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ORIGINAL ARTICLE

Reduced-intensity conditioning is effective and safe for transplantation of patients with Shwachman–Diamond syndrome

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Allogeneic hematopoietic stem cell transplantation (HSCT) is the only potentially curative treatment for the BM dysfunction seen in patients with Shwachman–Diamond syndrome (SDS). Historically, these patients have fared poorly with intensive conditioning regimens with increased regimen-related toxicity especially involving the heart and lungs. We report our institutional experience with a reduced-intensity-conditioning protocol in seven patients with SDS and BM aplasia or myelodysplastic syndrome/AML. The preparative regimen consisted of Campath-1H, fludarabine and melphalan. Four patients received matched related marrow and three received unrelated stem cells (two PBSCs and one marrow). All but one was 8 of 8 allele HLA matched. All patients established 100% donor-derived hematopoiesis. No patient in this cohort developed grades III–IV GVHD. One patient had grade II skin GVHD that responded to systemic corticosteroids and one had grade I skin GVHD, treated with topical corticosteroids. Two out of seven patients developed bacterial infections in the early post transplant period. Viral infections were seen in four out of seven patients and were successfully treated with appropriate antiviral therapy. All patients are currently alive. These data indicate that HSCT with reduced-intensity conditioning is feasible in patients with SDS and associated with excellent donor cell engraftment and modest morbidity.

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Introduction

Shwachman–Diamond syndrome (SDS) is a rare autosomal recessive disorder characterized by exocrine pancreatic insufficiency, skeletal abnormalities in the form of metaphyseal dysostosis and BM dysfunction manifested as cytopenias.[1–6] Additional clinical manifestations seen in some patients include short stature, variable immune dysfunction, delayed dentition and structural and functional abnormalities of the liver.[3,4,7,8] Patients with SDS are at an increased risk of developing aplastic anemia, myelodysplastic syndrome (MDS) and AML.[3,4,7,9–12] In the largest reported patient series, 20% of cases developed pancytopenia and 6% progressed to MDS.[4] Other authors have reported varying incidences of MDS ranging from 10 to 15% to as high as 44% of cases.[3,7,10,13] The risk of leukemic transformation in SDS patients is significant and increases with age, varying from 5% in childhood to nearly 24% as patients approach adulthood.[13] Infections and thoracic dystrophy are the leading causes of morbidity and mortality during infancy, and the likelihood of long-term survival correlates most closely with the degree of BM dysfunction. Alter and Young[14] calculated the projected median survival of SDS patients as more than 35 years, on the basis of a literature review. Survival is particularly reduced in patients who develop BM aplasia, MDS or acute leukemia, averaging 14 years in patients with aplastic anemia.[10] The development of acute leukemia portends a poor prognosis as SDS patients do not respond well to chemotherapeutic intervention.

Hematopoietic stem cell transplantation (HSCT) is the only curative treatment for BM dysfunction associated with SDS. However, the timing of transplantation remains a subject of controversy, and the apparent lack of genotype–phenotype correlation makes selection of patients for early preemptive HSCT impossible. Additionally, patients with SDS tend to have increased toxicity with intensive conditioning regimens. Tsai *et al.*[15] reported a case of fatal congestive heart failure following a Cy-containing-conditioning regimen. Other authors have described neurological complications,[16] pulmonary complications and multiorgan failure with typical ablative regimens.[17,18]

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In this report, we describe our institutional experience with the use of a reduced-intensity-conditioning regimen consisting of Campath-1H, fludarabine and melphalan in seven patients with SDS, all of whom achieved excellent hematopoietic recovery and full donor chimerism with acceptable toxicity.

Methods

All patients were enrolled on an institutional review board-approved protocol at the Cincinnati Children's Hospital Medical Center and informed consent was obtained from the patient or their legal guardian.

Patients

Seven consecutive patients with SDS were transplanted at the Blood and Marrow Transplant Program of Cincinnati Children's Hospital Medical Center from April 2005 to July 2007. Patient demographics are described in Table 1. All patients had the diagnosis of SDS confirmed by genetic testing to document Shwachman–Bodian–Diamond syndrome (SBDS) mutations.

