

## Case report

# Bone marrow transplantation in Shwachman–Diamond syndrome

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### Summary:

**Shwachman–Diamond syndrome is a rare autosomal recessive disorder characterized by exocrine pancreatic dysfunction, metaphyseal dysostosis and bone marrow dysfunction with a predilection towards severe hematologic complications. Allogeneic bone marrow transplantation has been used as a therapeutic approach for SDS patients with serious hematologic abnormalities with mixed results. There is some concern that these patients may be more susceptible to early (<100 days) transplant-related complications than other transplant groups. We report a patient who received a matched allogeneic transplant without developing serious early transplant-related complications, but eventually died from relapse of his disease. Although experience is limited, a review of the reported cases suggests patients with SDS may be transplanted without significant short-term morbidity and mortality.**

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patients with leukemia.<sup>2</sup> Supportive treatment with transfusions, antibiotics and pancreatic enzymes allow for prolonged survival without altering the risk of developing severe hematologic complications. Treatment of myelodysplasia or leukemic transformation with chemotherapeutic agents, however, is associated with low response rates and a poor prognosis.

Allogeneic bone marrow transplantation is emerging as a valuable therapeutic option, especially when leukemia or marrow aplasia have developed. Because of the rarity of the syndrome, experience is limited and no definitive indications for transplantation have been established. Early attempts were associated with significant toxicity and mortality which were thought to be related to nonspecific organ dysfunction caused by the syndrome.<sup>7</sup> We report a patient with SDS who received an allotransplant without significant 100 day transplant-related toxicity. We also reviewed the outcomes of other patients published in the literature and noticed several trends that may provide some guidance in the timing of allotransplants in patients with SDS.

### Case report

Shwachman–Diamond syndrome (SDS) is a rare autosomal recessive disorder first described in 1964.<sup>1</sup> The syndrome is characterized by exocrine pancreatic insufficiency, metaphyseal dysostosis and bone marrow dysfunction.<sup>2</sup> The hematologic abnormalities associated with SDS include varying cytopenias, marrow aplasia and myelodysplasia. About 20% of SDS patients develop aplastic anemia,<sup>3</sup> 20–33% develop myelodysplasia<sup>4,5</sup> and 12–25% eventually transform into acute leukemia.<sup>3–6</sup> Since its initial description, approximately 300 cases have been reported.

There is limited information on long-term survival. The projected median survival for all patients is 35 years, with infections and hemorrhage being the major causes of mortality. Predictably, survival is shorter for patients with significant hematologic problems with median survivals of 14 years in patients with aplastic anemia and 9 years in

A 30-year-old male was first evaluated when he was 2 years old for diarrhea, malabsorption and cytopenias. Exocrine pancreatic insufficiency was confirmed by an abnormal 72-h fecal fat balance study. He subsequently developed bone marrow failure and metaphyseal dysostosis. The diagnosis of Shwachman–Diamond syndrome was established by clinical criteria as per Ginzberg *et al.*<sup>5</sup> The patient had an unremarkable clinical course with occasional mild cytopenias and arthritis. During an ER visit for a suspected spider bite, he was found to have a hematocrit of 28.5%, a platelet count of  $92 \times 10^9/l$  and a MCV of 57.2 fl. A peripheral smear revealed no additional abnormalities. He was eventually discharged and a repeat blood count 1 month later showed a hematocrit of 29.8%, a platelet count of  $110 \times 10^9/l$  and a MVC of 55.1 fl. A peripheral smear showed dimorphic, hyperchromic, microcytic erythrocytes with several target cells, some basophilic stippling, and some large granular lymphocytes. A bone marrow biopsy and aspirate showed marked dysplasia with approximately 9% CD34<sup>+</sup> blasts. Cytogenetics revealed multiple abnormalities including 5q–, monosomy 7, and monosomy 13 (44, XY, del(2)(p21-23), del(5)(q14q23), add(6)(p23), –7, –13, add(21)(q22)[18]/46,XY[2]). He was diagnosed with mye-

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lodyplastic syndrome (MDS), refractory anemia with excess blasts subtype, and was advised to proceed with bone marrow transplantation. He had three brothers, one of whom was found to be an HLA-identical match.

He underwent a matched related allogeneic bone marrow transplant following a standard preparative regimen of busulfan 1 mg/kg p.o. four times a day on days -9 to -4 (total 16 doses) and cyclophosphamide 50 mg/kg i.v. daily on days -5 to -2 (total four doses). He developed pericarditis on the third day of cyclophosphamide but this was self limited and he was able to receive a T cell-depleted, CD34<sup>+</sup> enriched marrow graft ( $3.94 \times 10^6$  CD34<sup>+</sup> cells/kg with  $8.9 \times 10^4$  CD3<sup>+</sup> cells/kg) from his HLA-identical brother on day 0 without further difficulty. GVHD prophylaxis with cyclosporin A was started. His post-transplant course was complicated by grade II mucositis and neutropenic fever with negative cultures. His neutrophil count recovered on post-transplant day 11 and his bone marrow chimerism was > 95% donor at 63 days. He developed grade II skin GVHD confirmed by skin biopsy approximately 50 days after transplant. This was adequately treated with pulse steroids and daclizumab and he was tapered off immunosuppressive medications 5 months after transplant. On day 67, his peripheral blood counts had completely recovered while a bone marrow biopsy revealed a hypocellular marrow with normal maturation and no evidence of myelodysplasia.

