Hematopoietic stem cell transplantation for Shwachman-Diamond syndrome: experience of the French neutropenia registry

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Summary:

Our objective was to study the outcome of allogeneic hematopoietic stem cell transplantation (HSCT) for Shwachman-Diamond Syndrome (SDS). Among 71 SDS patients included in the French Severe Chronic Neutropenia Registry, 10 received HSCT between 1987 and 2004 in five institutions. The indications were bone marrow failure in five cases, and myelodysplastic syndrome (MDS) or leukemia in five cases. The median follow-up of patients who survived without relapse is 6.9 years (3.1–16.8 years). The conditioning regimen consisted of a busulfan–cyclophosphamide combination (n = 6) or total body irradiation plus chemotherapy (n = 4). Six patients received stem cells from unrelated donors and four from identical siblings. Engraftment was complete in eight patients and unassessable in two patients. These latter two patients died of infections 32 and 36 days after HSCT, with grade IV graft-versus-host disease and multiorgan dysfunction. A third patient died from an acute respiratory distress syndrome 17 months after HSCT with progressive granulocytic sarcoma. One patient had an MDS relapse 4 months after HSCT and died 10 months later. The overall 5-year event-free survival rate is 60 ± 15%. We conclude that HSCT is feasible for patients with SDS who develop bone marrow failure or malignant transformation. Bone Marrow Transplantation (2005) 36, 787–792. doi:10.1038/sj.bmt.1705141; published online 5 September 2005

Keywords: Shwachman-Diamond Syndrome; hematopoietic stem cell transplantation; bone marrow failure; myelodysplasia

Shwachman-Diamond Syndrome (SDS) (OMIN260400) is a multisystem autosomal recessive disorder characterized by exocrine pancreatic dysfunction, bony metaphyseal dysostosis, mild intellectual retardation, and variable neutropenia.1 Almost all patients have a mutation in the SBDS gene located on chromosome 7.2 Bone marrow failure and myelodysplasia/acute leukemia are the main life-threatening complications. Hematopoietic stem cell transplantation (HSCT) is currently the only potentially curative treatment for these latter patients. Only 24 HSCT procedures have been described in this setting, in 18 separate publications.3–20 Here we report the outcomes of 10 SDS patients included in the French Severe Chronic Neutropenia Registry who underwent HSCT during the last 15 years.

Patients and methods

Registry organization and disease definition

The French Severe Chronic Neutropenia Registry was created in 1994, with approval from the French computer watchdog commission (CNIL Certificate No 97075). The patients’ files are monitored by clinical research associates who visited each center at least once a year. All patients with SDS are included in the registry, even if they are not profoundly neutropenic. SDS was diagnosed on the basis of neutropenia associated with exocrine pancreatic deficiency and skeletal, skin or liver abnormalities, after Pearson’s syndrome had been ruled out. The patients or next of kin were required to give their informed consent to participation to the registry. The French SCN database was crossed with the French transplant database (Etablissement Français des Greffes). A total of 71 patients were included in the SDS database, and a complete report of the survey, analyzed at the cut-off date of March 2003, has been published elsewhere.21 In all, 11 patients developed bone marrow failure, which was transient in five cases and persistent (> 3 months) in six cases. Among these latter six patients, the patient who did not receive HSCT died. Eight patients developed MDS/leukemia, of whom three patients
who were not transplanted died. SBDS gene mutations were evaluated as described elsewhere. 2

Definition of hematological events

Acute leukemia was defined by WHO criteria, that is, at least 20% of blast cells on bone marrow smears. As dysplastic cytological abnormalities were nearly always present in these patients, myelodysplastic syndrome (MDS) was diagnosed if cytological abnormalities in addition to refractory anemia or thrombocytopenia requiring blood transfusion, as well as clonal cytogenetic abnormalities were present. Bone marrow failure was diagnosed in case of refractory anemia or thrombocytopenia requiring blood transfusion, if no cytogenetic clonal abnormalities were found. The time of bone marrow failure was recorded as the date of the first transfusion, and the time of MDS diagnosis was the date when the first cytogenetic abnormalities were detected.

Statistical methods

Stata® software version 8 was used for all statistical analyses. The end point for survival analyses was relapse (if MDS/acute leukemia (AL)) or death. The period taken into account was the interval between HSCT and either death or MDS/AL relapse or the last examination when no event occurred. The Kaplan–Meier method was used to construct survival rates. The cutoff date for this analysis was June 30, 2005. The median follow-up for the six disease-free surviving patients is 7.6 years (3.9–16.9 years).

