J Korean Med Sci 2003; 18: 242-7
ISSN 1011-8934

Autologous Stem Cell Transplantation for the Treatment of Neuroblastoma in Korea

Autologous stem cell transplantation (ASCT) for the treatment of high-risk neuroblastoma (NBL) is an accepted method for restoring bone marrow depression after high dose chemotherapy. We retrospectively analyzed eighty eight cases of NBL that underwent ASCT following marrow ablative therapy at 12 transplant centers of the Korean Society of Pediatric Hematology-Oncology between January 1996 and September 2000. Seventy nine children were of stage IV NBL and 9 were of stage III with N-*myc* amplification. Various cytoreductive regimens were used. However, the main regimen was 'CEM' consisting of carboplatin, etoposide and melphalan, and this was used in 66 patients. Total body irradiation was also added in 36 patients for myeloablation. To reduce tumor cell contamination, stem cell infusions after $CD34^+$ cell selection were performed in 16 patients. Post-transplantation therapies included the second transplantation in 18 patients, interleukin-2 therapy in 45, 13-cis retinoic acid in 40, 131-meta-iodobenzylguanidine in 4, conventional chemotherapy in 11, and local radiotherapy in 8. Twenty two patients died, sixty six patients are surviving 1 to 46 months after ASCT (median follow-up duration, 14.5 months). Although the follow-up period was short and the number of patients small, we believe that ASCT might improve the survival rate in high-risk NBL.

Key Words : *Neuroblastoma; Stem Cell Transplantation; Korea*

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Received : 13 August 2002
Accepted : 28 November 2002

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*This work was supported by grant (No. R01-2001-000-00128-0) from the Korea Science & Engineering Foundation.

INTRODUCTION

Neuroblastoma (NBL) is the most common extracranial solid tumor in children and accounts for about 8% of all childhood cancers. About two thirds of the children with NBL are metastatic at diagnosis, and often progressed despite treatment. Worldwide increase of autologous stem cell transplantations (ASCT) for NBL over the past decade has been made because there is a linear-log relationship between drug dosage and tumor response (1).

Age, stage and the N-*myc* gene copy number in tumor cells are generally considered the most important determinants of prognosis. Unfavorable tumor histology by the Shimada histopathologic grading system and diploid tumor DNA are additional risk factors that have been incorporated into a schema for stratifying patients into low, intermediate or high-risk groups (1).

Current management of NBL uses risk stratification to minimize late sequelae for patients with favorable features and to increase the survival of poor-prognosis patients by utilizing more intensive therapies. Whereas patients with localized stage I and stage II disease with non-amplified N-*myc* gene expression have excellent prognosis for long-term survival, children over one year of age with stage IV or metastatic disease and those with N-*myc* amplified tumors have a 5-yr disease-free survival of less than 20% by conventional multimodal therapeutic approaches (2, 3).

Autologous stem cell rescue after myeloablative chemotherapy or chemoradiotherapy is now offered as consolidation therapy to children with metastatic NBL and those with stage III NBL with poor-prognostic factors. Over the past fifteen years, several institutional and cooperative group clinical trials have explored the role of this therapy in managing high-risk NBL. Results from these trials show that 30-45% of patients with

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complete or partial remission after initial chemotherapy achieve long-term disease-free survival with myeloablative therapy followed by ASCT (4, 5).

The purpose of this retrospective study from 12 transplant centers of the Korean Society of Pediatric Hematology-Oncology, was to identify the dose of stem cell collection, $CD34^+$ purging effect, conditioning regimen, engraftment complication, additional post-transplantation therapy and survival.

MATERIALS AND METHODS

Patients

Surveys and medical records were analyzed retrospectively for eighty nine patients with NBL who underwent ASCT between January 1996 and September 2000. One patient was excluded because of loss during follow up. Twelve institutions involved the Korean Society of Pediatric Hematology-Oncology participated in this study. These cases were assessed in terms of age at diagnosis, sex, stage, N-*myc* gene copy number, disease status at transplantation, mobilization products, conditioning regimen, purging, engraftment, post-transplantation complications and additional post-transplantation therapy.

