Case Report

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Reduced-Intensity Unmanipulated Haploidentical Stem Cell Transplantation for Relapsed High-risk Neuroblastoma after Autologous Stem Cell Transplantation

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Abstract

Background: Neuroblastoma (NB) is one of the most common indications for autologous Stem Cell Transplantation (SCT) in pediatrics, however, the main cause of treatment failure after autologous SCT is relapse/progression. This unsatisfactory results, together with the growing insights in the mechanisms of graft-versus-tumor effects has inspired trials investigating allogenic SCT.

Case Reports: The first patient was a 20-year-old male with progression of high risk NB, 4 years after High Dose Chemotherapy with Autologous Peripheral Blood Stem Cell Rescue (HDCT/ASCT), referred with multiple 123-Metaiodobenzyl Guanidine (MIBG) avid metastatic lesions. He underwent salvage chemotherapy and MIBG-therapy, after which imaging revealed no MIBG-avid tumoral lesion throught the body. He received peripheral blood stem cell transplant from his HLA-haploidentical father and has remained disease free for more than 3 years, until the prestent time.

The second patient was a 14-year-old boy with high risk NB who presneted with multiple MIBG-avid tumoral masses 5 years after HDCT/ASCT. After salvage chemotherapy and MIBG-therapy, imaging demonstrated MIBG-avid tumoral lesion in the left 12th rib. He received peripheral blood stem cell transplant from his HLA-haploidentical father. The lesion remained stable on the MIBG scan, until +270 days post transplant, however, it showed progression in the CT scan conducted on +365 days post SCT.

Keywords: haploidentical; stem cell transplantation; relapsed high-risk neuroblastoma; autologous stem cell transplantation

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Introduction

Neuroblastoma (NB) is the most common extracranial solid tumor of childhood, accounting for 15% of all cancer caused mortality in pediatric population. Most children are classified as high risk groups and have metastatic disease at the time of diagnosis, demanding aggressive therapy with three consecutive components including induction of remission with multi-agent chemotherapy, surgical excision of the primary tumor, and radiotherapy; consolidation of remission with Highdose Chemotherapy followed by rescue with Autologous Stem Cell Transplantation (HDCT/ASCT); and maintenance therapy consisting of oral cisretinoic acid, known to decrease the proliferation and induce the terminal differentiation of neuroblastoma cells in vitro. Despite this aggressive therapy, disease recurrence remains the main cause of treatment failure, and 50-0% of patients with high-risk NB develop recurrence of disease with therapy-resistant metastatic foci. NB is one of the most common indications for autologous stem cell transplantation (auto-SCT) in pediatrics; however, the main cause of treatment failure after auto-HSCT is relapse/progression, rather than treatment-related mortality. Even after incorporation of post-transplant anti-GD2 antibody therapy, the 3-year disease-free survival rate is optimally 65%. This unsatisfactory results and poor prognosis in patients with primary chemotherapy-resistant or relapsed NB, together with the growing clinical experience with allogenic SCT for solid tumors, and the growing insights in the mechanisms of graft-versus-solid tumor effects has inspired

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clinicians to undertake trials investigating the effect of allo-SCT, in combination with adoptive donor T and/or NK cell therapy. Limited comparisons of autologous I allogeneic transplantation have not shown an advantage for allo-SCT. However, considering the relevant alloreactive effects mediated by Natural Killer (NK) cells in leukemia and possibly NB, together with improvements in supportive care and the advent of reduced intensity conditioning regimens, several groups have been re-exploring allo-SCT in NB. Along the same line, haploidentical allo-SCT is considered of particular interest because of the reported association of strong alloreactive NK cell-mediated graft versus tumoral responses. Here, we report the outcomes of haploidenticalallo-HSCT in two patients with NB who relapsed after auto-HSCT and were referred to Research Institute of Hematology, Oncology and Cell Therapy, Tehran, Iran.

Case report

Donor selection/stem cell mobilization/ graft composition

Donor evaluation comprised determining eligibility for mobilization and WBC crossmatch testing by flowcytometry. Peripheral blood stem cells (PBSCs) were mobilized by GCSF (10 µg/kg/day) administering for five consecutive days and then stem cell harvesting from donor was performed by leukapheresis on the fifth day of mobilization. The optimum cell dose was to achieve 8×106 $CD34^+$ progenitors per kg of recipients body weight.