The patients are sorted by type of hematological event and age of outcome.

Table 1

| Unique patient number | Gender | Time from diagnosis of SDS to bone marrow failure or MDS/AL (years) | Age at BMF or MDS/AL (years) | Cytology diagnosis (FAB classification) | Bone marrow cytogenetics | Interval between bone marrow failure or MDS/AL and HSCT (year) |
|-----------------------|--------|---------------------------------------------------------------|-----------------------------|----------------------------------------|--------------------------|-------------------------------------------------|
| 233015263             | M      | 0                                                             | 0.1                         | Mild cytological abnormalities         | NI                       | 1.9                                             |
| 233015170             | M      | 0                                                             | 0.34                        | Mild cytological abnormalities         | NI                       | 0.8                                             |
| 233015184             | F      | 5.8                                                           | 5.9                         | Mild cytological abnormalities         | NI                       | 1.2                                             |
| 233015128             | F      | 8.4                                                           | 12.2                        | Mild cytological abnormalities         | NI                       | 2.4                                             |
| 233015098             | F      | 1.63                                                          | 14.3                        | Mild cytological abnormalities         | NI                       | 1.83                                            |
| 233015253             | M      | 7.1                                                           | 7.3                         | MDS                                    | NI                       | 0.3                                             |
| 233015117             | M      | 7.4                                                           | 7.7                         | MDS                                    | 47, XY, del(5q inter), add(9q), +11, add(17p), –20, +22 | 0.16                                           |
| 233015082             | M      | 13.5                                                          | 15.8                        | MDS                                    | 46 XY [7], 46 XY, iso (7q) [13] | 0.71                                           |
| 233015038             | M      | 18.7                                                          | 19.1                        | MDS                                    | 46 XY/45, XY, del(5q15), del(5q15), del(8q12q13), –7, +14, +14, +21 | 0.16                                           |
| 233015081             | F      | 26.5                                                          | 27.2                        | AML 6                                   | 45, XX, add(1)(p11), –7, add(14)(q32), add(21) | 0.49                                           |

The patients are sorted by type of hematological event and age of outcome.
Engraftment

Chimerism analysis was performed by means of cytogenetics or polymerase chain reaction (PCR) amplification of microsatellites.

Results (Table 2)

Hematological recovery after HSCT and engraftment

Engraftment could not be evaluated in two cases because of early death, while full hematological recovery occurred in the other eight cases. The median time required for the neutrophil count to reach 0.5 × 10^9/l was 22 days (range 15–44 days). The platelet count reached 50 × 10^9/l after 19–155 days (median 29.5 days), without further transfusions. All the patients who are alive and disease-free are currently free of erythrocyte and platelet transfusions. Neutrophil counts normalized in every case.

Engraftment

Complete chimerism was found in all eight assessable patients.

Graft-versus-host disease

Three patients developed grade IV acute GVHD (skin/gut in two and skin/liver in one) after receiving a MUD transplant in two cases and a matched sibling transplant in one case. Two patients with grade IV GVHD died. Three patients had grade II GVHD. Two patients developed chronic GVHD, one case with a sicca syndrome and one case with chronic cutaneous GVHD, with persistent livido.

Survival, causes of death and complications

Four patients died. The overall 5-year event-free survival rate was 60±15%. Two early deaths occurred. One patient (UPN 233015081) developed acute grade IV GVHD, thrombocytopenic microangiopathy with multiorgan failure and Stenotrophomonas maltophilia sepsis, and died on day 32 of Coronavirus 229E pneumonia. The second patient (UPN 233015253) died 37 days after HSCT from acute grade IV GVHD, acute respiratory distress syndrome, and HHV6 infection. The third patient (UPN 233015038) developed granulocytic sarcoma of the knee, ischium and shoulder, 1 year after HSCT. Monosomy 7 was detected in tumor cells by FISH analysis. The granulocytic sarcoma was treated with local radiotherapy. At the time of death (due to an undocumented acute respiratory distress syndrome), the marrow morphology was normal and no cytogenetic aberrations were detected. The disease course of this patient was remarkable. On day 40 after bone marrow transplantation (BMT), blast cells were observed on a blood smear, concomitantly with partial chimerism (28% of donor cells). A donor lymphocyte infusion was given on day 90, resulting in the disappearance of blast cells and in full donor chimerism. A fourth patient (UPN 233015117) with MDS/AL relapsed 4 months after transplantation, and died 10 months later from a hemorrhagic syndrome.

