Pediatr Transplantation 2010: 14: 657–663

Pediatric Transplantation
DOI: 10.1111/j.1399-3046.2010.01319.x

Hematopoietic stem cell transplantation in patients with severe congenital neutropenia: An analysis of 18 Japanese cases

Oshima K, Hanada R, Kobayashi R, Kato K, Nagatoshi Y, Tabuchi K, Kato S; for the Hematopoietic Stem Cell Transplantation Committee of the Japanese Society of Pediatric Hematology. Hematopoietic stem cell transplantation in patients with severe congenital neutropenia: An analysis of 18 Japanese cases.
Pediatr Transplantation 2010: 14: 657–663. © 2010 John Wiley & Sons A/S.

Abstract: We studied the outcome of allogeneic HSCT in patients with SCN. Between 1989 and 2005, 18 patients with SCN in Japan received HSCT for reasons other than malignant transformation, i.e., because of the lack of or a partial response to treatment with r-HuG-CSF. The median age of the patients at the first HSCT was three and a half yr (range 0.2–16.7 yr). Nine patients received stem cells from an HLA-identical sibling donor and nine from an alternative donor. Twelve and six patients received myeloablative and non-myeloablative conditioning regimens, respectively. Engraftment occurred at the first HSCT in 12 patients, four patients received a second HSCT for graft failure, and two patients died. The cause of death was renal failure and graft failure at the first and second HSCT, respectively. The cumulative incidence of grade II–IV acute GVHD and TRM at the first transplantation was 11% and 5.6%, respectively. Of our patients, 16 are alive and in complete remission, with a median follow-up of six and a half yr. Our results suggest that HSCT is beneficial for patients with SCN refractory to r-HuG-CSF treatment.

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Key words: severe congenital neutropenia – Kostmann syndrome – stem cell transplantation

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Accepted for publication 13 November 2009

Kostmann syndrome, also known as SCN, is characterized by the maturation arrest of neutrophil precursors at the level of promyelocytes or myelocytes in the BM (1, 2). The ANC in PB are less than 200/μL. In the absence of treatment, the affected children develop recurrent fever, skin infections, oral ulcers, and gingivitis with the early onset of life-threatening bacterial infections. The availability of r-HuG-CSF has improved both the prognosis of SCN and the patients' quality of life (3–5). However, it is evident from the SCNIR that all patients with SCN, regardless of the treatment or response, are at risk of developing MDS or leukemia, with an actual incidence of 11.5% and a cumulative incidence of 21% after 10 yr (4, 6). The outcome of

Abbreviations: ANC, absolute neutrophil counts; Ara-C, cytarabine; ATG, anti-thymocyte globulin; BM, bone marrow; BU, busulfan; CB, cord blood; CMV, cytomegalovirus; CsA, cyclosporine A; CY, cyclophosphamide; DLI, donor lymphocyte infusion; FLU, fludarabine; GVHD, graft vs. host disease; HLA, histocompatibility leukocyte antigen; HSCT, hematopoietic stem cell transplantation; L-PAM, melphalan; MDS, myelodysplastic syndrome; MNC, mononucleated cell count; MTX, methotrexate; NA, not available; NE, cannot be evaluated; PB, peripheral blood; PBPCs, peripheral blood progenitor cells; PSL, prednisolone; r-HuG-CSF, recombinant human granulocyte colony-stimulating factor; SCN, severe congenital neutropenia; SCNIR, Severe Chronic Neutropenia International Registry; TAI, total abdominal irradiation; TBI, total body irradiation; TLI, total lymphoid irradiation; TNC, total nucleated cell count; TRM, transplant-related mortality; VOD, veno-occlusive disease; VP, etoposide.

transplantation after malignant transformation is poor (7). Therefore, HSCT plays an important role in the treatment of patients with SCN, particularly those with human HLA-compatible donors (8). Here, we report 18 patients with SCN in Japan who underwent HSCT between 1989 and 2005 for reasons other than malignant transformation.

Patients and methods

Patients

The patient data were registered with the HSCT Committee of the Japanese Society of Pediatric Hematology. All the patients or their legal guardians provided informed consent for transplantation. Although all treatments, including cytokine administration, were performed according to the generally accepted guidelines, each referring physician treated individual patients as per the medical indications.

