted of busulfan (3.2 mg/kg/day over 3 hours, days -8 and -7) and TT (2×5 mg/kg/day, days -5 and -4). After a second ASCT ($CD34^+$ count 10.87×10^6/kg) the patient obtained ongoing CR for now more than 12 months (Figure 1E).

PATIENT 2

A 41-year-old man was diagnosed with a single PCNSL; type diffuse large cell B-cell lymphoma (DLCBL). First-line therapy: HD-MTX followed by AraC and TT as induction therapy. For consolidation he received HDC-ASCT ($CD34^+$ count 9.68×10^6/kg) [4]. The patient refused whole-brain radiotherapy (WBRT) after ASCT, which was part of the protocol. One month after ASCT he was in ongoing CR for 7 years. At relapse, staging demonstrated multifocal lesions. Salvage treatment: 4 cycles of rituximab (375 mg/m^2, day 1), HD-MTX (4 g/m^2 over 4 hours, day 0), AraC (2 g/m^2/day, days 1-2), and TT (30 mg/m^2, day 3) as induction, leading to CR after the first cycle. For consolidation, we decided for a second ASCT ($CD34^+$ count 7.85×10^6/kg) after conditioning chemotherapy with busulfan (2×3.2 mg/kg/day over 3 hours, days -8 and -7) and TT (2×5 mg/kg/day, days -5 and -4). After 6 months an MRI showed ongoing CR.

PATIENT 3

A 47-year-old man was diagnosed with a single PCNSL; type DLCBL. First-line therapy consisted of 6 cycles according to the *Bonn protocol*, without intraventricular chemotherapy leading to CR [5]. Three months later, MRI revealed multifocal relapse. Salvage treatment: 2 cycles of AraC and TT, followed by HDC-ASCT consisting of BCNU and TT ($CD34^+$ count not given). Staging revealed CR. Fifteen months after successful salvage treatment, staging demonstrated a second relapse. A second salvage treatment consisted of 5 cycles rituximab and HD-MTX followed by 2 cycles rituximab, AraC, and TT according to our center's new PCNSL protocol (trail number: NCT00647049). Before the second ASCT, MRI revealed CRu. Conditioning regimen consisted of rituximab (375 mg/m^2, day -9), busulfan (3.2 mg/kg/day over 3 hours, days -8 and -7) and TT (2×5 mg/kg/day, days -5 and -4), leading to CR ($CD34^+$ count 9.88×10^6/kg at the second ASCT). More than 1.5 years afterward the patient is still in ongoing CR.

All patients collected stem cells after the first AraC/TT cycle. Patients 1 and 2 both had a second sufficient harvest before the second ASCT after 1 stimulation. Patient 3 used stem cells from the first harvest.