These four patients had received HSCT for MDS/AL. Although the number of patients is small, survival was significantly poorer in patients who received HSCT for malignancy than for bone marrow failure, four of the five deaths involving patients with MDS/AL and the other death involving a patient with BMF (log rank test, P = 0.01).

One patient had long-term complications, with aseptic osteonecrosis, cardiac hypokinesia, chronic keratitis and amenorrhea. Despite the correction of hematological abnormalities, other clinical characteristics of SDS such as pancreatic insufficiency, short stature and impaired cognitive performance are still present in all survivors, albeit with no apparent modifications related to HSCT.

Discussion

We report the outcome of HSCT in 10 patients with SDS and severe hematological complications (bone marrow failure in five cases and myelodysplasia/AL in five cases). Bone marrow aplasia and myelodysplasia/AL appear to be the most serious complications of SDS, and are always fatal despite conventional management with transfusions and chemotherapy. In SDS, AL is diagnosed on the basis of cytologic criteria. It can, however, be difficult to distinguish between bone marrow aplasia and myelodysplasia on the sole basis of cytologic bone marrow studies. Indeed, cellular dysplasia is present in both instances and the cytologic aspects do not correspond to the FAB classification of myelodysplasias. It is therefore crucial to follow cytologic bone marrow studies by cytogenetic examination in order to distinguish between simple bone marrow depletion and clonal progression (‘myelodysplasia’). In addition, the presence of a cytogenetic anomaly of iso chromosome 7, or a deletion of chromosome 20, as found in one of our patients, has also been observed in patients without transfusion requirements and with nonfatal outcome, complicating the decision to proceed with HSCT.

As shown here, marrow transplantation with both siblings and matched unrelated donors can correct the stem cell disorder encountered in SDS. Full and sustained engraftment was observed in eight patients, arguing against a major stromal defect in SDS. Despite the small number of patients, we found a significant difference in event-free survival between patients receiving HSCT for bone marrow aplasia and those undergoing the procedure for leukemic transformation. Such a difference, albeit nonsignificant, was also observed among the 23 published cases of HSCT for SDS for which this information is mentioned (11 deaths or relapses among 17 patients with MDS/AL; and one death among six patients with bone marrow failure, P = 0.07).

Several factors may explain the poor results of HSCT for myelodysplasia/AL in SDS. HSCT failed to correct the leukemia in one of our patients and in three of the 15 patients described in the literature. In addition, patients with SDS appear to be more susceptible to the toxicity
## Table 2: Main characteristics of HSCT in patients with SDS sorted by indication of HSCT and age of the hematological complications

