# Stem Cell Transplantation in Neuroblastoma: Iranian Experience

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## Abstract

*Introduction:* Neuroblastoma is the most common extracranial solid tumor in children, accounting for 8% to 10% of all childhood cancers. Significantly, autologous transplantation appeared to have the largest impact on survival for the high risk subset of patients, such as those with N-MYC amplified metastatic disease diagnosed after age 2 years.

*Patients and methods:* This study includes high risk, relapse, or refractory patients with NBL who underwent SCT from 1998 up-to 2009. There were nine patients with NBL consisting of seven males and two females. Among nine neuroblastoma patients who received transplantation, eight patients received autologous transplantation and one patient received allogenic transplantation of full matched sibling. The main conditioning regimen was CEM; consist of Carboplatin (400 mg/$m^2$ for 3 days), Etoposide (200 mg /m2 for 3 days), and Melphalan (75 mg /$m^2$ for 2 days). Patients transplanted after 2008 received 13-cis-retinoic-Acid 120-160 mg/$m^2$/2weeks in month, as maintenance from days sixty after SCT until one year.

*Results:* Median age of recipients was 5.5 years (range: 4-8 years). All patients were in stage IV of NBL. The common pathological result was stromal poor. Primary involved site at diagnosis was adrenal gland in patients. The source of stem cells was Peripheral Blood in seven patients and Bone Marrow in two patients. The median duration required to achieving an Absolute Neutrophil Count (ANC) $\geq 500\times10^9$/µl was 11 days (range: 8-14 days). The median duration required to achieving a platelet count of $\geq 20\times10^9$/µl was 19 days (range 10-70 days). Six of nine recipients had relapsed. At present four patients are alive that one of them had relapse and three ones are in complete remission and all of them passed 250 days after SCT. Relapse was the only cause of death.

*Conclusion:* Regarding to the studies we can conclude in Neuroblastoma patients Stem Cell Transplantation is better than chemotherapy alone, the allogeneic Stem Cell Transplantation has no preference to autologous SCT and Peripheral Stem Cell Transplantation is significantly better than Bone Marrow.

*Keywords:* Stem cell transplantation, Neuroblastoma, Peripheral blood.

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## Introduction

Few tumors have engendered as much fascination and frustration for clinical and laboratory investigators as neuroblastoma, the most common and deadly solid tumor of childhood. Neuroblastoma is the most common extracranial solid tumor in children, accounting for 8% to 10% of all childhood cancers. The prevalence is about 1 case per 7,000 live births, and there are about 800 new cases of neuroblastoma per year in the United States. Evidence indicates that this incidence is fairly uniform throughout the world, at least for industrialized nations.These tumors may regress spontaneously, particularly in infants, or they may mature into a benign ganglioneuroma. However, most children older than 1 year have extensive or metastatic disease at the time of diagnosis, and their overall prognosis has been poor. At diagnosis the finding characteristics of high risk neuroblastoma include an age of more than one year, metastases, amplification of N-MYC oncogene, and histologic findings (1, 2). The majority of high-risk neuroblastoma patients have metastases to the bone marrow at diagnosis. Thus, neuroblastoma serves as a model solid tumor in which the genetic and biologic analysis of tumor cells provides important information that guides optimal patient management. The challenge of the next decade is to

translate this information into more effective and less toxic therapy for these patients. Stage of disease by the INSS is clearly correlated with patient outcome and is used by all cooperative groups to stratify therapy. More recently, MIBG scintigraphy has become an imponant component of response evaluation, and the quality of MIBG response to induction chemotherapy is highly correlated with outcome. Significantly, autologous transplantation appeared to have the largest impact on survival for the ultra-high risk subset of patients, such as those with N-MYC amplified metastatic disease diagnosed after age 2 years. Thus, future clinical trials for high-risk neuroblastoma patients will most likely use autologous peripheral blood stem cells for myeloablalive rescue (3, 4).