Statistical Analysis

Results are presented as mean±SD, and median with ranges. Cumulative survival was analyzed using Kaplan-Meier curves and log-rank statistics with SPSS software for Windows. A p value of less than 0.05 was considered significant.

RESULTS

Pre-transplantation Patient Characteristics

The patients consisted of 45 males and 43 females with a median age at diagnosis of 3 yr 7 months (3 months-17 yr 2 months). Primary sites were the adrenal glands in 47 patients, retroperitoneum in 25, thoracic cavity in 14 and orbital cavity in 2. Pre-transplant disease status was complete response in 25 patients, partial response in 48 and relapse in 15. Seventy nine children were of stage IV NBL and 9 were of stage III with N-*myc* amplification. Common sites of metastases included the bone, bone marrow, lymph nodes, liver, orbit lung and soft tissue in the respective order. The majority of the prior therapy before ASCT was CCG 3891 that consisted of cisplatin, etoposide, doxorubicin and cyclophosphamide, and which was used in 59 patients (Table 1).

Table 1. Pre-transplantation patient characteristics (N=88)

Age at diagnosis, (months)	
Median	43
(range)	(3-206)
Sex	
Male:Female	45:43
Primary site	
Adrenal gland	47
Retroperitoneum	25
Thoracic cavity	14
Orbital cavity	2
N-*myc* amplification status	
Single	17
Amplification	26
Not checked	45
Metastatic sites at diagnosis	
None	9
Bone	65
Bone marrow	57
Others*	26
Pre-transplantation disease status	
Complete response	25
Partial response	48
Relapsed	15
Prior therapy before autologous stem cell transplantation	
Cisplatin, Doxorubicin, Etoposide, Cyclophosphamide	59
Cisplatin, Doxorubicin, Etoposide	16
Cisplatin, Doxorubicin, Etoposide, Cyclophosphamide, Vincristine, Dacarbazine	9
Cisplatin, Doxorubicin, Etoposide, Ifosphamide	4

Others*; liver, lymph node, lung, brain, and soft tissue.

Stem Cell Collection

In all patients, a double-lumen Hickman catheter was used for vascular access during the collection. All stem cells except one were collected by apheresis, bone marrow harvest and apheresis were combined in one case, and bone marrow harvest was used only in one case. CS-3000 cell separator (N=40) and COBE-Spectra cell separator (N=58) were used for the apheresis procedure including double harvest. Stem cell collections were performed in all patients with minimal problems, such as nausea and vomiting (N=12), headache (N=10), tingling sensation (N=5), clamping abdominal pain (N=2), and urticaria (N=1). The mean numbers of collected mononuclear cells (MNCs), $CD34^+$ cells, and CFU-GM were $12.1 \pm 9.3 \times 10^8$/kg, $9.1 \pm 9.8 \times 10^6$/kg and $11.8 \pm 14.5 \times 10^5$/kg, respectively. To reduce tumor cell contamination, stem cell infusion after $CD34^+$ positive cell purging was performed in 16 patients. The CEPRATE SC Stem Cell Concentration System (N=9) and the CliniMACS system (N=7) were used for $CD34^+$ cell selection. After column separation using monoclonal antibody, $CD34^+$ cells were reduced to $8.6 \pm 6.2 \times 10^6$/kg with a 27.7% cell loss.

Conditioning Regimens

The median duration from diagnosis to ASCT was 8.5 months (2 months-4 yr 3 months). Various cytoreductive regimens were used, but the main regimen was 'CEM' con-

sisted of carboplatin, etoposide and melphalan, and was used in 66 patients. TBI was also added in 36 patients for myeloablation (Table 2). The radiation dose ranged from 540 to 1,200 cGy in 3-5 fractions with or without kidney shielding.