Conditioning protocol

The reduced-intensity conditioning regimen (figure 1) consisting of fludarabine (40 mg/m2, days -9 to -6) , thiotepa (5 mg/kg, days -5 and -4) and melphalan (70 mg/m_2, days -3 and -2) was used to utilize alloimmunity with minimal transplant-related toxicity. For in vivo T cell depletion, antithymocyte globulin (thymoglobulin 2.5 mg/kg ,days -12 to -10) was given, as a preventive strategy for graft rejection and GvHD prophylaxis. Methylprednisolone (1 mg/kg) was administered on days -12 to +1 to avoid the side effects of antithymocyte globulin. For Graft Versus Host Disease (GvHD) prophylaxis, tacrolimus was started on day +5 and was continued for at least 6 months after HSCT and discontinued in the absence of GVHD. Cyclophosphamide was administered on days +3 and +4 (40 mg/kg/day) for GvHD prophylaxis by reduction of alloreactive T cells.

The protocol was approved by the ethics committee of Hematology, Oncology and Stem Cell Transplant Research Center (HORCSCT) and the Informed consent was obtained from the patients or their legal guardians.

Neutrophil and platelet engraftment were defined to occur on the first of 3 consecutive days in which the Absolute Neutrophil Count (ANC) was >0.5 × 109/L and an unsupported platelet count was >20 × 109/L, respectively. Chimerism was assessed in peripheral blood by Polymerase Chain Reaction (PCR) analysis of Short Tandem Repeat (STR) regions in peripheral blood on days 30, 60, 90, 180 and 365 after transplant. Acute GvHD was

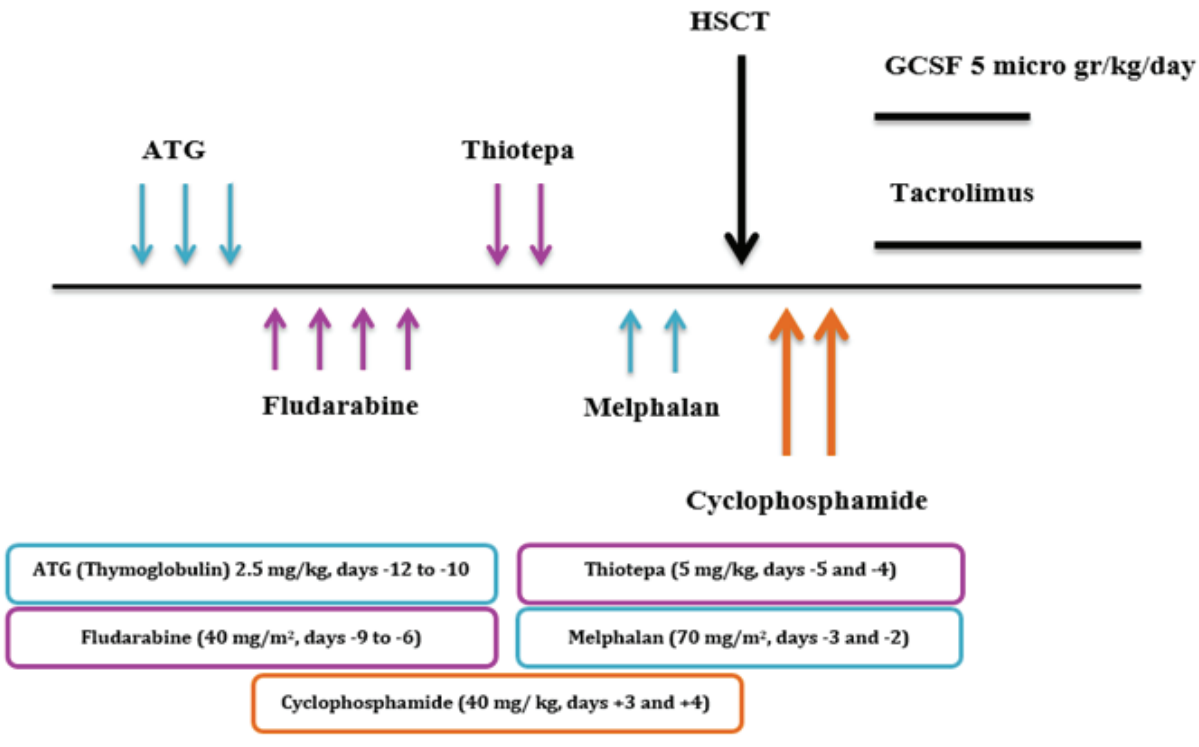

Figure 1 The conditioning regimen protocol.

graded according to the Glucksberg criteria , and chronic GvHD was staged as limited (Grade 1) or extensive disease (Grade 2) according to the Seattle criteria.