## Patients and methods

This study includes high risk, relapse, or refractory patients with NBL who underwent SCT from 1998 up-to 2009 in HORCSCT of Shariati Hospital (5). Among nine neuroblastoma patients who received transplantation, eight patients received autologous transplantation and one patient received allogenic transplantation of full matched sibling. There were some variants in this study such as age at diagnosis, sex, stage, pathology, N-MYC, disease status at transplantation, engrafment, post transplant complications, and patient's status post transplantation. Patients had prior chemotherapy in different centers before transplantation. The chemotherapy regimen before transplant was OPEC, which includes Vincristine (Oncovin), Cyclophosphamide, Cisplatin, and Etoposide. Two patients received salvage regimen after OPEC. Before transplantation, parents were informed about transplant's side effects and advantages parental consent was obtained for transplant and clinical intervention. The most number of transplantations (5 of 9) were done in the year 2008. One of these patients, received transplantation in the year 1998, 2 patients received in 2004 and 1 patients received in 2005. Bone Marrow aspiration and biopsy, Bone Scan, CT-Scan, Meta iodobenzyl guanidine (MIBG) scintography were done on all recipients who received transplantation in the year 2008. The patients were in different status before transplantation, Consist of 6 patients in complete remission, one patient in partial remission, one patient in refractory and one patient in relapse status. The main conditioning regimen used in seven patients was CEM; consist of Carboplatin (400 mg/$m^2$ for 3 days), Etoposide (200 mg /m2 for 3 days), and Melphalan (75 mg /$m^2$ for 2 days). Conditioning regimens were myeloablative. Patients received all agents in-patient. All recipients received Acyclovir (5 mg/kg IV), Trimethoprim/sulfamethoxazole (5 mg/kg/TMT/BD) for infection prophylaxis. A median of $12.66\times10^8$/Kg Nucleated cells (range: 4-$17.28\times10^8$/Kg), $8.7\times10^8$/Kg Mononucleated cells (range: 2.14-$10.89\times10^8$/Kg) and $2.18\times10^6$/Kg CD34 cells (range: 0.9-$8.9\times10^6$/Kg) were infused (Table 1). After discharge, patients followed in out patient clinics. Patients transplanted after 2008 received 13-cis-retinoic-Acid 120-160 mg/$m^2$/2weeks in month, as maintenance from days sixty after SCT until one year.

## Results

There were nine patients with NBL consisting of seven males and two females (Table 2). The median age of transplantation was 5.5 years (range: 4-8 years). All patients were in stage IV of NBL (Table 2). The common pathological result was stromal poor. From five patients witch had done MIBG before transplantation one of them was MIBG positive. Since 2008 tumor N-MYC amplification was done for patients and it was present in three cases. Primary involved site at diagnosis was adrenal gland in patients. The common site of metastasis consist of bone marrow in six patients, liver in four, bone in three, lymph node in two, paraaortal in two, para vertebral in one and retroperitoneal in one recipient. Some patients had multiple sites for metastasis. The source of stem cells was Peripheral Blood in seven patients and Bone Marrow in two patients (Table 3). The median duration of hospitalization was 25 days (range: 18-31 days). The median duration required to achieving an Absolute Neutrophil Count (ANC) $\geq 500\times10^9$/µl was 11 days (range: 8-14 days). The median duration required to achieving a platelet count of $\geq 20\times10^9$/µl was 19 days (range 10-70 days).

**Table 1. Patients demographic characteristics**

| | |
|---|---|
| Median age, y (range) | 5.5 (4-8) |
| Sex (male/female) | 7/2 |
| Median number of mononucleated cells, $10^8$/kg (range) | 8.7 (2.1-10.9) |
| Median number of nucleated cells, $10^8$/kg (range) | 12.7 (4-17.3) |
| Median number of CD34, $10^6$/kg (range) | 2.2 (0.9-8.9) |
| Median days to ANC>$500\times10^9$/µl engraftment, (range) | 11 (8-14) |
| Median days to Plt>$20\times10^9$/µl engraftment, (range) | 19 (10-32) |

ANC: Absolute Neutrophil Count

**Table 2. Characteristics of the patients before treatment**

| Sex | Pathology | Primary site | Secondary site | Chemotherapy | Status before Tx. | MIBG | N-MYC |
|---|---|---|---|---|---|---|---|
| Male | | Adrenal | BM, retroperitoan, paraaort, liver | OPEC | refractory | | |
| Male | Stromal poor | Adrenal | lynphadenophaty, paraaort | OPEC | relapse | | |
| Female | | Adrenal | BM, Neck lymphadenopathy | OPEC | remission | | |
| Female | Stromal poor | Adrenal | BM, liver | OPEC | remission | - | + |
| Male | Stromal poor | Adrenal | BM, Bone, liver | OPEC, SALVAGE | PR3 | + | - |
| Male | Stromal poor | Adrenal | Bone | OPEC, SALVAGE | remission | - | + |
| Male | | Adrenal | BM | OPEC | remission | | |
| Male | Stromal poor | Adrenal | Bone, paravertebral(thorax) | OPEC | remission | - | + |
| Male | Stromal poor | Adrenal | BM, liver | OPEC | remission | - | - |