Engraftment and Post-transplantation Complications

A mean $10.2 \pm 9.3 \times 10^8$/kg MNCs and $7.3 \pm 7.8 \times 10^6$/kg $CD34^+$ cells were reinfused. Nausea and vomiting were the most common complications followed by reinfusion (76.6%), abdominal pain, headache, arrhythmia, and fever also developed in such order, but no adverse effects were found in 18.3%. Cells were infused in one dose, but in one case they were infused twice, once on day 0 and day 1 because DMSO toxicity and fluid overload were expected. G-CSF and/or GM-CSF were administered to assist hematopoietic reconstitution. The mean duration required to achieve an absolute neutrophil counts (ANC) of $\geq 500/\mu L$, $\geq 1{,}000/\mu L$ and platelet counts of $\geq 50{,}000/\mu L$ were 10, 12 and 30 days, respectively. No patient had shown signs of graft failure except for one-death patients before engraftment.

Gastrointestinal tract problems, such as mucositis and diarrhea were the most common post-transplantation complications (88.0%). Fever developed in 77.6%, but the cause was proven in only 6 patients, who had cellulitis, pneumonia, catheter infection, and sepsis. In all cases except 9 prophylac-

Table 2. Myeloablative chemoradiotherapy protocol (N=88)

Myeloablative chemoradiotherapy	with TBI	without TBI
Cisplatin, Doxorubicin, Teniposide, Melphalan	7	1
Carboplatin, Etoposide, Melphalan	28	38
Melphalan, Etoposide	0	5
Others*	1	8

Others*; Carboplatin, Thiotepa, Melphalan, Ifosfamide, Melphalan, Neoplatin, Vepocid. TBI; Total body irradiation.

Table 3. Additional post-transplantation therapy for neuroblastoma in Korea

Post-transplantation therapy	Number
Second transplantation	18
13-*cis* retinoic acid	40
Interleukin-2	45
MIBG* therapy	4
Conventional chemotherapy	11
Local radiotherapy	8
No additional therapy	30

MIBG*; 131-meta-iodobenzylguanidine.

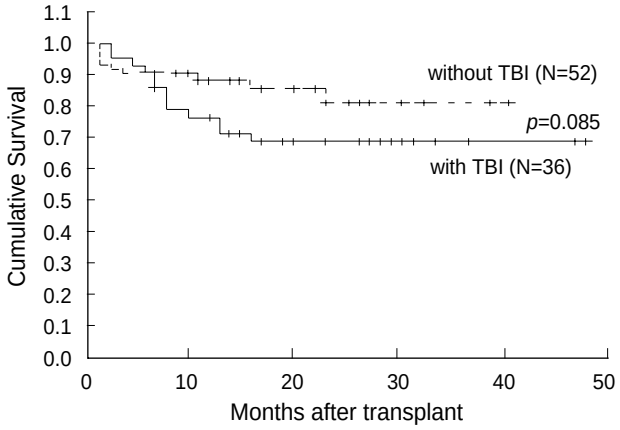

Fig. 1. Kaplan-Meier probability survival curve for high-risk neuroblastoma patients after autologous stem cell transplantation according to total body irradiation in Korea (N=88). The survival rate of non-treated group (----) was superior to that of the treated group (—), but it was not statistically significant (p=0.085). Ticks indicate censored data.

