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Stem Cell Mobilization and Haploidentical Transplantation for Treating Relapsed Neuroblastoma

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Abstract

This study investigates the application of haploidentical stem cell transplantation (HSCT) combined with stem cell mobilization as a treatment strategy for relapsed neuroblastoma. Neuroblastoma, a pediatric cancer, poses significant challenges when it recurs, necessitating alternative therapeutic approaches. The research examines the process of stem cell mobilization, including the use of growth factors and chemotherapy to enhance stem cell harvest, and the subsequent role of haploidentical transplantation in re-establishing hematopoietic function. Key considerations such as donor selection, graft-versus-tumor effects, and post-transplantation management are explored. By evaluating clinical outcomes, including survival rates and relapse prevention, the study aims to shed light on the effectiveness and potential of HSCT in improving prognosis for children with relapsed neuroblastoma.

Keywords: Melphalan; Fludarabine; Thiotepa; Mycophenolate

Introduction

The median follow-up time was 8.1 years. Prior to SCT, patients who were in complete remission had a considerably better prognosis than those who still had a residual tumour load. Before SCT, every patient with a progressing illness relapsed within a year. Acute graftversus- host disease (GVHD) in grades II and III occurred in 31 and 12 percent of the patients, respectively. 28 percent of people developed chronic moderate GVHD, while 10 percent developed chronic extensive GVHD. According to our research, haploidentical SCT is a viable therapeutic approach that can lead to long-term remission in some NBL patients with manageable side effects and may facilitate the growth of additional post-transplantation organs [1]. Patients with refractory or relapsed metastatic neuroblastoma (NBL) continue to have a dismal prognosis despite advancements in chemotherapy, surgery, and radiotherapy.

Method

According to a recent meta-analysis, second-line chemotherapy followed by high-dose chemotherapy with autologous stem cell rescue had a 15% 5-year survival rate, compared to only 4% for nonmyeloablative second-line chemotherapy and 2% for palliative treatments. There have been several attempts to assess the function of allogeneic SCT in NBL patients. There are also signs of a graft-versus-tumor (GVT) impact in NBL, in addition to the generally acknowledged graft-versus-leukemia effect [5]. Due to transplantation-related mortality, earlier research contrasting allogeneic SCT and autologous SCT has demonstrated that the latter method does not give any advantages (TRM). However, this tactic needs to be reevaluated. Considering the use of reducedtoxicity and reduced-intensity conditioning programmes and current advancements in supporting care. The Center for International Blood and Marrow Transplant Research (CIBMTR) recently published a sizable retrospective analysis that examined allogeneic SCT from matched donors [2]. Whereas the focus of our current investigation was on whole haplotype-mismatched family donors. Natural killer (NK) cells have been implicated in a number of significant alloreactive effects in leukaemia, and it is possible that these effects also apply to patients with NBL. In order to evaluate haploidentical (haplo-) SCT with T and B cell-depleted grafts and a melphalan-based conditioning regimen in juvenile recurrent/refractory NBL, we have presented results from two prospective trials. Our goal was to demonstrate that low TRM haplo-SCT in relapsed NBL is possible [3]. In study 1, donor peripheral blood stem cells were extracted via 1 or 2 leukapheresis procedures after being stimulated with granulocyte colony-stimulating factor at a dose of 10 g/kg body weight (BW) each day for 5 days. To get 10 to 20 106 CD34+ progenitors/kg BW was our aim [4]. According to the manufacturer's recommendations, T and B cells were eliminated using CD3- and CD19-coated microbeads and an automated CliniMACS equipment. For cell processing, largescale tubing sets and the Depletion programme were employed. The identical technique and thresholds were applied in study 2 as in study 1, with the exception that antiCD20 antibody (rituximab) was employed to deplete B cells in vivo rather than CD19 in vitro. Moreover, cultivated donors after haplo-SCT, mesenchymal stem cells were given to all but two patients to promote engraftment. Fludarabine (25 to 40 mg/m2/day; total dose 125 to 200 mg/m2), thiotepa (2 5 mg/kg BW for 1 day), and melphalan (60 to 70 mg/m2/day for 2 days; total dose 120 to 140 mg/m2) made up the conditioning regimen for 24 of the 26 patients. Melphalan was not administered to one patient (due to safety concerns) and fludarabine was replaced with clofarabine (50 mg/m2 on days 8 to 5) in another patient [5]. In order to prevent graft rejection, OKT3 was administered (0 to 1 mg/kg/day, with a maximum dose of 5 mg, on days 8 to +14). To counteract the negative effects of OKT3, methylprednisolone was given on days 8 to 5 (4 mg/kg) and on days 4 to 1 (2 mg/kg). Beginning on day 0 and continuing with a maximum dose of two was applied up until day +11 to taper steroids [6-8].