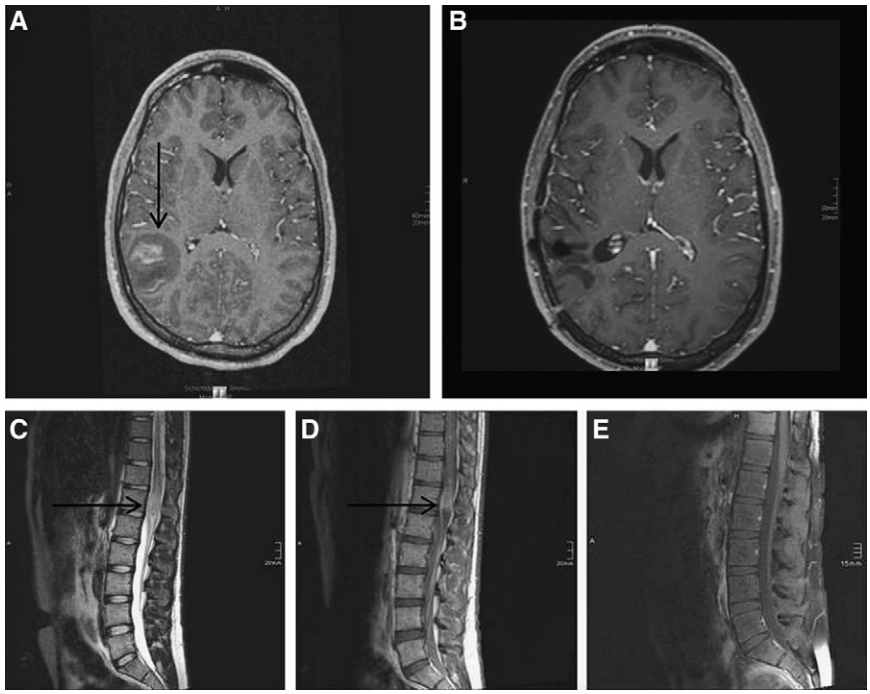

Figure 1. (A) Right parietal lymphoma at time of diagnosis; (B) complete remission after the first HDC-ASCT; (C,D) spinal lymphoma relapse; (E) complete remission after the second HDC-ASCT (A, B, D, E contrast-enhanced T1-weighted MRI; C, T2-weighted MRI).

Hematopoietic recovery around the second HDC-ASCT was unremarkable in all patients. Time of leucopenia (<1000/μL) and thrombopenia requiring substitution (<10,000/μL) lasted 8 days in all patients. There were no severe infectious complications. Up to now, all 3 patients are in an excellent clinical condition without neurocognitive impairments.

Recurrence of PCNSL remains a substantial problem, but there is little consensus on second-line treatments. WBRT has an important role in patients with chemorefractory or relapsed disease [6]; however, long-term survivors often suffer from neurocognitive impairment [7]. HDC-ASCT in PCNSL has been investigated in single-arm prospective trials for first-line and salvage treatment leading to high remission rates. Treatment-related mortality (TRM) remains a main concern, and severe neurotoxicity is observed particularly in patients receiving HDC-ASCT plus WBRT, or when WBRT was applied during prior therapy (reviewed by [8]). In our patients, time to relapse after the first HDC-ASCT varied strongly from 15 months to 7 years. The first patient was diagnosed with anaplastic large-cell T cell lymphoma. Whether this rare subtype has an unfavorable prognosis is unknown. Regarding time of relapse in this patient, it fits to the range observed in PCNSL of B-cell origin. The second patient shows a relapse after 7 years and belongs to the rare cases in which relapse occurs after long-term remission [1]. The third patient experienced 2 relapses. The first occurred 8 months after being treated according to the modified *Bonn protocol*, which led to impressive survival rates, but because the intraventricular therapy was omitted, the following study needed to be stopped because of early relapses [5,9]. Concerning induction therapy, regimens slightly differed: in the third patient, HD-MTX was omitted because of the early onset of relapse 3 months after MTX containing therapy. Concerning patients 2 and 3, rituximab became part of our protocols. In all cases, we decided for busulfan instead of BCNU before the second ASCT, because of the potential cumulative toxicity of BCNU. We also considered WBRT as salvage or consolidation treatment; however, having in mind the risk of leucoencephalopathy in these young patients, WBRT was not applied, but this remains a debatable issue. Granted, one also needs to consider the risk for development of secondary MDS in long-term after remobilization for second ASCT, but because the induction treatment based on antimetabolites (MTX, AraC) with rather low stem cell toxicity we assume a lower over all risk for MDS development in the long term, but still, this has to be awaited. Allogeneic SCT instead of second ASCT might also be considered because a graft-versus-lymphoma effect in the brain has been described, but this is still controversial [10]. Although follow-up is still short, this series demonstrates the feasibility and high efficacy of a second HDC-ASCT in relapsed PCNSL. Our patients were in excellent clinical condition; thus, this approach needs to be cautiously considered basing on tumor-related and patient-related characteristics.

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Biol Blood Marrow Transplant 17: 281-283 (2011)

doi:10.1016/j.bbmt.2010.11.011