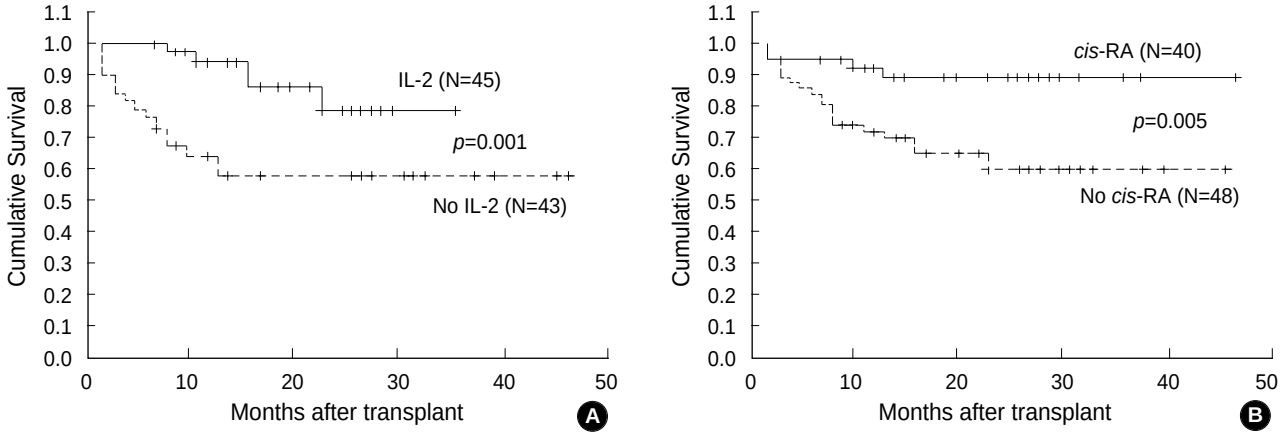

Fig. 2. Kaplan-Meier probability survival curve for high-risk neuroblastoma patients after autologous stem cell transplantation according to additional post-transplantation therapy in Korea (N=88). Patients treated (—) with interleukin-2 (A) and 13-*cis* retinoic acid (B) had significantly higher rates of survival than those in the non-treated (----) group (p=0.001 and p=0.005, respectively). Ticks indicate censored data.

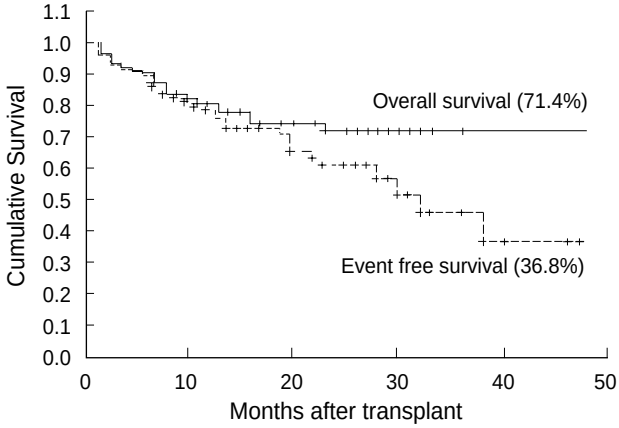

Fig. 3. Kaplan-Meier probability survival curve for high-risk neuroblastoma patients after autologous stem cell transplantation in Korea (N=88). Overall survival (—) rate was 71.4% and event free survival (----) rate was 36.8%. Ticks indicate censored data.

tic antibiotics were used.

Additional Post-transplantation Therapy

Details concerning additional post-transplantation therapy are listed in Table 3. Post-transplantation therapies were as follows; second transplantation in 18 patients, interleukin-2 (IL-2) therapy in 45, 13-*cis* retinoic acid (*cis*-RA) in 40, conventional chemotherapy in 11, local radiotherapy in 8 and 131-meta-iodobenzylguanidine (MIBG) therapy in 4.

Survival

Various prognostic factors were evaluated in this study. Firstly, those with bone involvement group had a poorer prognosis than those with bone marrow involvement, but this was not statistically significant (p=0.634). The survival rate differed according to the duration from diagnosis to ASCT. Early ASCT group with transplantation done within 1 yr from initial diagnosis had a better prognosis than late ASCT group after 1 yr, but this was not statistically significant (p=0.055). The survival rate was affected by the pre-transplantation disease status. The complete remission status was the most superior prognostic factor (p=0.004). No significant difference was found between the survivals of the purging and non-purging groups (p=0.987) and TBI also caused no significant difference in terms of survival (p=0.085) (Fig. 1). IL-2 and *cis*-RA therapy were more effective factors of survival than no further additional treatment (p=0.001 and p=0.005, respectively) (Fig. 2).

