

Relapse Primary Central Nervous System Lymphoma Successfully Consolidated with Allogeneic Stem Cell Transplantation with Thiotepa/Busulfan/Fludarabine Conditioning

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Keywords

Allogeneic stem cell transplantation · Primary central nervous system lymphoma · Myelodysplasia

Abstract

Primary central nervous system lymphoma (PCNSL) is generally characterized by a poor prognosis and frequent relapsing disease. Consolidation therapy in the upfront setting usually consists of an autologous stem cell transplantation. We report the case of a 19-year-old Caucasian male who had previously undergone an allogeneic stem cell transplantation with complete engraftment for the treatment of juvenile myelomonocytic leukemia when he was 1 year old. He presented with two episodes of (donor-derived) PCNSL from allogeneic stem cells; however, after induction chemotherapy, he failed to harvest stem cells for the consolidation with autologous stem cell transplantation. He was consolidated successfully with a second allogeneic stem cell transplantation with another donor after conditioning with thiotepa, busulfan, and fludarabine.

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Introduction

Primary central nervous system lymphoma (PCNSL) is generally characterized by a poor prognosis and frequent relapsing disease, especially in older patients [1]. In selected patients with relapsed disease, autologous stem cell transplantation (SCT) can still cure 40–50% of patients fit enough to undergo this treatment [2–4]. In the upfront setting, consolidation with autologous SCT after combinations of high doses of thiotepa with busulfan, cyclophosphamide (TBC) or carmustine (Car/TT) has been shown to be comparably effective to whole-brain radiotherapy [5, 6]. Important limitations of high-dose chemotherapy, however, are that not all patients are physically fit to undergo this treatment, and that successful stem cell harvest is indispensable. We report the case of a 19-year-old Caucasian male who had previously undergone an allogeneic SCT with complete engraftment, presenting with a donor-derived PCNSL failing to harvest autologous stem cells, who was consolidated successfully with a second allogeneic SCT.

Case Report

Written informed consent was obtained from the patient for publication of this case report. Our patient was diagnosed in 1998 with a juvenile myelomonocytic leukemia when he was 1 year old. He was treated with chemotherapy based on the EWOG-MDS 98 protocol [7]. Afterward, he was consolidated with an allogeneic SCT with a matched unrelated donor (MUD). The conditioning regime at the time consisted of busulfan, cyclophosphamide, melphalan, and alemtuzumab. A complete response was achieved and maintained with a complete donor chimerism at 6 months.

In February 2015, at the age of 17, he presented with paresthesia in the left leg and blurred vision. An MRI of the brain showed lesions in the thalamus, mesencephalon, and hippocampus on the right side with several smaller lesions in both hemispheres. After a negative lumbar puncture and brain biopsy, the diagnosis of PCNSL was established on a biopsy of the vitreous humor, thereby also confirming ocular disease localization. Notably, analysis of genomic polymorphisms (short tandem repeat loci) showed the PCNSL in the vitreous humor to be donor-derived. The patient was treated with chemotherapy based on the C3-Inter-B-NHL ritux 2010 trial [8] consisting of vincristine, cyclophosphamide, and prednisone (COP), vincristine, prednisone, methotrexate, cyclophosphamide, and doxorubicin (COPADM), and cytarabine; etoposide (CYVE) with intrathecal methotrexate, prednisone, cytarabine (11 times), and systemic rituximab. Given the ocular localization intravitreal methotrexate and rituximab were added 6 times. Among others, he received a cumulative doses of 32.000 mg/m² methotrexate, 24.540 mg/m² cytarabine, and 5.503 mg/m² cyclophosphamide. In September 2015, a complete response was achieved, both intracerebral and ocular. As a complication, the patient had developed an invasive pulmonary aspergillosis treated initially with voriconazole and later with liposomal amphotericin B and posaconazole. During follow-up, the patient developed myelodysplastic changes in the granulopoiesis and megakaryopoiesis without cytogenetic abnormalities, but with loss of donor chimerism decreasing to 10% in the blood and bone marrow and to 47% in the T-cell fraction of the blood.

In February 2017, at the age of 19, the patient presented with a generalized epileptic seizure. On MRI, a new large lesion was seen in the left parietal lobe extending to the occipital and temporal lobe with also a smaller lesion in the pons and internal capsule, suspicious for lymphoma. A cerebral biopsy confirmed relapsed PCNSL. There was no evidence of other disease localizations.

The patient was retreated with a chemotherapy scheme used for PCNSL in adults, consisting of two cycles of methotrexate, teniposide, carmustine, and prednisolone (MBVP) [9]. The first cycle was complicated by a toxic hepatitis after which posaconazole was switched to inhalations with liposomal amphotericin B, and an epileptic seizure for which the dose of levetiracetam was increased. At response evaluation after two cycles, a very good partial response was achieved. Mobilization of autologous stem cells failed, probably due to the intensive treatment in the past and the myelodysplastic changes. We decided to treat the patient with a conditioning of carmustine/thiotepa as used in autologous SCT, and to re-transplant with the original MUD. Unfortunately, the original stem cell donor withdrew consent, resulting in a change of plan and the necessity to give a third cycle of MBVP as a bridging, while searching for an alternative donor. This third cycle of MBVP was complicated by chemotherapy-induced cardiomyopathy which resulted in postponing consolidation treatment for 2 months.