Liver dysfunction was noted prior to transplant in three of seven patients. One of these patients underwent a liver biopsy due to persistent elevation of liver enzymes that showed mild portal and periportal fibrosis, unchanged in comparison with a previous biopsy. Cardiac function was normal in all patients prior to transplant though trivial mitral and/or aortic regurgitation was noted in three out of seven patients. Patient number 1 had bronchiolitis obliterans of the lower lobe of the left lung as a consequence of repeated pulmonary infections during childhood. Patient number 7 had bronchopulmonary dysplasia and chronic pulmonary insufficiency as a consequence of thoracic dysplasia as part of the SDS phenotype. She had pulmonary hypertension in the neonatal period but pretransplant echocardiogram (ECHO) was normal.

The indication for HSCT was worsening cytopenias with increasing transfusion dependence and/or the appearance of clonal hematopoeisis in six of seven patients. Patient number 6 had AML at the time of presentation to our institution. She was treated with cytarabine and L-asparaginase in a modified Capizzi regimen prior to transplant.

Stem cell sources

Stem cell sources and cell doses are described in Table 2. Four of seven patients received marrow from a sibling donor. One of these patients (Patient number 4) received stored umbilical cord blood (UCB) together with marrow from the same sibling donor, collected because the UCB cell dose was low. High-resolution HLA typing was performed at HLA-A, B, C and DRB1 for all cases. Stem cells were 8 of 8 allele matched in all but one case. Patient number 6 received PBSCs from an unrelated donor, mismatched at a single antigen at the DRB1 locus.

Preparative regimen

The conditioning regimen consisted of Campath-1H (10 mg on day 1, 15 mg on day 2 and 20 mg on day 3) i.v. on 3 successive days (between days −28 and −19), after a test dose (3 mg over 2 h, given not more than 7 days prior to starting conditioning). In this treatment plan, we administered the campath-1H on days −21, −20 and −19 to ensure that negligible levels of Campath-1H remained in the patients at the time of donor stem cell infusion. The intent was to intensely immunosuppress the recipient pretransplant (in addition to the fludarabine and melphalan used as part of the conditioning) to improve the likelihood of engraftment of donor stem cells. Fludarabine (30 mg/m^2 per day) was given for 5 days on days −8 to −4. Melphalan was given at 140 mg/m^2 on day −3. Doses were modified for recipients <10 kg as follows: Campath-1H 10 mg on 3 consecutive days (days −21 to −19), fludarabine 1 mg/kg and melphalan 4.7 mg/kg.

GVHD prophylaxis

CYA and MTX were used for GVHD prophylaxis unless the stem cell source was UCB, when methylprednisolone 1 mg/kg was used in place of MTX. CYA was commenced on day −2 at a dose of 2.5 mg/kg per dose every 12 h given i.v. Trough CSA levels were measured two times weekly with dose adjustments as needed until therapeutic levels were achieved (250–350 ng/ml) and weekly thereafter. Therapeutic levels were maintained until day +100. Patients were switched to oral CYA at the time of discharge from hospital if they could tolerate the drug orally. From day +100 to 6 months post transplant, CSA was tapered in patients without significant acute or chronic GVHD by approximately 5–10% per week. MTX was given at a dosage of 10 mg/m^2 on day +1 and 7.5 mg/m^2 per day on days +3 and +6. Methylprednisolone was used until day +28 and then tapered slowly by day +56.

Patient number 6 initially received GVHD prophylaxis with mycophenolate mofetil and CSA. However, CSA was changed to tacrolimus due to intolerance.

Supportive care

All patients were hospitalized at the Blood and Marrow Transplant Unit at Cincinnati Children's Hospital Medical Center until evidence of myeloid engraftment was seen. Patients were housed in single rooms ventilated with high efficiency air filtration systems. G-CSF (5 μg/kg per day) was given s.c. or i.v. starting day +7 for PBSC or BM recipients and on day +1 for UCB recipients until ANC was >1500 per 100 ml for 3 consecutive days. Intravenous immunoglobulin replacement was given every 3 weeks until patients were weaned off immunosuppression and for the first 6 months post transplant when cord blood was the stem cell source. Antimicrobial prophylaxis was as follows: voriconazole or liposomal amphotericin (10 mg/kg weekly) as antifungal prophylaxis; acyclovir for herpes simplex virus -seropositive patients; i.v. pentamidine for *Pneumocystis carinii* prophylaxis until engraftment. Trimethoprim/sulfamethoxazole was substituted as clinically indicated after hematologic recovery (ANC >1500 per 100 ml) and continued for a minimum of 1-year post transplant. Other