In total, 21 patients with SCN underwent HSCT between May 1989 and September 2005. Of these, three patients underwent HSCT because of malignant transformation. Herein we report those 18 patients who underwent HSCT for reasons other than malignant transformation. The indication for HSCT in these patients primarily included the lack of or a partial response to r-HuG-CSF treatment.

Pretransplant conditioning regimens

The conditioning regimens at the first transplantation are summarized in Table 1. Twelve patients received conditioning regimens used for leukemia (myeloablative regimens), including CY (120–200 mg/kg) and BU (16–20 mg/kg or 560 mg/m^2 administered orally, generally divided into 16 doses) or TBI (12 Gy). In addition to the BU and CY combination, the agents used for conditioning included ATG in seven patients and FLU and TLI in one patient each. In one patient, VP (50 mg/kg) and ATG were used for conditioning in addition to the TBI and CY combination. Six patients received conditioning regimens that are used for non-malignant diseases such as aplastic anemia (non-myeloablative regimens). One patient received BU (16 mg/kg), Ara-C (24 g/m^2), ATG, and TLI (7.5 Gy). Two patients received CY (200 mg/kg), with TLI (8 Gy) for one patient and TAI for the other. One patient received BU (8 mg/kg), FLU (180 mg/m^2), and ATG. The other two patients received FLU (125 mg/m^2) and L-PAM (140 mg/m^2), with ATG for one patient and TBI (4 Gy) for the other.

Four patients received a second transplantation because of graft failure. The conditioning regimens at the second transplantation are summarized in Table 2. Three patients received myeloablative regimens containing CY (120–200 mg/kg) and TBI (8–12 Gy). One patient received a non-myeloablative regimen containing CY (200 mg/kg) and TLI (7.5 Gy).

Stem cell source (Tables 1 and 2)

Nine patients received cells from the BM of an HLA-identical sibling. Four patients received HLA-matched unrelated donor BM. The remaining five patients received single-antigen-mismatched CB (n = 3), single-antigen-mismatched sibling BM (n = 1), or HLA-matched unrelated donor CB (n = 1).

Two patients who had received BM from their respective HLA-identical siblings at the first transplantation received same-donor PBPCs or BM at the second transplantation. One patient who had received HLA-matched unrelated donor BM received another different HLA-matched unrelated donor BM. One patient who had received single-antigen-mismatched sibling BM received PBPCs from the same donor.

GVHD prophylaxis (Tables 3 and 4)

Six of nine children who had received allografts from HLA-identical siblings were administered CsA and short-term MTX, while the others were administered CsA alone. Most

Table 1. HSCT characteristics at the first transplantation

No.	Sex	Age at the first HSCT (yr)	Stem cell source	TNC/kg ($\times 10^8$)	Donor	Conditioning regimen
1	Female	2.7	BM	6.1	HLA-identical sibling	BU/CY + ATG
2	Female	6.1	BM	5.8	HLA-identical sibling	BU/CY + ATG
3	Male	2.1	BM	5.6	HLA-identical sibling	BU/CY + ATG
4	Female	16.7	BM	3.7	HLA-identical sibling	BU/CY + ATG
5	Female	6.4	BM	7.52	HLA-identical sibling	BU/CY + TLI (7.5 Gy)
6	Female	1.8	BM	5.3	HLA-identical sibling	BU/CY
7	Male	4.1	BM	5	HLA-identical sibling	BU/CY
8	Male	0.2	BM	13.4	HLA-identical sibling	BU*/FLU + ATG
9	Female	2.1	BM	8.1	HLA-identical sibling	TAI 9 Gy + CY
10	Female	4.3	BM	NA	One antigen-mismatched sibling	BU/CY + ATG
11	Female	5	BM	4.3	HLA-matched unrelated donor	TBI (12 Gy)/CY + VP + ATG
12	Male	14.2	BM	4.5	HLA-matched unrelated donor	BU/Ara-C + TLI (7.5 Gy) + ATG
13	Female	2.9	BM	5.4	HLA-matched unrelated donor	FLU/L-PAM + ATG
14	Female	15	BM	3	HLA-matched unrelated donor	TLI (8 Gy) + CY
15	Male	0.6	CB	0.64 (MNC)	HLA-matched unrelated donor	BU/CY + ATG
16	Male	0.3	CB	0.82 (MNC)	One antigen-mismatched unrelated donor	BU/CY + ATG
17	Male	0.9	CB	0.08 (MNC)	One antigen-mismatched unrelated donor	BU/CY + FLU
18	Female	4	CB	NA	One antigen-mismatched unrelated donor	TBI (4 Gy) + FLU + L-PAM

Dose of BU: *, 8 mg/kg and other cases, 16–20 mg/kg or 560 mg/m^2.