OPEC: vincristine, cisplatin, etoposide, and cyclophosphamide, BM: Bone marrow,

**Table 3. Transplant information of the patients**

| Graft type | source of SCT | Conditioning regimen | Complications | Status after treatment |
|---|---|---|---|---|
| Auto | PB | Carboplatin, Etoposide, Melphalan | Severe mocusitis | Expire due to relapse (2 mo 17 d) |
| Auto | BM | Carboplatin, Etoposide, Melphalan | | Expire due to Relapse (4 mo 12 d) |
| Auto | BM | Cyclophosphamide, Etoposide | | Expire due to Relapse (7 mo 2 d) |
| Auto | PB | Carboplatin, Etoposide, Melphalan | Fever, Seizure | Alive with Remission (9 mo 5 d) |
| Auto | PB | Carboplatin, Etoposide, Melphalan | | Alive with Relapse (12 mo 4 d) |
| Auto | PB | Carboplatin, Etoposide, Melphalan | | Expire due to relapse (5 mo 28 d) |
| Allo | PB | Busulfan, Cyclophosphamide | Gastrointestinal problem, Ptosis | Expire due to Relapse (1 mo 15 d) |
| Auto | PB | Carboplatin, Etoposide, Melphalan | Staphilucucus epidermis | Alive with Remission (7 mo 27 d) |
| Auto | PB | Carboplatin, Etoposide, Melphalan | UTI, Herpes zoster | Alive with Remission (9 mo 15 d) |

PB: Peripheral blood, BM: Bone marrow, UTI: Urinaty tract infecton.

Some transplant complications in ward were gasterointestinals (GI) problems, mcusitis, fever, infection and seizure. One patient had petosis and retro-orbital cavity relapse. Six of nine recipients had relapsed. From six patients with relapse four patients had bone marrow involvement. At present four patients are alive that one of them had relapse and three ones are in complete remission and all of them passed 250 days after SCT. Relapse was the only cause of death.

## Discussion

NBL was newly classified in low, intermediate, and high risk groups according to age at diagnosis, stage, histopathology, N_MYC gene status and DNA ploidy by the Pediatric oncology Group (POG) and the children cancer group (CCG). High risk patients group are candidate for Autologous SCT with myeloablative therapy (6). Myeloablative therapy became the standard of care in the united states after the children's cancer Group compared the outcome of 198 patients randomly assigned to receive myeloablative chemotherapy with Autologous stem cell transplantation with the out come of 190 patients who were randomly assigned to receive chemotherapy alone and 3 year PFS rate ±SE: 34% ± 4% v 22%± 4%,respectively P=0.34), (1). In the retrospective study that performed in Korea: eighty eight cases of NBL underwent autologous SCT following marrow ablative therapy at 12 centers of Korean society of pediatric Hematology oncology between January 1996 and September 2000. In this study, the mean duration required to achieve an ANC $\geq 500\times10^9$ /µl and Platelet count of $\geq 50000\times10^9$/µl were 12 and 30 days after transplantation, respectively and the most post transplant complication (88%) were gasterointestinal tract problems such as mocusitis (7). Researchers showed that high dose therapy with tandem autologous stem-cell rescure is effective for treating high risk neuroblastoma, with encouring long-term survival. CNS relapse and secondary malignancies are rare after this therapy (8). Patients transplanted by peripheral stem cell collection did significantly better than both the bone marrow transplantation and chemotherapy-alone group (9). In our study, all patients had stage IV NBL. Five patients who received transplantation in the year 2008 were assessed by N-MYC gene. Tumor N-MYC amplification was present in three cases. At present in our center few NBL patients received SCT and it needs to more transplantation for validation. Starting of N-MYC and MIBG tests, determination of the risk group patients, patients precise administration in complete remission or at least partial remission, also stem cell collection from peripheral blood instead of bone marrow (for purging) and prescription of cis-retinoic Acid after stem cell transplantation are the new process in our center. Finally Regarding to the studies we can conclude in NBL patients Stem Cell Transplantation is better than chemotherapy alone, the allogeneic SCT has no preference to autologous SCT and Peripheral Stem Cell Transplantation is significantly better than Bone Marrow (7, 8).

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