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CASE REPORT

Allogeneic stem cell transplantation for relapsed primary central nervous system lymphoma: Is it feasible?

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Abstract
Primary central nervous system lymphoma (PCNSL), has an aggressive course and in untreated patients median survival is limited to three months. For relapsed PCNSL, the treatment options are few and results are usually unsatisfactory. Allogeneic Hematopoietic Stem Cell Transplantation (allo-HCT) has been widely used for treatment of relapsed/refractory NHL patients. However there are limited data whether graft versus lymphoma effect can work in PCNSL patients. Here, we present a relapsed refractory PCNSL case treated by allo-HCT.

Introduction

Primary central nervous system lymphoma (PCNSL), is a relatively rare extra-nodular non-Hodgkin's lymphoma and consists of approximately 4% of primary central nervous system tumors. In the past three decades more than a 10-fold increase has been reported among the immunocompetent patients [1]. Although, it is generally highly responsive to therapy, high relapse rates remains to be a problem to be solved. There is no consensus for salvage treatment of relapsed and refractory disease and it involves Whole Brain Radiotherapy (WBRT), High dose chemotherapy (HDC) and autologous hematopoietic stem cell transplantation (auto-HCT) and systemic chemotherapy [2]. The choice of the salvage treatment depends on patient's age, previous treament response and comorbidities.

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The duration of first remission was defined as independent prognostic factor in PCNSL patients. Patients who relapsed within a year from initial diagnosis were shown to have a very poor prognosis (median overall survival (OS) = 3.7 months) [3]. Allogeneic Hematopoietic Stem Cell Tranplantation (allo-HCT) is an alternative strategy in relapsed/refractory lymphoma setting for achieving remission status. Although, there is limited experience with allo-HCT in PCNSL, it may offer some advantages, such as enabling ablative doses of chemotherapy and graft versus lymphoma effect and could provide benefit among selected patients with relapsed and refractory disease [4]. In this paper, we present a male patient with PCNSL who relapsed after consolidative HDC/auto-HCT, received salvage treatment and underwent allo-HCT.

Case presentation

A thirty three years-old male patient, referred to our outpatient clinic with the complains of abrupt onset seizures, headache and numbness of the left arm. Complete blood count and serum biochemistry was within normal limits. Cranial magnetic resonance imaging (MRI) demonstrated diffuse contrast enhancement in leptomeningeal areas and nodular hyperintense lesions located in periventricular white matter (Fig. 1A and B). The cerebrospinal fluid (CSF) analysis results were as follows; protein: 1.96 g/dL, albumin: 1.50 g/dL (0—350), glucose: 1 mg/dL, IgG: 7.62 mg/dL (0—34), leukocyte: 100/mL, erythrocyte: 2000/mL, LDH: 951 U/L, negative for viral meningitis. Cytological examination of CSF was consistent with the diagnosis of diffuse large B cell lymphoma and also confirmed by immunocytochemistry from cytosine preparations (Fig. 2A and B). Tumor cells were positive for CD45 and CD20 antibodies. The CT of thorax and abdomen was within normal limits. Bone marrow biopsy showed increased reactive T lymphocytes. We diagnosed the patient as primary central nervous system lymphoma and started chemotherapy regimen; rituximab (375 mg/m^2, day 1), Mtx (3.5 g/m^2, day 1) with a leucovorin rescue and cytarabine (4.4 g/m^2, days 2—3) every 3 weeks. He was also given intratechal chemotherapy with Mtx 12 mg, cytarabine 40 mg and dexamethasone 4 mg twice every cycle and complete remission (CR) was achieved. Subsequently, auto-HCT was performed with the conditioning regimen containing thiotepa (900 mg/m^2, days -5 and -4) and carmustine (600 mg/m^2, day -6) in the 6th month of diagnosis for consolidation. Post-contrast T1-weighted MR images at the coronal plane showed absence of the lesions and he was followed in CR (Fig. 1C and D).