To prevent immunological suppression, mycophenolate mofetil (MMF; 2 600 mg/m2) was administered (recommended duration, 60 days). 13 patients received high-dose MIBG therapy with an anticipated

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dosage of 12 mCi/kg between 15 and 44 days (median, 20 days) prior to SCT. A precise measurement showed that the mean dosage was 11.4 2.8 mCi/kg. Platelet recovery was defined as the absence of platelet replacement for at least 7 days with a platelet level 20,000/L [9]. The day of engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count (ANC) >500/L. Chimerism was determined in peripheral blood by flow cytometry using monoclonal antibodies against HLA antigens or by polymerase chain reaction (PCR) analysis of variable number tandem repeat regions. Chronic GVHD was classified as limited (grade 1) or substantial (grade 2) according to the Seattle criteria, while acute GVHD was evaluated using the Glucksberg criteria [10].

Result

Prophylactic liposomal amphotericin B or caspofungin, cotrimoxazole, and metronidazole were given to all patients. Intravenously, immunoglobulins were given every week until day +30 and then every three weeks until day +100. Seronegative recipientdonor pairs received prophylactic aciclovir up until day +180. Seropositive patients for CMV received ganciclovir prophylaxis prior to transplantation, foscarnet prophylaxis following transplantation, and then valganciclovir until day +180 or the CD4 count was >100/L. Only post-transplant foscarnet prophylaxis was given to seronegative patients with seropositive donors, then valganciclovir. Weekly PCR checks were made for the presence of CMV in the blood. If the results were favourable, the dose of foscarnet was raised or the course of treatment switched to ganciclovir. Weekly antigen and PCR analyses of stool samples were used for adenovirus (ADV) surveillance; if the When PCR analysis of the blood was performed, the results were positive. During febrile episodes, further PCR testing for human herpesvirus 6 and Epstein-Barr virus (EBV) was carried out. No preventative defibrotide was administered. 15 patients received one donor lymphocyte infusion or more (DLIs; 2.5 to 5 104 CD3+ cells/kg BW) to cure lingering recipient chimerism or to cause GVT effects. Per patient, a median of 2 DLIs were given. Patients with growing autologous signals in the T cell compartment detected on two subsequent flow cytometry-based chimerism studies or who had more autologous T cells over a certain threshold of 5% received treatment for residual recipient chimerism. After three weeks, if autologous signals weakened, no further DLI was administered. The CD3+ cell dose was quadrupled the next week if autologous signals remained or got stronger. DLI was used at the treating physician's discretion to induce GVT effects.

Discussion

The National Cancer Institute Common Terminology Criteria (NCI CTC), version 3, were modified for use in evaluating toxicity. Twentyone patients (81%) experienced nausea (50%) and mucositis (81%) as grade 3 or 4 gastrointestinal side effects. Seven patients (27%) had high bilirubin (more than five times the ULN) and/or serum glutamic oxaloacetic transaminase/glutamic pyruvic transaminase, which were both >3 times the ULN. Three patients experienced transient hypoxia that necessitated additional oxygen. No grade 3–4 toxicity to the neurologic, cardiac, renal, or dermatologic systems was detected. There was no veno-occlusive illness in any patient. 24 patients have data available for killer cell immunoglobulin-like receptor (KIR) mismatch analysis. According to the ligand-ligand model and the homozygosity model presented by Pfeiffer et al., there was no discernible difference in the likelihood of relapse between recipient-donor combinations that were mismatched and those that were not, nor between recipients who were homozygous for the Cw1 allele and those who were heterozygous (data not shown).

Conclusion

Additionally, we looked at whether the NK cell reconstitution at day +30 had any impact on the results and discovered no difference between patients with NK cell levels below and above the median of 336 cells/L. Full haplotype-mismatched stem cell transplants are now routinely used to treat leukemias, and research has demonstrated that these transplants considerably lower relapse rates when NK cells mediate alloreactive graft versus leukaemia reactions. Our research has shown that the use of CD3/CD19-depleted grafts from haploidentical donors in conjunction with reduced-intensity conditioning regimens has been particularly beneficial in terms of immunological constitution and TRM. Therefore, we thought about whether this strategy may also be possible in patients who had had rigorous pre-treatment but still had refractory/relapsed NBL, and whether NK cell-mediated GVT effects might help to improve the prognosis. We pooled data from 2 comparable prospective clinical studies in the current study. Following administration of a melphalan-based myeloablative and reduced-dose chemotherapy regimen, both trials examined the use of T and B celldepleted haploidentical stem cells.

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