Patient Characteristics

Case number 1: A 20-year-old male with progression of high risk NB, 4 years after HDCT/ASCT, was referred with multiple MIBG-avid metastatic lesions in the lower mediastinum and para-aortic lymph nodes at T_{12} and L_2 level, in left humeral head, L_2 vertebrae, right pedicle of the L_5 vertebrae, left acetabular roof and distal part of the right femur suggestive of osteometastase (figure 2). Before allo-HSCT, he underwent chemotherapy followed by MIBG therapy with 300 mci I131- MIBG and no MIBG-avid tumoral lesion throught the body was detected in the multiple spot views imaging which was performed a week after therapy. He received allo-HSCT from his HLA-haploidentical father and unmanipulated PBSCs consisting of 5.44×106 (351×106) $CD34^+$ ($CD3^+$) cells/kg body weight were infused.

Neutrophil and platelet engraftment were reached after 10 and 13 days, respectively, and complete donor lymphocyte chimerism was achieved 30 days post-HSCT. No acute and chronic GVHD occurred. No CMV and EBV reactivation was found. No bacterial or fungal infection occurred. Disease status was evaluated on days +100, +180, +365 post transplant, with I123-MIBG scan that revealed no MIBG-avid tumoral lesion through the body (complete response). He is followed for 3 years until the present time and he has remained disease-free.

Case number 2: A 14-year-old boy with progression of high risk NB, 5 years after HDCT/ASCT, was referred with MIBG-avid tumoral mass in the lower posterior aspect of the T12 vertebrae, parietal pleura on the left hemithorax and the adjacent muscles of the same region extending downwards to the level of L2 vertebra (figure 3.A-D). He recieved five courses of salvage chemotherapy with ICE (Ifosfamide, Carboplatin And Etoposide) regimen and he was referred to our center for allo-HSCT. Tumor status at before HSCT evaluated by I123-MIBG scan demonstrated an MIBG-avid tumoral lesion in the posterior arch of the left 12th rib. He received allo-HSCT from his HLA-haploidentical father. Unmanipulated PBSCs consist of 5.8×106 (311×106) $CD34^+$ ($CD3^+$) cells/kg Body Weight (BW) were infused. Neutrophil and platelet engraftment was reached after 11 and 13 days, respectively and complete donor lymphocyte chimerism was achieved 30 days post-HSCT.

No acute and chronic GVHD occured during follow up. No CMV and EBV reactivation was found. No bacterial or fungal infection occurred. Patient's creatinine raised as an adverse effect due to tacrolimus and so it was changed in to mycophenolate mofetil. Disease status was evaluated on days +90, +180, and +270 post transplant with 123-MIBG scan and CT scan that revealed a stable lesion on the left 12th rib (Figure 3F). However, on the +365 days post-HSCT conducted CT scan, the mentioned lesion showed increase in size and he underwent imaging guided core needle biopsy of the lesion on the left 12th rib, which unfortunately small round cell tumor was reported.