Six months after transplantation, he was admitted for progressive dyspnea on exertion and nasal congestion. His initial chest X-ray was normal and an aggressive pulmonary workup revealed no evidence of pneumonia. His pulmonary function tests were not significantly different from his pre-transplant evaluation. He was started on antibiotics with some symptomatic relief and was eventually discharged. At his 6 month post-transplant evaluation, he was noted to be pancytopenic with white cell count of  $3060/\text{mm}^3$  with 3% blasts, hematocrit of 24.8%, and a platelet count of  $51 \times 10^9/\text{l}$ . Chimerism studies revealed 20% donor cells and a bone marrow biopsy showed 80% cellularity with limited myeloid maturation and 5% blasts. This was consistent with recurrence of his myelodysplasia and plans were made for donor lymphocyte infusion. He was readmitted 1 week later for fever of 40°C and pustular lesions on his jaw. Biopsies of these lesions revealed neutrophilic dermatosis consistent with acute febrile neutrophilic dermatosis (Sweet's syndrome). Antibiotics were started, but his clinical status declined rapidly and he eventually died. A post-mortem examination was significant for neutrophilic dermatosis, recurrence of his myelodysplasia, some fatty replacement of the pancreas, and aseptic necrotizing bronchopneumonia.

## Discussion

This case describes a patient who did not experience significant early transplant-related complications, but ultimately died from complications related to relapse of his myelodysplasia. Including this case, there are 15 known cases of allotransplants in SDS reported in the literature (Table 1). The primary indications for transplant were either MDS or marrow aplasia, and these were roughly div-

ided equally among the patients. Half of the patients received unrelated donor transplants. The most common cytogenetic abnormalities seen were aberrations in chromosome 7 and complex cytogenetic abnormalities. Overall, nine patients died after allotransplant. Of these nine patients, three were in relapse, placing the overall transplant-related mortality at 40%. Length of observation after transplant ranged from 9 months to almost 3 years.

It is impossible to make definitive recommendations given the current information available on allotransplantation in SDS patients. There are, however, some general points that can be made. It appears that patients who underwent allotransplantation for myelodysplasia or leukemia had considerably worse survival than patients transplanted for other conditions. There also does not appear to be a significant increase in transplant-related morbidity and mortality in SDS patients compared to other transplant populations, in contrast to previous observations.<sup>7</sup>

Patients who received an allotransplant for marrow aplasia had a considerably better survival compared to patients transplanted for other reasons. Four of the five patients with marrow aplasia were disease free for at least 9 months after transplant in contrast to other indications where only two patients survived beyond a year. This is similar to outcomes seen in the general population, where patients with myelodysplasia and secondary AML had a more unfavorable outcome to transplantation compared to patients with primary AML.

Almost all the SDS patients who were transplanted for MDS/AML had an abnormality in chromosome 7. Spirito *et al*<sup>8</sup> characterized the cytogenetic abnormalities of 19 patients with MDS/AML and noted a significant number with alterations in chromosome 7. Chromosome 7 aberrations are not unique to SDS and are relatively common in MDS, especially in MDS associated with exposure to alkylating agents. If one divides the MDS population by cytogenetics according to the International Prognostic Scoring System, the 7-year event-free survival (EFS) for patients after allotransplant is 51%, 40% and 6% for the good-, intermediate-, and poor-risk subgroups, respectively.<sup>9</sup> Non-relapse mortality (NRM), although not statistically significant, was 37%, 54% and 68%, respectively. The observed EFS and NRM in SDS patients is 14% and 57%, respectively. This places SDS patients in a risk category comparable to the poor-risk cytogenetic subgroup. Because of the small number of cases, it is impossible to determine whether the observed differences are significant.