In September 2017, the patient finally underwent a second allogeneic SCT from a HLA-identical sibling, his 17-year-old sister. The conditioning regimen consisted of thiotepa (2 days 5 mg/kg), busulfan (3 days 3.2 mg/kg) and fludarabine (3 days 50 mg/m²), and graft-versus-host prophylaxis with cyclosporine and mycophenolic acid. After thiotepa infusion, the patient developed an epileptic seizure. Other complications included grade 2 mucositis and a CMV reactivation treated with valganciclovir.

During follow-up, chimerism was >95% donor in all fractions, and there were no signs of recurrent disease after 5 years of follow-up. Complications were severe chronic graft-versus-host disease of the liver and muscle treated with prednisolone and mycophenolic acid; bilateral avascular necrosis of the femoral head which hip endo-prostheses were inserted; and avascular necrosis of the bilateral humeral head, not yet needing surgery. Nevertheless, quality of life is reasonable with the patient resuming his education and recently finishing a trip through several European countries. To summarize, a graphical timeline is provided in Figure 1.

Discussion

Treatment options for relapsed/refractory PCNSL are limited. The prognosis is generally poor [10]. Re-induction with high-dose methotrexate can achieve a response rate of 85–91% with a median overall survival of 41–62 months. Whole-brain radiotherapy can achieve a response rate of 74–79%, with a median overall survival of 10–16 months, respectively [10].

For consolidation, autologous SCT is the preferred treatment modality in our center, if not given in first line. However, stem cell mobilization failed in our patient. Therefore, a rather unique situation occurred with a patient having a donor-derived relapsed PCNSL and declining bone marrow chimerism with myelodysplastic changes and almost complete autologous reconstitution 17 years after the first allogeneic SCT. Because the T-cell chimerism was still 47%, we aimed to perform a re-transplant with the original MUD. This approach would not have resulted in a graft-versus-disease effect for the PCNSL, as the disease was donor-derived. Therefore, a re-transplant with the original donor would most closely resemble the standard treatment of performing an autologous SCT after high-dose chemotherapy. However, after the withdrawal of the original donor, the sister of the patient was suggested as an alternative stem cell donor, which would result in a graft-versus-disease effect for both the PCNSL and the myelodysplasia the patient suffered from. After the stem cell source was defined, the next challenge was to determine the conditioning regime because we did not perform an allogeneic SCT for this indication before and because our patient was heavily pre-treated with chemotherapy.