Table 1 Patient demographics

Patients	*Patient no. 1*	*Patient no. 2*	*Patient no. 3*	*Patient no. 4*	*Patient no. 5*	*Patient no. 6*	*Patient no. 7*
Age at transplant (years)	8	10	12	6	3	29	1
Gender	Male	Male	Male	Male	Male	Female	Female
SBDS mutation	183_184 TA to CT IVS2+2 T to C	183_184 TA to CT IVS2+2 T to C	K62X IVS2+2 T to C	183_184 TA to CT IVS2+2 T to C	183_184 TA to CT IVS2+2 T to C	IVS2+2 T to C Homozygous	183_184 TA to CT IVS2+2 T to C
Cytopenias at time of HSCT	Anemia Neutropenia Thrombocytopenia	Neutropenia Thrombocytopenia	Neutropenia Thrombocytopenia	Neutropenia	Neutropenia Thrombocytopenia	Neutropenia Thrombocytopenia Anemia	Neutropenia Thrombocytopenia Anemia
Pancreatic dysfunction	Fatty replacement of pancreas Low lipase level	Fatty replacement of pancreas, low amylase and trypsin levels in duodenal fluid	Fatty replacement of pancreas	Atrophic pancreas	Fatty replacement of pancreas, low serum isoamylase	Fatty replacement of pancreas	Fatty replacement of pancreas
Metaphyseal chondrodysplasia	Present	Absent	Absent	Present	Absent	Absent	Present
Transplant indication	Transfusion dependence, recurrent infections, appearance of del20q12 in marrow	Worsening cytopenias, isochromosome 7q in marrow	Cytopenias, clonal population with del20q12	Myelodysplastic changes in granulocytic series Increasing del 7q clone in marrow	Cytopenias, appearance of clone with del20q12 in marrow	AML, Complex karyotype including monosomy 7, del5q	Dysplasia, severe pancytopenia
Liver function	Mildly abnormal	Normal	Normal	Normal	Abnormal	Normal	Mildly abnormal
Cardiac function	Normal	Normal Trivial MR and AR	Normal Trivial AR	Normal Trivial MR	Normal Bicommissural aortic valve	Normal	Normal
Other organ dysfunction	Bronchiolitis obliterans left lower lobe	None	None	None	None	Dental caries	Bronchopulmonary dysplasia; small thoracic size
Marrow cellularity at time of HSCT	10–20%	15%	60–70%	50–60%	50–60%	70–80%	0–10%
Marrow cytogenetics	41.2% cells del20q12, 70.8% cells showing del7q31	16 of 20 cells with isochromosome 7q or i(7)(q10)	6.2% cells with del20q12	3.6% cells with del20q12	38.5% cells with del20q12	70–80% myeloid blasts. Complex karyotype including monosomy 7, del5q	Normal

Abbreviations: HSCT = hematopoietic stem cell transplantation; SBDS = Shwachman–Bodian–Diamond syndrome.

Table 2 Stem cell source and dose

Patients	*Patient no. 1*	*Patient no. 2*	*Patient no. 3*	*Patient no. 4*	*Patient no. 5*	*Patient no. 6*	*Patient no. 7*
HLA match (A, B, C, DRB1)	6/6 (8/8)	6/6 (8/8)	6/6 (8/8)	6/6 (8/8)	6/6 (8/8)	5/6 (7/8) (Patient 1102/1303; donor 1301/1303 at DRB1 locus)	6/6(8/8)
Donor source (sib, unrelated, cord)	Unrelated PBSC	Sibling marrow	Sibling marrow	Sibling cord + marrow	Sibling marrow	Unrelated PBSC	Unrelated marrow
Cell dose CD34 $\times 10^6$ per kg	7.9	6.3	3.3	0.19 (cord) 9.0 (marrow)	5.7	11.2	6.4
Recipient CMV status	Pos	Pos	Neg	Neg	Neg	Pos	Pos
Donor CMV status	Neg	Pos	Pos	Neg	Neg	Neg	Pos

Abbreviations: Neg = negative; pos = positive; sib = sibling.

antimicrobial prophylaxis was continued for 6 months post transplant, or until immunosuppression was discontinued, whichever was later. CMV, EBV and adenovirus surveillance was instituted 7 days after stem cell infusion, and treatment was commenced preemptively if the CMV test was positive, with continued monitoring for response.