Table 2. HSCT characteristics at the second transplantation

No.	Reason for the second transplantation	Age at the second HSCT (yr)	The interval between the first and second transplantation (yr)	Stem cell source	TNC/kg ($\times 10^8$)	Donor	Conditioning regimen
9	Graft failure	3.8	9.8	BM	7	HLA-identical sibling	TBI/CY + TLI
5	Graft failure	16.2	1.7	PB	7.9	HLA-identical sibling	TBI (8 Gy)/CY + FLU
10	Graft failure	4.9	0.9	PB	NA	One antigen-mismatched sibling	CY + TLI (7.5 Gy)
14	Graft failure	15.8	0.5	BM	4.3	HLA-matched unrelated donor	TBI (12 Gy)/CY + Thiotepa

Table 3. GVHD prophylaxis and results at the first transplantation

No.	GVHD prophylaxis	Engraftment	Complications	Maximum GVHD		Outcome
				Acute	Chronic	
1	CsA	Yes	–	1	Limited	Alive, 180 months
2	CsA	Yes	–	0	No	Alive, 86 months
3	CsA	Yes	–	0	No	Alive, 78 months
4	CsA + MTX	Yes	CMV pneumonia	0	No	Alive, 80 months
5	CsA + MTX	No	–	0	No	Graft failure, 118 months (second transplantation)
6	CsA + MTX	Yes	–	0	Limited	Alive, 119 months
7	CsA + MTX	Yes	–	0	No	Alive, 111 months
8	CsA + MTX	Yes	–	0	No	Alive, 13 months, DLI due to mixed chimerism
9	CsA + MTX	No	–	0	No	Graft failure, 20 months (second transplantation)
10	CsA + MTX	No	–	0	No	Graft failure, 6 months (second transplantation)
11	CsA + MTX	Yes	–	1	No	Alive, 19 months
12	–	NE	Renal failure	0	No	Death, day 1 (renal failure)
13	Tacrolimus + MTX	Yes	–	2	No	Alive, 12 months
14	PSL	No	–	0	No	Graft failure, 10 months (second transplantation)
15	CsA	Yes	–	0	No	Alive, 56 months
16	CsA	Yes	CMV pneumonia	0	No	Alive, 11 months
17	CsA + MTX	No	–	0	No	Graft failure and alive, 38 months
18	CsA + MTX	Yes	–	2	No	Alive, 12 months

of the patients who had received allografts from unrelated donors were administered CsA and short-term MTX or CsA alone.

At the second transplantation, all four patients were administered CsA and short-term MTX.

Results (Tables 1–4)

Our patients included seven boys and 11 girls with a median age of three and a half yr (range, 0.2–16.7 yr) at the first HSCT. At the time of this report, the post-transplantation follow-up ranged from one day to 15 yr (median follow-up, six and a half yr), and 16 of the 18 patients are currently alive. Three of the four patients who received a second transplantation because of graft failure are alive. The engraftment rate at the first transplantation was 71%, and the overall survival rate, estimated by the product-limit method (Kaplan–Meier estimate), was 86.6%. The cumulative incidence of grade II–IV acute GVHD and TRM at the first transplantation was 11% and 5.6%, respectively.

Two of the nine patients with HLA-identical sibling donors showed graft rejection. Before transplantation, one of them had received a myeloablative regimen (Patient 5), while the other had received a non-myeloablative regimen (Patient 9). Although both patients received a second transplantation, one of them showed

Table 4. GVHD prophylaxis and results at the second transplantation

No.	GVHD prophylaxis	Engraftment	Complications	Maximum GVHD		Outcome
				Acute	Chronic	
9	CsA + MTX	No	Renal failure	0	No	Graft failure and death, day 51 (renal failure)
5	CsA + MTX	Yes	VOD	0	No	Alive, 12 months
10	CsA + MTX	Yes	–	0	Extensive	Alive, 112 months
14	CsA + MTX	Yes	–	1	No	Alive, 67 months

engraftment and is currently alive (Patient 5), while the other showed graft rejection and died because of renal failure on day 51 after the second transplantation (Patient 9). One patient (Patient 8) who received a DLI because of mixed chimerism is currently alive. These nine patients did not demonstrate grade II–IV acute GVHD. However, two patients demonstrated chronic GVHD (limited form).