Sixty six patients are alive with a median follow-up of 14.5 months (1-46 months) after ASCT. The Kaplan-Meier post-transplantation survival curve is shown in Fig. 3. Overall and disease free survival rate at 46 months after ASCT were 71.4% and 36.8%, retrospectively. Twenty two patients died after a median of 6.4 months (1-22 months) post-transplant and 18 patients had recurred. Out of the 22 deaths, 15 patients were due to complications, such as veno-occlusive disease, hemorrhage, disseminated intravascular coagulopathy, sepsis, pneumonitis and pulmonary edema.

DISCUSSION

Cure of high-risk NBL requires the destruction or removal of 10^{11} to 10^{12} tumor cells by a combined modality therapy. For most patients with high-risk NBL, current non-myeloablative therapy is insufficient to eradicate the tumor cells (1, 6). Autologous stem cell rescue after myeloablative chemotherapy or chemoradiotherapy is now offered as a standard consolidation therapy to such children (7). Peripheral blood stem cells (PBSC) are being increasingly utilized as a source of stem cells for ASCT in NBL and a number of other childhood solid tumors (8).

NBL was newly classified into 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 Childrens Cancer Group (CCG) (1). High-risk group patients are candidates for ASCT with myeloablative therapy. In this study, we could not adjust these criteria because of the retrospective nature of our analysis, but the majority of patients were of stage IV NBL and 9 were of stage III NBL with N-*myc* amplification. Histopathologic grading and DNA ploidy were not considered in selecting the high-risk group.

Successful peripheral blood stem cell harvests can now be performed in children weighing less than 20 kg (9). PBSC mobilization was performed with G-CSF alone at 150-300 $\mu g/m^2$/day or in combination with chemotherapy. Cells were collected using CS-3000 or a Cobe Spectra separator using a previously inserted central line. Stem cells were estimated by mononuclear cells, $CD34^+$ cells, and CFU-GM, and were sufficient for transplantation.

A theoretical advantage of using PBSC is lower tumor cell contamination of PBSC harvests, but minimal residual NBL cells can be detected by several methods. Laver et al. (10) reported tumor cell contamination of autografts utilizing a sensitive reverse transcriptase-polymerase chain reaction (RT-PCR) based method that targets a neuroendocrine protein gene product found on NBL cells, and which can identify one tumor cell in 10^7 mononuclear cells. Their results show that, although both PBSC and marrow products had a high tumor cell contamination rate, purged bone marrow samples had a higher level of tumor contamination than unpurged G-CSF-mobilized PBSC (8, 10, 11). In our previous study, NBL cells were detected in the peripheral blood of patients at diagnosis and at relapse using fluorescence in situ hybridization for the N-*myc* gene and RT-PCR for thyrosine hydroxylase induced from cells producing catecholamine, irre-

spective of identifiable marrow involvement (data not shown). In particular, we found the mRNA for thyrosine hydroxylase in mobilized cells, and it was not detected in morphological analysis. In any future prospective study, it should be emphasized that these methods are used routinely for the detection of NBL cells in mobilized PBSC.

Since the purging of multiple PBSC harvests is logistically difficult, most PBSC transplants performed to date have used non-purging PBSC. A two to three log depletion of tumor cells from PBSC harvests can be accomplished using immunomagnetic $CD34^+$ selection. Autologous transplantation utilizing $CD34^+$-selected PBSC has been carried out in advanced NBL and other poor prognosis pediatric solid tumors (12, 13).

The majority of post-transplantation relapses in NBL occur in sites of bulk disease or in previously involved sites, suggesting that tumor cell contamination of the autograft is unlikely to be the major source of relapse (14). However, gene marker studies by Rill et al. have conclusively shown that tumor cells contaminating the autograft can contribute to relapse (15). In this study, sixteen patients were used with $CD34^+$-selected PBSC, but no favorable effects on disease outcome were found. Hematologic recovery was not delayed, however they did not achieve lower relapse rates than the non-purging group.

Drugs that are appropriate for high-dose therapy with NBL should be tolerated at three to ten times the non-myeloablative dose, and should have steep and linear dose-response curves over many logs of tumor cell kill. As with conventional chemotherapy the most effective intensive therapy is likely to result from using a combination of three or more agents that are individually effective against NBL. In choosing combination agents, non-cross-resistance and non-overlapping toxicities are important considerations. The effectiveness of TBI is controversial. Level of destruction to the microenvironment required for the restoration of hematopoiesis may be induced by TBI, but engraftment may be delayed or even fails.