Early (<100 days) transplant-related morbidity and mortality does not appear to be increased compared to other transplant populations. The initial attempt at allotransplantation in an SDS patient was complicated by CHF and the patient ultimately died from apparent cyclophosphamide induced pancarditis.<sup>10</sup> Okcu *et al*<sup>7</sup> reported a series of eight patients: six had significant, life-threatening complications, most occurring early (within 100 days) of the transplant course. There is some evidence that SDS may involve organs in addition to the bone marrow and pancreas.<sup>2</sup> Savilathiti *et al*<sup>11</sup> described eight patients with SDS who had significant myocardial changes on autopsy. These observations led to the conclusion that patients with SDS were at high-risk for post-BMT complications.<sup>7</sup>

**Table 1** Allogeneic transplant cases in Shwachman–Diamond syndrome

Year	Age	Diagnosis	Cytogenetics	Donor type	Marrow type	BMT regimen	Prophylaxis	Complications	Outcome	Ref.
1990	10	Marrow aplasia	N/A	MSD	Unmanipulated	BUCY + ATG	MTX	CHF	Death day +23	10
1991	17	Marrow aplasia	N/A	MSD	Unmanipulated	CY/TBI	CsA, MTX	GVHD, diarrhea	Disease free 9 months	14
1993	38	Marrow aplasia, post AML	−18, t(21;?) (q22;?)	MUD	N/A	BUCY	CsA, prednisone	None	Disease free 97 days	15
1995	5	AML M5a	Del(7), t(4;7)(q31;q11)	MUD	Unmanipulated	CY/TBI	CsA, MTX	Graft rejection	Relapse, death 1 year	16
1996	?	Marrow aplasia	N/A	HLA-A mismatch unrelated donor	T-deplete	Ara-C/CY/TBI	CsA, prednisone	VOD, liver transplant	Disease free 10 months	17
1996	24	MDS, AML M4	inv(9)	MSD	N/A	BUCY	CsA, MTX	Delayed engraftment, mucositis grade III, cardiac, renal, CNS grade II, CMV, staph septicemia	Relapse, death 10 months	18
1997	13	MDS	del(7), +21	MUD	N/A	CY/TBI	CsA, MTX	None	Disease free 1 year	19
1997	7.5	MDS	t(6;13)(q21;q32), −7	MUD	N/A	CY/TBI	CsA, MTX	Graft rejection	Death 2 months	19
1997	8	MDS	i7q	HLA-B mismatch unrelated donor	N/A	CY/TBI	CsA, MTX	GVHD grade II, ARDS	Death 2 months	19
1997	25	AML M6	N/A	MSD	N/A	CY/TBI + Campath-1G	MTX	CHF, GVHD, <i>Aspergillus</i> pneumonia	Death 6 months	20
1998	9	MDS RA	−7, i7q	2 antigen mismatch parent	T-deplete, CD34 <sup>+</sup> supp.	Thiotepa + CY/TBI	CsA, MTX, MP	CNS grade IV, GVHD grade IV, pulmonary hemorrhage	Death day +31	7
1998	8	MDS RAEB	−7	MUD	T-deplete	Thiotepa + CY/TBI	CsA, MTX, MP	CNS grade IV, GVHD grade III, RTA, hyperglycemia	Death day +93	7
1999	5	MDS	inv(14)(q11;q32)	MSD	Unmanipulated	BUCY	CsA, MTX	None	Disease free 18 months	21
2001	4	Marrow aplasia	N/A	MUD	Unmanipulated	Thiotepa + BUCY + ALG	CsA, MTX	None	Disease free 32 months	22
2001	30	MDS RAEB	5q <sup>−</sup> , −7, −13	MSD	T-deplete, CD34 <sup>+</sup> supp.	BUCY	CsA	Mucositis grade II, GVHD grade II	Relapse, death 7 months	Case

N/A = not available; MUD = matched unrelated donor; MSD = mismatched sibling donor; BU = busulfan; CY = cyclophosphamide; TBI = total body irradiation; ATG = anti-thymocyte globulin; ALG = anti-lymphocyte globulin; CsA = cyclosporin A; MTX = methotrexate; MP = methylprednisolone; VOD = veno-occlusive disease.

Since Okcu *et al*'s report, subsequent allotransplants for SDS did not report significant transplant related mortality. Four patients did not develop any significant complications during their transplant, and no apparent differences were seen between related and non-related donors. Grade II or greater GVHD was the most common complication seen. The overall 100 day survival rate for allotransplants in SDS is 66%. Locatelli *et al*<sup>12</sup> reported transplant related mortality for pediatric MDS of 21%. The difference in early mortality between the two groups is not dramatic and it is unclear whether the difference is statistically significant given the small size of both cohorts. This implies that SDS patients proceeding towards allotransplantation may not be at increased risk for early transplant related complications.

Bone marrow transplantation does appear to be a viable option for SDS patients with severe cytopenias. Dror *et al*<sup>13</sup> suggest abnormalities in both the hematopoietic progenitors and the marrow microenvironment as the cause of the variable cytopenias found in these patients. Because of the poor outcomes associated with transplantation for myelodysplasia and leukemia in patients with SDS, early bone marrow transplantation prior to the development of myelodysplasia or leukemia deserves serious consideration. These patients do not appear to be at increased risk of complications. As experience in allotransplantation in SDS accumulates, more definitive recommendations can be established.

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