Three of the nine patients with alternative donors showed graft rejection and one patient died because of renal failure on day 1. Before transplantation, two of the three patients who showed graft rejection had received a myeloablative regimen (Patients 10 and 17), while the other had received a non-myeloablative regimen (Patient 14). Two of these three patients (Patients 10 and 14) received a second transplantation and showed engraftment, while the third patient (Patient 17) did not require a second transplantation and is currently alive. Four patients received unrelated CB transplantation following myeloablative or non-myeloablative regimens, and three of them showed engraftment. Two of the nine patients with alternative donors demonstrated grade II acute GVHD at the first transplantation, and one patient demonstrated chronic GVHD (extensive form, including the lungs) at the second transplantation.

Discussion

Previously, BMT was the only curative treatment available for patients with SCN with HLA-compatible donors (9). However, the availability of r-HuG-CSF dramatically changed the prognosis of SCN and the quality of life of patients with SCN (3–5). More than 90% of patients with SCN in clinical trials responded to r-HuG-CSF treatment (6, 10). However, all patients with SCN, regardless of the treatment or response, are at risk of developing MDS/leukemia with an actual incidence of 11.5% and a cumulative incidence of 21% after 10 yr (4, 6). Therefore, HSCT remains the only currently available treatment for patients who are refractory to r-HuG-CSF treatment or show evidence of impending malignant transformation (7). We report 18 patients with SCN who underwent transplantation between 1989 and 2005 in Japan for reasons other than malignant transformation.

An important observation was that two of the nine patients with HLA-identical sibling donors showed graft rejection. Of these two patients, rejection might have been attributed to an insufficient dose of the conditioning regimen in one patient and numerous blood transfusions (red blood cell transfusion, seven times; granulocyte transfusion, 21 times) in the other patient.

There is only one previous report with a sizable number of patients with SCN who underwent HSCT for reasons other than malignant transformation with HLA-identical sibling donors (7). The conditioning regimen included chemotherapy only, usually BU and CY. Eight patients received HLA-identical sibling donor transplantation, all are alive; one patient who received a non-myeloablative regimen rejected the graft. Three patients received tissue from alternative donors and only one survived with extensive chronic GVHD. These results indicated that reduced conditioning regimens and a history of massive blood transfusions were risk factors of graft rejection even in matched sibling donor transplantation.

Three of the four patients who received unrelated CB transplantation showed engraftment. The low stem cell number is thought to have contributed to graft rejection in the remaining patient. Although unrelated CB may become a source of stem cells in SCN, only CB containing sufficient numbers of nucleated cells should be selected (11–13). Two patients received PBPCs from HLA-identical sibling or one antigen-mismatched sibling in the second transplantation and showed engraftment. It may be possible to use PBPCs in patients who show graft rejection or are at a high risk of rejection at the first transplantation. However, the possibility of chronic GVHD must be carefully considered (14–16).

There was no significant difference between the survival rates of patients who received myeloablative or non-myeloablative regimens. However, patients with SCN without malignant transformation normally do not receive chemotherapy prior to HSCT and are considered to have a potent T-cell repertoire. Therefore, special consideration should be provided to conditioning regimens that enable the strong suppression of T cells. The two largest previous studies associated with HSCT for patients with SCN encouraged the use of myeloablative regimens (7, 17). Although the less toxic non-myeloablative regimens might reduce TRM and late effects including second malignant neoplasms, experience with such regimens is limited, particularly in non-malignant diseases (18–20). In our study, three patients, who received non-myeloablative regimens, including FLU and ATG or low-dose TBI, showed engraftment regardless of whether the donor was HLA-identical. It is possible that

non-myeloablative regimens containing FLU and ATG or low-dose TBI will be effective in patients with SCN. Although the use of ATG seemed to contribute to better engraftment, it was not statistically significant (Fisher's exact test, $p = 0.06$).