Hematological reconstitution
Neutrophil engraftment was defined as the day on which the ANC rose to $\geqslant 500$ cells per 100 ml for 3 consecutive days after the postpreparative regimen neutrophil nadir. Platelet engraftment was defined as the first day on which the platelet count rose to $\geqslant 50\,000$ per 100 ml over a 7-day interval without transfusion support. Chimerism assessment by variable number of tandem repeats (VNTR) analysis (or XY FISH in sex-mismatched donor–recipient pairs) and/or cytogenetic studies was performed approximately 4 weeks post transplant, and initially every 2–4 weeks thereafter, then every 3 months or as clinically indicated.

Results

Engraftment
Hematopoietic recovery was prompt in all cases, and all patients have stable full donor chimerism, with no evidence of late loss of donor cell engraftment (Table 3). Myeloid engraftment occurred at a median of 14 days (range, 11–15 days) and platelet recovery at a median of 33 days (range, 14–68 days).

GVHD
No patient in this cohort developed grades III–IV GVHD. One patient had grade II skin GVHD that responded to systemic corticosteroids and one had grade I skin GVHD, treated with topical corticosteroids. Both these patients received PBSCs from an unrelated donor. No patient needed or received donor lymphocyte infusions.

Survival and regimen-related toxicity
All seven patients are surviving with a median follow-up of 548 days (range, 93–920 days). Patient number 1 entered transplant with bronchiolitis obliterans of the lower lobe of the left lung. Bronchoalveolar lavage done during the pretransplant period grew *Pseudomonas aeruginosa* that resolved following appropriate antibiotic therapy. He was hospitalized for left lower lobe pneumonia on day 170 post transplant that responded to antibacterial therapy directed at *P. aeruginosa*. This patient also had persistent emesis and secretory diarrhea. Gastrointestinal endoscopy revealed mild chronic duodenitis with focal cryptitis and apoptosis believed to be the consequence of prior infection, as CMV was detected by *in situ* hybridization and symptoms resolved following treatment with ganciclovir. This patient also had evidence of EBV antigenemia by PCR that responded to a single dose of rituximab. Additional bacterial infections occurred in three out of seven patients. There were two patients with documented bacteremia, one gram-negative and the other with oxacillin-resistant

Table 3 Patient outcomes

Patients	*Patient no. 1*	*Patient no. 2*	*Patient no. 3*	*Patient no. 4*	*Patient no. 5*	*Patient no. 6*	*Patient no. 7*
Time to myeloid engraftment (days)	15	12	15	11	14	14	13
Platelet recovery (>50 000 per 100 ml for 7 days) (days)	27	39	33	18	68	14	59
Donor chimerism (at last time-point studied)	100%	100%	100%	100%	100%	99.8%	100%
Hospital stay (days)	29	32	35	28	29	85	46
Length of follow-up (days)	908	920	863	535	339	176	93
Acute GVHD	II	None	None	None	None	Grade I skin	None
Grade	Skin						
Organ involvement							
Infections	EBV antigenemia Pseudomonas pneumonia	ORSA bacteremia CMV reactivation	None	None	Adenoviral diarrhea	Enterobacter cloacae bacteremia Enteroviral Diarrhea Disseminated adenoviral disease *E. coli* UTI	None
Lansky/Karnofsky scale	100%	100%	100%	100%	100%	90%	80%
Other toxicity	Hyperglycemia requiring insulin Secretory diarrhea		Transient renal insufficiency			Transient renal insufficiency	Grade I mucositis

Abbreviations: *E. coli* = *Escherichia coli*; ORSA = oxacillin-resistant *Staphylococcus aureus*; UTI = urinary tract infection.