Moreover, if kidney shielding is not appropriate, hemolytic uremic syndrome is likely to develop. Moreover, hormonal imbalance including growth retardation and the possibility of the development of a secondary malignancy cannot be excluded. In this study, various kinds of conditioning regimen were used with or without TBI. Most of them were CEM protocol containing carboplatin, etoposide, and melphalan, while no statistically significance was attached to TBI as part of the conditioning regimen in terms of prognosis.

Hematologic recovery was linked directly to the number of infused $CD34^+$ cells and MNCs. We confirmed that the early neutrophil recovery after myeloablative conditioning was followed by higher dose of infused hematopoietic stem cells. Compared to neutrophils, the time variation until normalization of platelet counts was more pronounced. Time to platelets $\geq 50{,}000/\mu L$ was 30 days.

Despite the better results attributed to ASCT in the recently completed CCG-3891 trial, most patients still relapse following myeloablative chemotherapy or chemoradiotherapy and autologous stem cell transplantation (6). If minimal residual disease following stem cell transplantation can be eradicated, better cure rates might be expected (16). Two alternative approaches being studied in poor prognosis NBL include the use of differentiating agents and targeted immunotherapy (17-19). Both approaches are attractive in that they offer minimal cross-resistance or overlapping toxicity with chemotherapy.

In vitro treatment of NBL cell lines with the synthetic *cis*-RA results in the morphologic differentiation and growth arrest of tumor cells and the decreased expression of the N-*myc* gene. These effects can also be demonstrated for cell lines from patients whose tumors are resistant to cytotoxic chemotherapy. The validity of this approach was confirmed in the CCG-3891 trial where patients were randomized to receive *cis*-RA versus no further therapy after undergoing either autotransplant or consolidation chemotherapy. Those patients who received *cis*-RA had a three-year event-free survival of 47% compared to 25% for those that received no further therapy (p=0.013) (4). Future cooperative group trials will test whether the addition of *cis*-RA during induction chemotherapy will improve survival in poor-prognosis NBL. The administration of immunomodulators such as GM-CSF or IL-2 in conjunction with these antibodies may increase their tumoricidal efficacy by enhancing anti-GD2 mediated antibody dependent cellular cytotoxicity (20). Tumor-targeted therapy has also been used as an additional therapeutic approach for NBL, either with antibodies directed against NBL cells or with radiolabeled antibodies or radiolabeled molecules such as MIBG. This latter molecule has been widely used in Europe for many years and induces responses in about 30% of patients with refractory disease. In this study, additional post-transplantation therapies were undertaken, mainly IL-2 and *cis*-RA therapies (Table 3). IL-2 and *cis*-RA therapy were more effective factors of survival than no further additional post-transplantation treatment (p=0.001 and p=0.005, respectively).

Over the past fifteen years, several institutional and cooperative group clinical trials have explored the role of therapy in managing high-risk NBL. Results from these trials show that 30-45% of patients with complete or partial remission after initial chemotherapy achieve long-term disease-free survival with myeloablative therapy followed by ASCT (5). In this study, 22 patients died, and 66 patients are surviving 1 to 46 months after ASCT. Overall survival and disease free survival of these patients is 71.4% and 36.8%, respectively, which are very good survival results. However, in this study, multivariate analysis failed to identify any of the following as statistically significant prognostic factors except post-transplantation IL-2 or *cis*-RA therapy: remission status at time of transplant, purging of bone marrow, TBI, myeloablative

regimen, age, N-*myc* status and sex.

In this paper, we compare the outcome of a relatively small number of cases of patients who prevents our drawing definitive conclusions. A well-designed trial that specifically addresses prospective protocols is warranted. Nonetheless, some general conclusions can be drawn from these trials relating to the indications, optimal timing, toxicity, and effectiveness of ASCT in treatment of advanced NBL.

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