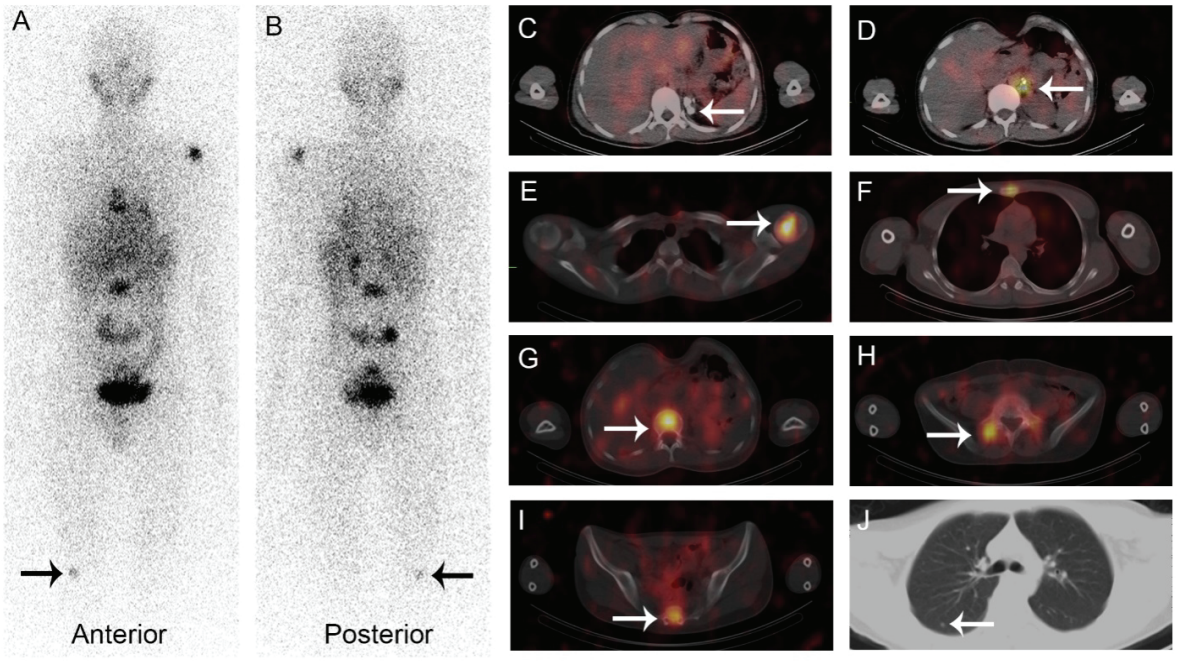

Figure 2 Planar (A and B) and SPECT/CT (C-J) views of [131I], C); MIBG avidity, D); MIBG scan, show an [131I] MIBG-avid lesion in the paraaortic region, E); as well as multiple [131I], F); MIBG-avid bone metastases in the left humeral head, sternum, G); T_{12}, H); L_5, I); sacrum, and distal right femur (black arrow). The calcified tumoral lesion in the left adrenal gland shows no [131I] J); MIBG avidity, indicating a response to prior treatments. Also, a subcentimetric pulmonary nodule in the left lower lobe demonstrates no uptake

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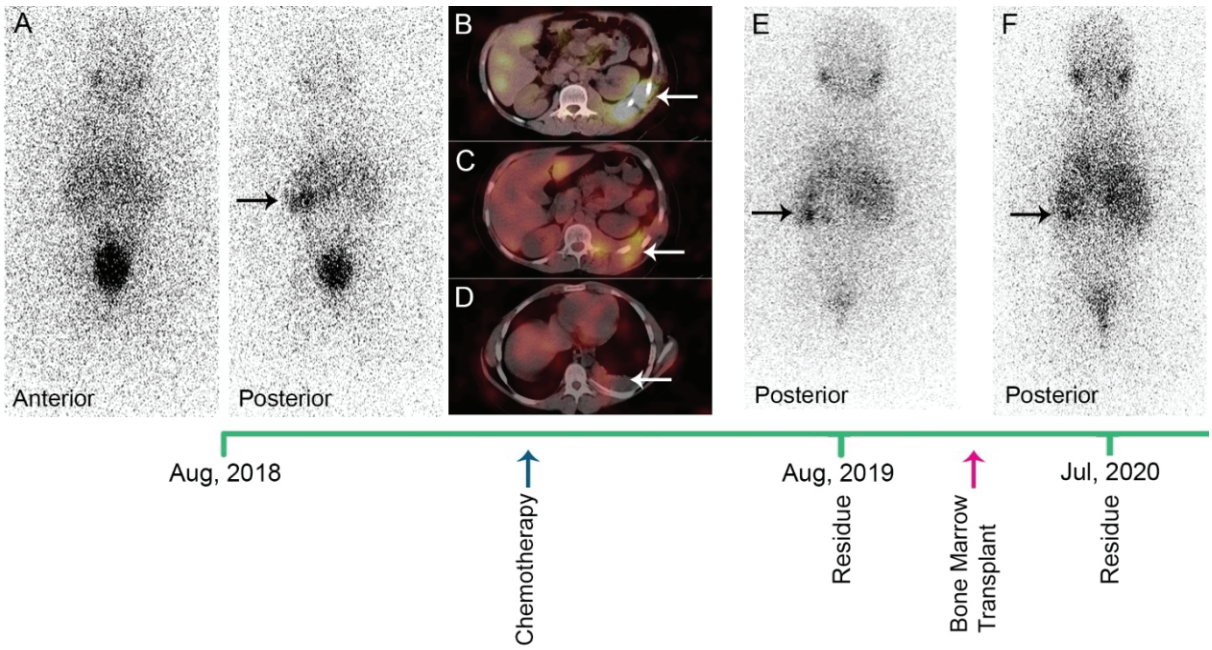