Staphylococcus aureus and one with a urinary tract infection (Table 3). Adenoviral diarrhea was seen in two patients whereas one patient had enteroviral diarrhea, all of which resolved with supportive care alone. Patient number 6 had evidence of disseminated adenoviral infection 5 months post transplant that resolved after treatment with cidofovir. This emphasizes the need for close monitoring and early treatment of infection, particularly viral infections with sensitive methods early in the post transplant period.

Biochemical evidence of renal insufficiency occurred in two out of six patients that responded to fluid administration. No cardiac toxicity was seen.

Discussion

In this report we describe a case series of patients with the rare disorder, SDS treated with a reduced-intensity-conditioning regimen prior to allogeneic hematopoeitic stem cell transplantation. Our patient population showed prompt myeloid engraftment with full donor chimerism in all cases. Regimen-related toxicity was modest with no patients developing grades III–IV GVHD, and all patients are currently alive.

Hematopoietic stem cell transplantation is the only known curative treatment for the hematological abnormalities seen in Shwachman–Diamond syndrome. The available literature on HSCT in SDS patients is limited and consists mainly of case reports.[19–29] Vibhakar *et al*.[30] recently reviewed the published experience with HSCT in SDS patients and reported a total of 28 patients, including their own. All but four patients received ablative conditioning regimens containing CY with or without TBI/TLI. Most patients received unrelated BM as a source of stem cells, though Vibhakar *et al*. reported three cases where UCB was used successfully as a source of stem cells. At the time of reporting, 17 of these patients were alive, that is, mortality approached 40%. More than 50% of the patients died in the early post transplant phase of cardiopulmonary complications. Similarly, in a recent review of the European experience with HSCT in SDS patients, Cesaro *et al*.[17] reported an overall treatment-related mortality of 35.5% at 1 year. Interestingly, they found a significantly higher mortality rate in patients receiving a TBI-conditioning regimen (67 vs 20% for TBI vs non-TBI-containing regimen, $P = 0.03$).

Though the mechanism is unclear, patients with SDS seem to have a predilection for increased cardiac toxicity with CY-containing-conditioning regimens.[15,23,28,31] Savilahti and Rapola[31] reported significant cardiac dysfunction in patients with SDS even without exposure to CY. In their series of 16 Finnish patients, 8 had cardiac abnormalities on necropsy including cardiac fibrosis and areas of necrosis. Clinical reports also suggest that patients with SDS are more susceptible to transplant-related toxicity as compared to patients with other myelodysplastic disorders like Kostmann's syndrome and juvenile myelomonocytic leukemia.[32,33] Dror and Freedman[34] have demonstrated that the BM mononuclear cells from patients with SDS show an increased propensity for apoptosis mediated by hyperactivation of the Fas-signaling pathway. The same authors

have also reported decreased telomere length in the marrow-derived mononuclear cells from patients with SDS.[35] It is possible, although currently unexplored, that similar mechanisms are important in the increased susceptibility to organ toxicity with intensive conditioning regimens seen in SDS.

The significant regimen-related toxicity observed during HSCT in past reports of HSCT for SDS has led to recent interest in reduced-intensity preparative regimens that might ameliorate cardiac and pulmonary toxicities. Sauer *et al*.[36] reported three patients with SDS and BM failure transplanted using a regimen consisting of fludarabine, treosulfan and melphalan. All three patients engrafted rapidly with 100% donor chimerism. Although two of the patients tolerated the regimen with minimal toxicity, one patient died on day 98 secondary to idiopathic pneumonitis syndrome. The first two patients had the common 183_184 TA to CT mutation in the SBDS gene, whereas the third patient who died carried a c.297-300delAAGA deletion, leading the authors to speculate on whether genotype is predictive of treatment-related toxicity.

Attempts have been made to predict the clinical phenotype from the genetic mutation but no correlation has been found thus far between the hematologic or skeletal manifestations and the genotype in the small numbers of patients that were studied.[37–39] However, with widespread availability of genetic testing, it may be possible to collect this data in a prospective fashion to see if there is a correlation between genotype and outcome, particularly treatment-related toxicity. However, such efforts are likely to be limited due to the rarity of SDS.

In summary, our data indicate that transplantation of children with SDS using reduced-intensity conditioning is feasible and associated with modest morbidity. Increased understanding of the genetic and biochemical basis for this disorder, and prospective careful data collection will hopefully allow optimization of therapy for this complex group of patients.

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