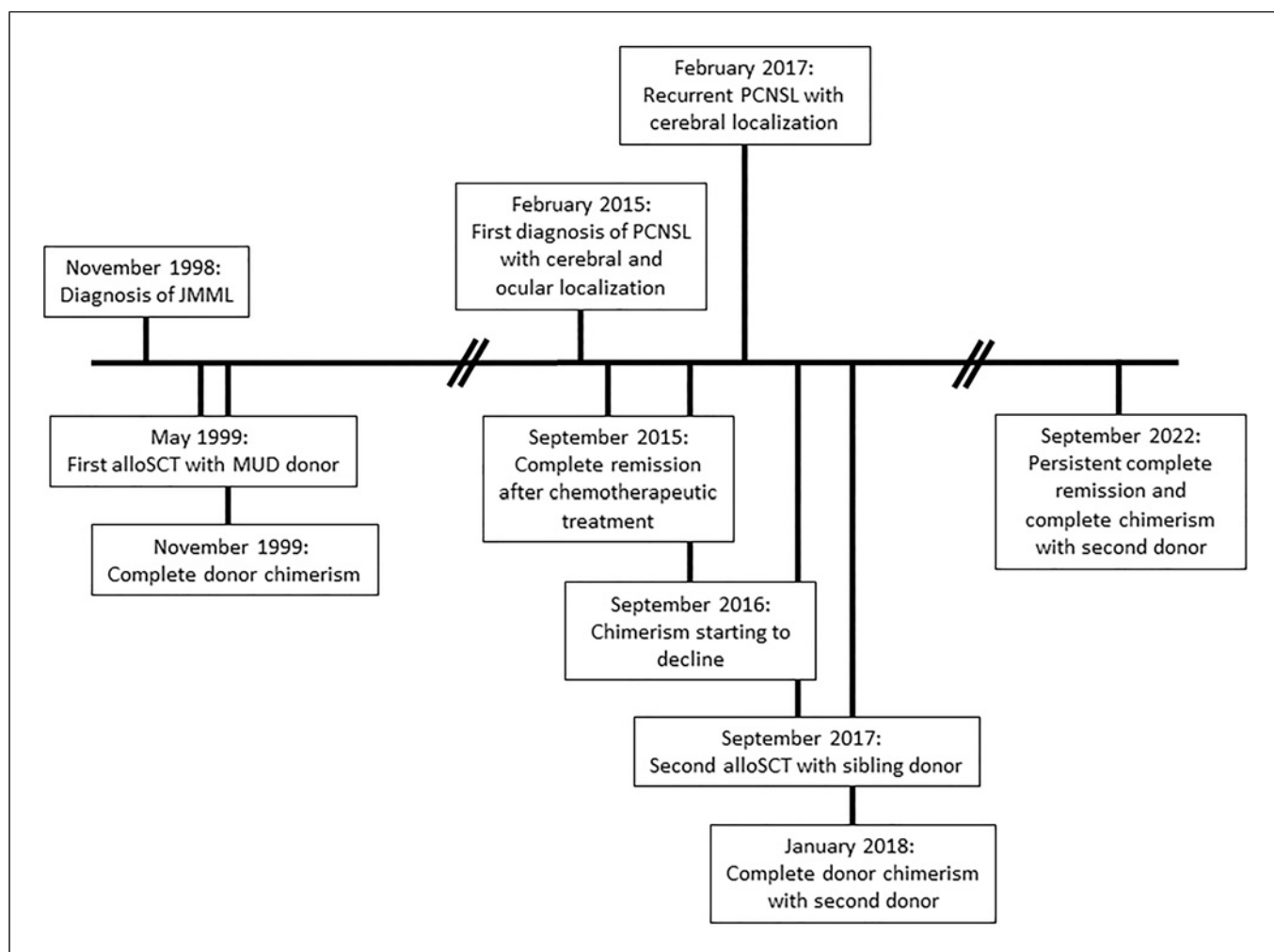


Fig. 1. Graphical timeline providing an overview of the different diseases, treatments, and outcomes after treatment. alloSCT, allogeneic stem cell transplantation; JMML, juvenile myelomonocytic leukemia; PCNSL, primary central nervous system lymphoma.

Thiotepa, carmustine, and busulfan are generally known for their ability to penetrate in the CNS. We used a thiotepa/busulfan-based conditioning regimen because these drugs are able to cross the blood-brain barrier and have acceptable toxicity [11]. Combining thiotepa with carmustine may be more efficacious due to its lesser toxicity. However, relapse rates may be higher (18–40%) [12]. Moreover, our patient had already been treated with carmustine during the re-induction courses MBVP. As conditioning for allogeneic SCT, thiotepa can also be combined with busulfan (9.6 mg/kg) and fludarabine (150 mg/m²) in TBF conditioning, but with lower doses of thiotepa (10 mg/kg) [13]. In acute lymphocytic leukemia, where the CNS is also often involved, favorable results are achieved with thiotepa, yielding comparable overall

survival to cyclophosphamide/total body irradiation conditioning [14, 15].

Literature on the role of allogeneic SCT in the treatment of PCNSL is scarce. There are a few reports on the use of allogeneic SCT in consolidating PCNSL, either successful [16] or unsuccessful [17]. In a case series of 6 German patients, 4/6 patients were alive 3–5 years after allogeneic SCT with a mean of 2.3 earlier therapies [18]. For re-induction, rituximab, methotrexate, cytarabine, carmustine, and thiotepa were used in various combinations. In this series, conditioning consisted of fludarabine (125 mg/m²), busulfan (9.6 mg/kg), and cyclophosphamide (120 mg/kg). Thiotepa was not used in this series because all patients had been treated earlier with this agent. A potential graft-versus-tumor effect has not been established in PCNSL, but it may

seem hard to believe that chemotherapy alone (with also 50% of thiotepa normally used for PCNSL) could achieve cure after 5 years in our heavily pre-treated patient and the 4/6 German patients who were also heavily pre-treated. Also, it has been demonstrated that donor T-cells can enter the central nervous system of the recipient after allogeneic SCT [19]. Moreover, recent studies with chimeric antigen receptor-modified T-cells in PCNSL demonstrate that T-cells can indeed induce an anti-tumor effect in the CNS. The role of cellular therapy in PCNSL, and central nervous system tumors in general, therefore remains an interesting area of research [20].

Conclusion

We present a case of a recurrent PCNSL in a patient previously treated with an allogeneic SCT. He is successfully treated with a thiotepa-based conditioning before a second allogeneic SCT with another donor. This regimen may be suitable for treatment consolidation in relapsed or recurrent PCNSL in a fit patient when no other therapeutic options are available including autologous SCT.

Acknowledgments

All authors were involved in the treatment of the described case and critically reviewed the manuscript. The manuscript was written by Noij.

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Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Daniel P. Noij wrote the case report. Martin van den Bent was the neuro-oncologist involved in the case and helped in editing the case report. Jeannette K. Doorduijn was the hematologist involved in the case and helped in editing the case report. Nick Wlazlo was the case manager for the case and helped edit the case report.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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