The patient presented with the complaints of somnolence and seizures six months after the auto-HCT. Findings on repeat cranial MRI were nodular contrast enhancement on leptomeningeal areas and edema in the left parietal lobe and consistent with relapse (Fig. 1E). As a salvage therapy, WBRT with a dose of 4500 cGy was delivered in 25 fractions, each of which was 180 cGy with dexamethasone 16 mg per/-day. Concurrently, intratechal chemotherapy with Mtx 12 mg, cytarabine 40 mg and dexamethasone 4 mg was administered twice weekly. Two cycles of temozolomide 150 mg/-day, 1—5 days, every 28 days was administered. Control computerized tomography revealed stable disease. He underwent an allo-HCT from his HLA-full-matched sibling with reduced intensity conditioning regimen; fludarabine (50 mg/m^2/day, days -5, -4 and -3), busulphan (3.2 mg/kg/-day, days -5, -4 and -3) and thiotepa (5 mg/kg/day, days -7 and -6). Graft versus host disease (GvHD) prophylaxis was Mtx and cyclosporine. Neutrophil engraftment was achieved on posttransplantation day 18, however couldn't achieve platelet engraftment. Bone marrow biopsy was normocellular and the patient was found to be full donor chimeric. Post allo-HCT cranial MRI showed disappearance of enhancing lesions and the patient was followed in CR (Fig. 1F). The patient was also treated for cytomegalovirus viremia with ganciclovir, received liposomal amphoteracin B for invasive pulmonary aspergillosis and cidofovir for BK-related hemorrhagic cystitis. During the follow up, grade IV acute gastrointestinal graft versus host disease (GVHD) was diagnosed and patient responded to steroid treatment. At 7th month of allo-HCT, billuribin levels were elevated and he was diagnosed by liver GVHD, steroid was initiated. In his control cranial MRI, relapse of the lesion was detected and he died at 8th month following allo-HCT.

Discussion

PCNSL, is an aggressive non Hodgkin lymphoma subtype. Poor Prognostic factors for survival in PCNSL patients have been defined as age older than 50 years, poor performance status (PS), elevated serum LDH, elevated CSF protein and involvement of deep structures in the brain [5]. Our case has favorable features as being a young patient with good PS, normal LDH and normal CSF protein level except having periventricular disease.

High dose Mtx therapy remains the most effective first line therapy achieving 60—70% response rates with long-term survival in 15—30% of patients with PCNSL [6,7]. Addition of cytarabine to high dose Mtx has been shown to improve overall response rates [6]. Administration of high dose cytarabine after high dose Mtx aims to increase cytotoxicity due to continuance of the exposure of cells to S-phase cytostatics. Immunotherapy could be an option for treatment intensification of PCNSL. In particular, rituximab is studied for this purpose. Despite limited penetration of rituximab to central nervous system after systemic administration, it is reported to preserve anti-tumor activity [8]. However, there is conflicting evidence for combining rituximab with chemotherapy for PCNSL [9]. Response rates in prospective studies are encouraging, but no survival advantage has yet been shown [10]. In a retrospective study, when combined with high-dose Mtx based chemotherapy, rituximab improved overall survival (OS) [11].

In order to eliminate residual disease, the use of consolidative therapies such as WBRT and HDC/auto-HCT have been suggested. Consolidative WBRT has been reported to provide no additional benefit in OS after high dose MTX alone or in combination with ifosfamide [9]. However, WBRT can successfully induce immediate responses in patients with PCNSL. WBRT alone as upfront therapy have resulted in complete radiographic response in 62% of the patients, but the response was transient with a median OS of 11.6 months [12]. Its use is limited due to insufficient control of lymphoma, dissemination of lymphoma cells