We observed no significant difference between the rate of acute GVHD in patients who received MTX and CsA and those who received CsA alone; however, in prospective trials, the latter regimen was detrimental even in patients with HLA-identical sibling donors (21, 22). HSCT in patients with SCN without malignant transformation does not require any consideration of graft-versus-leukemia effects. Therefore, the transplantation procedure should aim to minimize transplantation-related toxicity and optimize GVHD prophylaxis. The low GVHD rate in this study might be influenced by the preemptive use of ATG in more than half of the patients (23–26).

There was no significant difference between the mean age of patients with engraftment (3.9 yr) and patients with graft rejection or treatment-related death (7.2 yr). However, as the age of the patient increases, the chances of granulocyte transfusion, severe infection, and impending malignant transformation also increase. Therefore, early transplantation in patients with SCN, even of unrelated CB, may yield favorable results. Shannon commented that HSCT will remain the preferred treatment for patients with SCN with HLA-identical sibling donors until definitive guidelines are developed, indicating the guidelines for deciding whether a patient should remain on r-HuG-CSF or should be referred for HSCT (27). However, it remains difficult to recommend transplantation to patients with SCN who respond well to r-HuG-CSF treatment and show no evidence of impending malignant transformation, even if the patient has an HLA-identical sibling donor (7). A high rejection rate was observed in our study, with four of the 18 patients developing post-transplant complications, including renal failure ($n = 1$), chronic GVHD ($n = 2$), and bilateral basal ganglia necrosis ($n = 1$) (28) after the first transplantation. However, some results of this study might have been affected by the long study duration. The high rejection and complication rates mentioned in our manuscript can be lowered in the current scenario with the availability of improved technology and supportive care. If the risks associated with transplantation can be decreased, perhaps by the use of a non-myeloablative regimen, then HSCT, particularly from an HLA-identical sibling, will play an important role in the treatment of SCN, even among patients responding to r-HuG-CSF treatment.

We conclude that HSCT is beneficial for patients with SCN who are refractory to treatment with r-HuG-CSF (10) and have no evidence of malignant transformation. Although the further accumulation of cases is a prerequisite to evaluate various conditioning regimens and the appropriate age at which to perform HSCT, we recommend that HSCT should be performed in those patients as early as possible, even with CB containing sufficient numbers of nucleated cells. The development of definitive guidelines is expected, and these will indicate (i) how to decide whether a patient should remain on r-HuG-CSF or can be referred for HSCT and (ii) how to make the correct choice from the available conditioning regimens and donor sources.

Although we did not study the mutations in causative genes (29–32) of SCN, acquired G-CSFR mutations are detected in approximately 80% of patients with SCN who develop acute myeloid leukemia independent of the ELA2 or HAX1 genetic subtype (33, 34). Furthermore, the subgroup of patients with SCN with the Gly185Arg missense mutation of ELA2 is at an increased risk of MDS/leukemia (35, 36). These genetic backgrounds must also be considered when deciding whether HSCT is indicated in a patient (37).

Appendix

The following institutions enrolled patients in this study.

1 Department of Pediatrics, Hokkaido University Graduate School of Medicine, Sapporo, Japan.
2 Division of Hematology and Oncology, Children's Medical Center, Japanese Red Cross Nagoya First Hospital, Nagoya, Japan.
3 Section of Pediatrics, National Kyusyu Cancer Center, Fukuoka, Japan.
4 Division of Hematology and Oncology, Saitama Children's Medical Center, Saitama, Japan.
5 Department of Pediatrics, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.
6 Department of Reproductive and Developmental Medicine, Akita University School of Medicine, Akita, Japan.
7 First Department of Pediatrics, Toho University School of Medicine, Ota, Japan.
8 Department of Pediatrics, Kyoto City Hospital, Kyoto, Japan.
9 Department of Pediatrics, Gunma University School of Medicine, Maebashi, Japan.
10 Department of Pediatrics, Ibaraki Children's Hospital, Mito, Japan.
11 Department of Pediatrics and Cell Transplantation, Mie University School of Medicine, Tsu, Japan.

12 Division of Hematology and Oncology, Osaka Medical Center, Research Institute for Maternal and Child Health, Izumi, Japan.
13 Division of Hematology and Oncology, Nagano Children's Hospital, Minami-Azumi, Japan.
14 Department of Pediatrics, Tohoku University School of Medicine, Sendai, Japan.
15 Department of Pediatrics, Hamanomachi Hospital, Fukuoka, Japan.

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