Successful treatment with haploidentical PBSCT with post-transplant cyclophosphamide in a child with relapsed neuroblastoma after autologous PBSCT

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Title

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Neuroblastoma (NB) is the most common extra-cranial solid tumor of childhood.[1] High dose chemotherapy (HDCT) with autologous hematopoietic stem cell transplantation (Auto-HSCT) rescue as consolidation therapy has improved outcomes.[2] However, the relapse rate of high-risk NB in children over one year of age is still high. Despite recent advances, children with relapsed and refractory NB have a poor long-term survival.[3] Some reports highlight a graft-versus-tumor (GvT) effect with adopted allogeneic hematopoietic stem cell transplantation (Allo-HSCT) approaches. Haploidentical hematopoietic stem cell transplantation (Haplo-HSCT) is a feasible option in high-risk malignancy capable of inducing long-term remission due to GvT effect. Relapsed NB after Auto-HSCT treated with Haplo-HSCT with post-transplant cyclophosphamide (PTCy) have not been reported.

We reported a 4 years-old male who was admitted due to persistent fever for two weeks. Severe pain in the bilateral thighs was told. After admission, the laboratory data were within normal range, except elevated serum lactate dehydrogenase level of 1269 IU/L (normal range: 180-240IU/L) and urinary vanillylmandelic acid (VMA) level of 76.58mg/day (normal range for children: 1-3 mg/day). The abdominal magnetic resonance imaging revealed an 8.6 × 8.9 cm ill-defined mass arising from the left adrenal gland. The nearby tissue and great vessels were involved. Bone scan showed multiple bone metastasis. The bone marrow biopsy revealed invasion of NB cells that were positive for neuron-specific enolase and synaptophysin. NB stage IV with bone and bone marrow metastasis was confirmed. Then, he received neoadjuvant chemotherapy, which included four courses of CDV (cyclophosphamide, dactinomycin, and vincristine) and two courses of CiE (cisplatin and etoposide). After completing neoadjuvant chemotherapy, he received grossly total surgical resection of residual tumor only because of great vessels embracing by the residual tumor. Subsequently, he received autologous peripheral blood stem cell transplantation (PBSCT) as consolidation therapy. The conditioning regimen consisted of carboplatin, etoposide, and melphalan. After blood cell recovery, this patient received local radiotherapy and six months of oral 13-cis-retinoic acid for maintenance therapy. Following positron emission tomography-computed tomography (PET-CT) scan after treatment revealed no evidence of active tumor.

Ten months after completing maintenance treatment, some enlarged masses on the right neck and submandibular area were noted. Computed tomography of head and neck revealed local tumor recurrence (Fig 1). The biopsy confirmed relapsed NB. This patient received salvage chemotherapy with TOTEM (Topotecan, Temozolomide)[4] alternative to ICE (ifosfamide, carboplatin, and etoposide)[5]. After the six cycles of salvage chemotherapy, haploidentical PBST with PTCy from his father was performed. Fludarabine (90 mg/m^2) plus total body irradiation (12 Gy) was used for conditioning regimen[6]. Cyclophosphamide (50 mg/kg/day) was given on days 3 and 4 after haploidentical PBSCT. Intravenous cyclosporine 3mg/kg/day every 12 hours and mycophenolate mofetil (MMF) 15mg/kg three times per day were started on day five after transplantation. Neutrophil engraftment was found on day 13. He completed haploidentical PBSCT with PTCy smoothly. Only graft-versus-host disease grade (GVHD) I in skin and cytomegalovirus reactivation were encountered. MMF was stopping on day 35, and cyclosporine was discontinued within six months after transplantation. When preparing this manuscript (52 months after haploidentical PBSCT), the PET-CT scan confirmed no evidence of active tumor and normalized urine VMA levels. He is doing well and has good quality of life. The clinical course and treatment are summarized in Fig 2.

The outcome of relapsed NB remains dismal. Mody et al. reported that objective responses (complete or partial) were seen in 22 (41.5%) of 53 children with refractory or relapsed NB treated with irinotecan, temozolomide, and dinutuximab, and GM-CSF.[7] However, dinutuximab is not available in many places and very expensive. Because of inferior outcomes in relapsed NB, more feasible treatment is urgently needed. Haplo-HSCT is expected to treat relapsed and refractory NB. Illhardt et al. reported that event-free survival and overall survival at five years were 19% and 23%, respectively, in refractory or relapsed NB receiving Haplo-HSCT with T and B cells ex vitro depleted by CliniMACS device. No transplantation-related mortality was observed.[8] This study indicates that Haplo-HSCT is a feasible treatment and can induce long-term remission in some refractory or relapsed NB. However, T cell ex vitro by the device is also not available in many places. In contrast, Haplo-HSCT with PTCy is feasible and safe in many hospitals.

Immunotherapy with anti-GD2 Antibody has documented effective treatment for NB.[7,9] Besides, some basic studies have found that immunotherapy is one of the good ways to cure NB.[10]Therefore, immunotherapy for NB is expecting.[11] PTCy regimen developed by Luznet al. al was adapted to overcome graft failure and severe GVHD after haplo-HSCT.[12] Haplo-HSCT with PTCy has been reported a valid treatment in advanced Hodgkin lymphoma.[13] These findings indicate that the GvT effect after Haplo-HSCT with PTCy may be practical and cure some types of malignancies. In addition to the GvT effect, the high dose cyclophosphamide after Haplo-HSCT also kills the undetectable residual NB tumor cells. Therefore, we speculate that Haplo-HSCT with PTCy may be effective in treating relapsed and refractory NB.

In the present patient, he is the first case with relapsed NB after Auto-HSCT and has been found tumor-free

survival 52 months after Haplo-HSCT with PTCy. We expect the GvT effect of Haplo-HSCT with PTCy, which effectively treats advanced Hodgkin lymphoma, may also be valid to treat relapsed NB. Because of available donors, fast donation, feasibility, and safety in Haplo-HSCT with PTCy, more and more patients will receive this treatment. Further studies are warranted to confirm the effect of Haplo-HSCT with PTCy in relapsed NB.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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Figure legends

FIGURE 1 Computed tomography scan revealed a recurrent tumor on right neck.

FIGURE 2 Timeline of clinical course, treatment, and outcome. Abbreviations:

CDV (cyclophosphamide, dactinomycin, vincristine), CiE (cisplatin and etoposide), CEM (carboplatin, etoposide, and melphalan), PBSCT (peripheral blood stem transplantation), TOTEM (topotecan and temozolomide), ICE (ifosfamide, carboplatin, and etoposide), PTCy (post-transplant cyclophosphamide), TBI (total body irradiation), PET-CT (positron emission tomography-computed tomography)