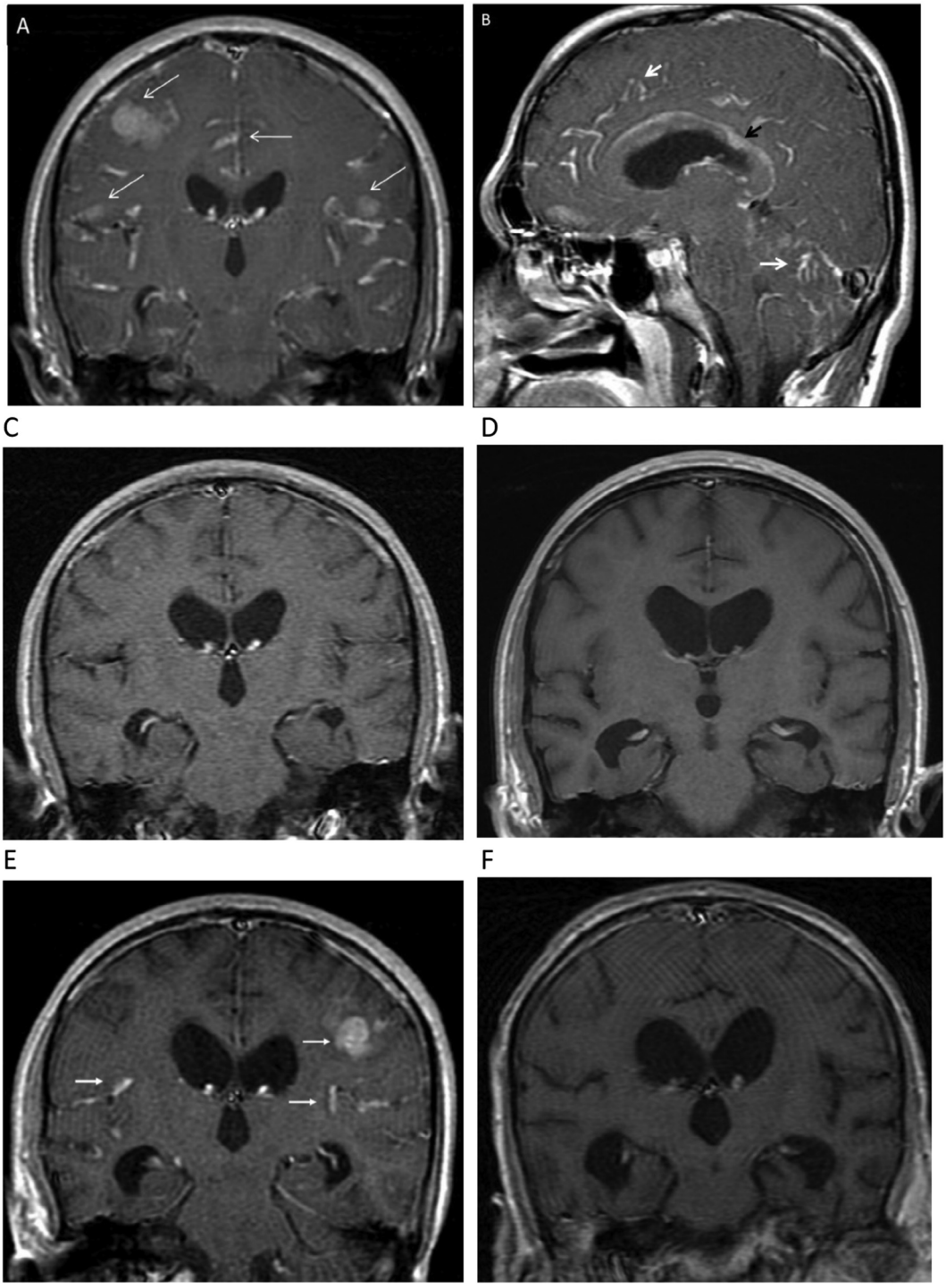

Fig. 1 (A and B) Initial MRI examination. Coronal and sagittal post-contrast T1-weighted MR images Show irregular, nodular and mass-forming enhancement typically in contact with subarachnoid surfaces (white arrows). (C) Post-contrast T1-weighted MR image at the coronal plane after the conclusion of chemotherapy demonstrates complete disappearance of the enhancing lesions. (D) Post-contrast T1-weighted MR images at the coronal plane, shows absence of the lesions after autologous bone marrow transplantation. (E) Post-contrast T1-weighted MR image at the coronal plane, one year later after the first presentation of the lesions, show recurrence of the enhancing nodular lesions (arrows). (F) Post-contrast T1-weighted MR images at the coronal plane of the patient after allogeneic peripheral blood stem cell transplant. There are no enhancing lesions.