| Unique patient number | Indication | Date of HSCT | Age at HSCT (years) | CR | Donor | GVH prevention | Nb of nucleated cells/kg | Acute GVHD | Chronic GVHD | Days ANC > 500 | Days Platelets > 50,000 without transf. | Toxicity grade | Vital status and FU duration since HSCT |
|-----------------------|------------|--------------|---------------------|----|-------|----------------|--------------------------|------------|---------------|----------------|--------------------------------------|---------------|----------------------------------------|
| 233015263             | BMF        | 26/05/00     | 1                   | BU 16 CY 200 | MUD 10/10  | CSA           | 13.8 10⁸ cells 17.4 10⁶ CD34 | Grade I skin | No            | 44             | 67                                    | No            | Alive/5.1 years                          |
| 233015170             | BMF        | 08/04/97     | 1.15                | BU 16 CY 200 | MUD 10/10  | CSA 10/10  | 29.8 10⁶ cells 4.5 10⁶ CD34 | Grade II skin | Livedo        | 17             | 26                                    | No            | Alive/8.2 years                          |
| 233015184             | BMF        | 25/10/94     | 7.2                 | TBI 12 Melphalan 180 | MUD 10/10  | Steroid 10/10  | 4 10⁶ cells | No            | No            | 36             | 30                                    | CMV infection | Alive/10.7 years                          |
| 233015128             | BMF        | 27/07/88     | 14.6                | TBI 7.5 Cy 120 | Sib 10/10  | CSA MTX 10/10  | 2 10⁶ cells | Grade II skin gut | GVH sicca syndrome | 22             | 29                                    | No            | Cardiomyopathy Osteonecrosis         |
| 233015098             | BMF        | 02/08/01     | 16.2                | BU 16 CY 200 | MUD 9/10  | CSA MTX (DP) 10/10  | 3 10⁶ cells 3.5 10⁶ CD34 | Grade I skin | No            | 24             | 115                                   | Chronic respiratory insuf. with obstructive syndrome | Died/36 days |
| 233015253             | MDS        | 05/10/01     | 7.6                 | Bu 16 Cy 200 | MUD 9/10  | CSA MTX 10/10  | 10.7 10⁶ cells 10⁶ CD34 | Grade IV skin liver | /              | 23             | Not achieved | ARDS at day 10 HHV 6 infection | Died/36 days |
| 233015117             | MDS        | 15/04/04     | 7.9                 | BU 13 Cyc 200 | Sib 10/10  | CSA 10/10  | 4.4 10⁶ cells 4.3 10⁶ CD34 | Grade IV skin gut | No            | 20             | 19                                    | No            | Death from MDS 14 months after HSCT and 9 months after relapse Alive/6.9 years |
| 233015082             | MDS        | 17/07/98     | 16.5                | BU 16 CY 200 | Sib 10/10  | CSA MTX 10/10  | 4.6 10⁶ cells 3.8 10⁶ CD34 | No            | No            | 20             | 25                                    | No            | Died from ARDS/1.7 years                |
| 233015038             | MDS        | 16/03/95     | 19.3                | TBI 10 single Cy 120 | Sib 10/10  | CSA MTX 10/10  | 0.7 10⁶ cells DLI at day 90 1.9 10⁶ T cells | No            | No            | 15             | 155                                   | Blasts cells at day 40? Relapse not confirmed by cytogenetic VOD (limited) at day 50 Granulocytic Sarcoma (knee, shoulder) –7 at 14 months | Died/32 days |
| 233015081             | AL         | 18/09/01     | 27.7                | TBI 12 Cy 120 | MUD 9/10  | CSA MTX Steroid 10/10  | 3.8 10⁶ cells 3.5 10⁶ CD34 | Grade IV skin gut | /              | Not achieved | Not achieved | Kidney toxicity (MAT) Sepsis maltophilia ARDS coronavirus | Died/32 days |

Pt = patient; Tx = transplantation; CR = conditioning regimen; sib = matched sibling donor; TCD = T cells depletion; Donor column: number in bracket = number of antigens difference; RRT = regimen-related toxicity; FU = follow-up; BU = busulfan (mg/kg); ATG = antithymocyte globulin; MDS = myelodysplastic syndrome; pbs = problems; GVHD = graft-versus-host disease; CMV = cytomegalovirus.
of the HSCT procedure than are patients with other myelodysplastic disorders associated with monosomy 7, like the Kostmann syndrome and juvenile myelomonocytic leukemia. This susceptibility may be related to older age or to disease characteristics. Indeed, there is a marked age difference between patients receiving HSCT for bone marrow aplasia and for leukemic transformation, both in our series and in the literature (median age 4.5 and 13 years, respectively). Several risk factors could progress with age in this setting, including the nutritional consequences of exocrine pancreatic insufficiency, liver disease, repeated infections and cardiac disorders. A risk of cardiomyopathy has been reported in patients with SDS who become transfusion-dependent, owing to pre-existing poor nutritional status. It is therefore necessary to carefully assess nutritional, cardiac and hepatic status prior to transplantation.

All the patients received a myeloablative-conditioning regimen prior to HSCT, usually consisting of the busulfan–cyclophosphamide combination. In patients with bone marrow aplasia, who are generally under 5 years of age, this conditioning appears effective and well tolerated. Stability of the engraftment over several years suggests that more intensive conditioning is not warranted. In contrast, the poor results in patients with leukemic transformation suggest that milder conditioning would be inappropriate and that very careful attention must be paid to nutritional status.

In conclusion, allogeneic HSCT can be envisaged for patients with SDS who become transfusion-dependent, with or without clonal cytogenetic features, and for those who develop overt leukemia. Our results indicate that BMT is associated with significant morbidity, potentially owing to pre-existing poor nutritional status, immune deficiency and/or the underlying disease. These patients should be closely monitored for infections after HSCT, and their nutritional status should be optimized before the procedure.

Acknowledgements

This work was supported by Grant RAF0007 from the Inserm AFM Network for Rare Diseases, Société d’Hématologie et Immunologie Pédiatrique, Amgen SA, and Chugai Aventis. We thank Florence Mesnil (Établissement Français des Greffes) for her participation in patient screening and David Young for editorial assistance.

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