Figure 3 The study (A-D) demonstrated an [131I] A); MIBG-avid mass in the left lower posterior chest wall, B); involving its bony and soft-tissue C); structures and the pleura D); concomitant with pleural effusion. The subsequent [131I] E); MIBG scan demonstrated decreased uptake and partial regression of the mass. The patient underwent the HSCT after chemotherapy and the follow-up study post-HSCT revealed a smaller residual disease with [131I] F); MIBG-avidity in the same location.

Immune Reconstitution

We assessed T and B cells reconstitution on day +180 after HSCT in both patientsand in both of them, CD19 B- cells and CD4/CD8 T cells had reached 20/µL and 200/µL, respectively.

Discussion

The prognosis of advanced NB is extremely poor and no efficient curative option can be currently proposed for refractory metastatic NB after completion of conventional treatments. A 5-year survival rate for second-line chemotherapy followed by HDCT/ASCT has been shown to be about 15%, compared with only 4% for non-myeloablative second-line chemotherapy and 2% for palliative approaches. In therapy-resistant NB patients, survival is not improved by HDCT/ASCT or antibody-mediated immunotherapy, retinoids, or immune modulation with interleukin-2. Allo-HSCT might be a potential curative treatment option for these patients; however, children who have undergone HDCT/ASCT might be at risk of developing regimen-related co-morbidities that preclude them from receiving standard allo-HSCT. Several groups have described relevant alloreactive effects mediated by Natural Killer (NK) cells in leukemia and such effects might also be extrapolated to NB patients. In the allogeneic setting, the biological targets of the Graft Versus Tumor (GvT) effect in NB is still questionable. Primary NB cells lack high-level expression of major histocompatibility antigen (MHC) class 1 and 2 antigens, however, they may become good targets for a cellular immune response if exposure to proinflammatory cytokines leads to upregulation of their MHC molecules. Considering the potential described GVT effects, Inoue et al. reported the first patient with refractory advanced NB who underwent HLA haploidentical bone marrow transplantation from his father in 2003. Thereafter, several attempts have been made to evaluate the role of allo-HSCT in patients with NB. In 2006, allo-HSCT for high-risk NB was categorized as a clinical (with sibling donor) or developmental (with well-matched unrelated donor) therapeutic option in European Bone Marrow Transplant (EBMT) annual meeting. In a retrospective study in 2013 conducted by the Center for International Blood and Marrow Transplant Research (CIBMTR), 143 cases of NB who underwent allo-HSCT from matched related and unrelated donors were analyzed, and found a transplant related mortality (TRM) of 25% at one year. In 2018, llhardt et al. analyzed data from two prospective trials, who conducted haploidentical HSCT on 26 patients with refractory, metastatic relapsed or locally relapsed MYCN-positive NB, with a conditioning regimen comprising melphalan, fludarabine, thiotepa, OKT3, and a short course of mycophenolate mofetil post-transplantation and reported a 5-years EFS and OS of 19% and 23%, respectively. In their study, patients in complete remission before HSCT had a significantly better prognosis than those with residual tumor load. This could be in agreement with our report, as one of our patients who had a remnant lesion before allo-HSCT, experienced progression. Therefore, we suggest to induce complete remission before transplantation, as the antitumoral effect of NK cells might not be sufficient to overcome a residual tumor burden.

In conclusion, after achieving complete remission in patients with relapsed high risk NB, haploidentical allo-HSCT could be considered as a potentially effective therapeutic strategy leading to improved long term relapse-free survival.

Conclusion

After achieving complete remission in patients with relapsed high risk NB, haploidentical allogenic SCT could be considered as a potentially effective therapeutic strategy leading to improved long term relapse-free survival.

Conflict of interest

Non declared.

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