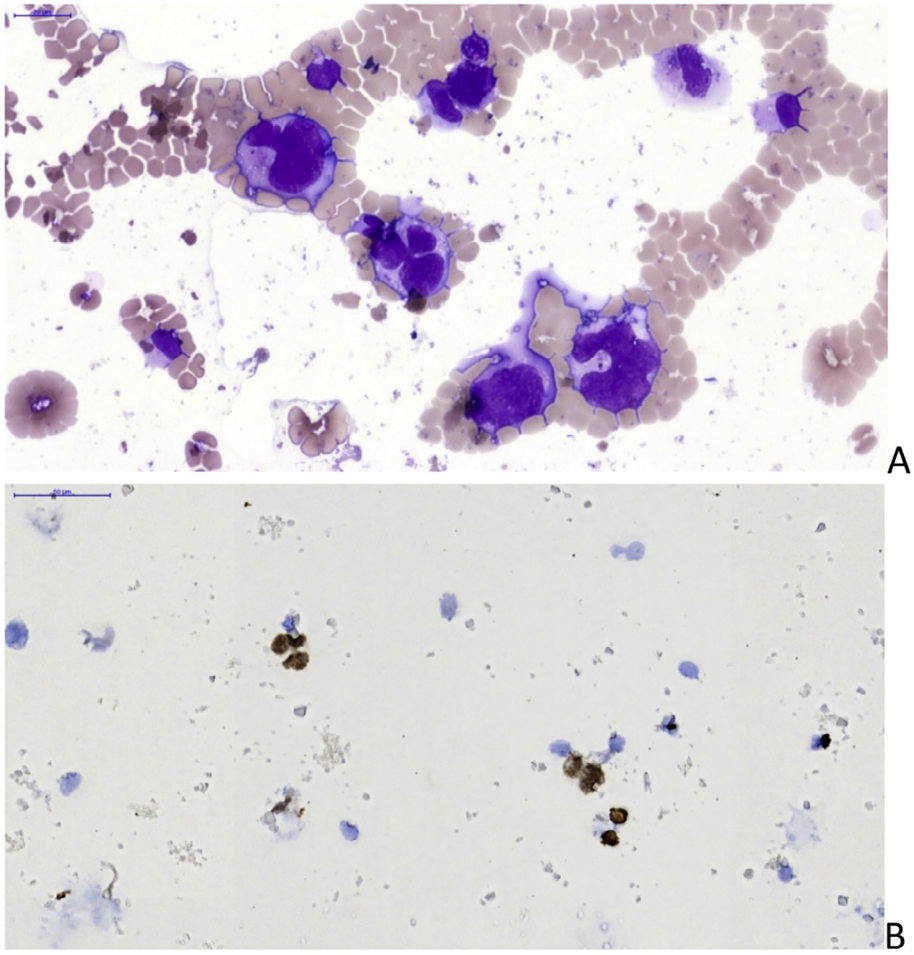

Fig. 2 (A) Atypical large lymphoid cells showing significant nuclear irregularity, coarse chromatin and distinct nucleoli, consistent with aggressive large cell lymphoma, May- Grünwald -Giemsa stain X77.1. (B) Immunocytochemically, tumor cells showing CD20 positivity (Brown colored staining).

within the CSF circulation and causing neurocognitive dysfunction.

Most investigators focused on HDC/auto-HCT as a consolidation after primary chemotherapy and proved to be highly effective [13,14]. In a retrospective analysis of patients with young age and good clinical performance, who underwent auto-HCT after receiving induction with various protocols including high-dose Mtx, cytarabine, thiotepa, ifosfamide, mitoxantrone, vincristine with or without rituximab, median OS have been reported to reach around ten years with 95% response rate. The conditioning regimens used were BCNU plus thiotepa, busulphan plus thiotepa or BEAM (carmustine, etoposide, cytarabine, melphalan) [15]. European Association of Neuro-Oncology Guidelines recommend up-front HDC/auto-HCT as an experimental treatment on the other hand National Comprehensive Cancer Network guidelines refers HDC/auto-HCT as an alternative to WBRT in patients who achieved CR after induction [16]. In our case we preferred to use auto-HCT with thiothepa/carmustin conditioning regimen as consolidative therapy, after MTX/cytarabine based induction considering his young age, good performance status and achievement of good tumor response.

For relapsed PCNSL, the treatment options are limited and results are usually unsatisfactory. HDC/auto-HCT was first used in patients with relapsed or refractory setting with 3-year event-free survival (EFS) of 53% and overall survival (OS) of 64%, respectively [17]. Indeed, 32% of patients developed neurologic toxicity. In phase 2 trial, CR rate was 60% in 43 relapsed refractory PCNSL patients and 2 year OS was 45% [18]. In another prospective multicenter study with 39 enrolled patients, 2-year progression free survival and OS rates were detected as 46% and 56.4% [19]. In relapsed setting temozolomide, topotecan, carboplatin and cytarabine achieve response rates of 26—37%. WBRT has a high but undurable response with a median OS of 11—16 months [20]. Temozolomide, an orally used alkylating agent, has emerged as a treatment option for PCNSL because of its good penetration of blood-brain barrier and mild toxicity profile. There are reports in the literature of effectiveness of temozolomide as a salvage treatment [21]. Our case has relapsed six months after auto-HCT, steroid and radiotherapy was started urgently. After achievement of disease stabilization, allo-HCT has been planned and temozolomide was preferred as bridge treatment until allo-HSCT for achieving the best response.

Although allo-HCT has been widely used for treatment of relapsed/refractory NHL patients, there has been only few reports for PCNSL patients [4]. The evidence is scarce since the particular patient population is fragile and might have high risk for early death from the toxicities of treatment. Reduced number of natural killer (NK) cells of the innate immune system and T cells of the adaptive immune system after allo-HCT yield patients to viral and fungal infections. Slow B cell recovery is observed in patients with non-myeloablative conditioning compared to myeloablative which is associated with higher risk of graft vs host disease (GVHD) [22]. Our patient developed serious viral and fungal infections as well as GVHD following reduced-intensity conditioning.

Central nervous system is known as an immune privileged environment and it has been questioned whether graft versus lymphoma effect can work in PCNSL patients. However, Wynn et al. demonstrated tumor response to immunotherapy with EBV specific T-cells in EBV associated PCNSL patients [23]. Krivit et al. also suggested that microgilial immunoreactivity they had observed in allogeneic transplant recipients might represent a central nervous system manifestation of GvHD and also GvL [24]. Interestingly, GVL effect was shown in a medulloblastoma patient by infiltration of CD3+ and CD56+ donor lymphocytes following allo-HCT [25]. Although GVT effect was previously documented in central nervous system, the effective eradication of tumor is contradictory. Varadi et al. described a treatment resistant PCNSL patient who underwent allo-HCT with a non-myeloablative conditioning regimen. Three months after transplant, the cerebral mass was no longer evident and 30 months after transplantation, the patient continued to be disease free [4]. However, our patient relapsed after 8 months of allo-HCT might be because our case had a pre-transplant residual aggressive disease and reduced-intensity regimen was unable to control the tumor before the generation of GVT effect for rapidly proliferating lymphoma.

In conclusion, the prognosis of relapsed PCNSL remains poor. Despite the high chemosensitivity and radiosensitivity of the tumor, the remission durations are not durable and relapse rate is high. New modalities in treatment strategies progressed within the past two decades with inadequate conclusions. Allo-HCT might be an alternative option in hypothesis for relapsed refractory PCNSL but seems conflicting with a high toxicity rate and low efficacy in our experience.

Conflict of interest

The authors declare no conflict of interest.

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