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Improved Survival after Allogeneic Hematopoietic Stem Cell Transplantation in Recent Years. A Single-Center Study

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We analyzed the outcome of allogeneic hematopoietic stem cell transplantation (HSCT) over the past 2 decades. Between 1992 and 2009, 953 patients were treated with HSCT, mainly for a hematologic malignancy. They were divided according to 4 different time periods of treatment: 1992 to 1995, 1996 to 2000, 2001 to 2005, and 2006 to 2009. Over the years, many factors have changed considerably regarding patient age, diagnosis, disease stage, type of donor, stem cell source, genomic HLA typing, cell dose, type of conditioning, treatment of infections, use of granulocyte-colony stimulating factor (G-CSF), use of mesenchymal stem cells, use of cytotoxic T cells, and home care. When we compared the last period (2006-2009) with earlier periods, we found slower neutrophil engraftment, a higher incidence of acute graft-versus-host disease (aGVHD) of grades II-IV, and less chronic GVHD (cGHVD). The incidence of relapse was unchanged over the 4 periods (22%-25%). Overall survival (OS) and transplant-related mortality (TRM) improved significantly in the more recent periods, with the best results during the last period (2006-2009) and a 100-day TRM of 5.5%. This improvement was also apparent in a multivariate analysis. When correcting for differences between the 4 groups, the hazard ratio for mortality in the last period was 0.59 (95% confidence interval [CI]: 0.44-0.79; $P < .001$) and for TRM it was 0.63 (CI: 0.43-0.92; $P = .02$). This study shows that the combined efforts to improve outcome after HSCT have been very effective. Even though we now treat older patients with more advanced disease and use more alternative HLA nonidentical donors, OS and TRM have improved. The problem of relapse still has to be remedied. Thus, several different developments together have resulted in significantly lower TRM and improved survival after HSCT over the last few years.

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BACKGROUND

Hematopoietic stem cell transplantation (HSCT) is a curative treatment for patients with hematologic malignancies, bone marrow failure syndromes, and some inherited disorders [1-3].

The main obstacles to success after HSCT are relapse of the underlying disease, graft-versus-host disease (GVHD), and infection [4-7]. To improve the results after HSCT, efforts have been made to solve these problems by earlier detection, reduction of incidents,

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and improvement of treatments. This has resulted in considerable changes in the transplantation procedure, in treatment, and in patient selection. In particular, the introduction in the early 1980s of a combination of cyclosporine and methotrexate has significantly reduced severe aGVHD and improved TRM [8,9]. The number of patients eligible for HSCT has increased as a result of better treatments, and the introduction of less toxic reduced-intensity conditioning (RIC) regimens has made it possible to admit older patients and those with comorbidities [10-12]. During the late 1990s, the source of stem cells shifted from bone marrow to peripheral blood stem cells (PBSCs) [13-17]. Genomic tissue typing has been employed to better match unrelated donors [18,19]. The introduction of preemptive therapy for cytomegalovirus (CMV) infection has improved outcome and reduced the risk of fatal CMV disease [20,21]. In our unit, the use of liposomal amphotericin B after HSCT has significantly reduced the risk of invasive fungal infection from 11% to around 5% [22]. Today, there is a large number of efficient antifungals from which to choose. Other antiinfectious agents include new antibiotics and antiviral drugs such as acyclovir, ganciclovir, and foscarnet [23]. By the introduction of PCR methods to detect donor-recipient chimerism, there has been improved diagnosis of graft failure [24]. Minimal residual disease detection of threatening relapse has also been developed [25]. Donor lymphocyte infusions (DLIs) are used for treatment of graft failure and relapse [26,27]. Home care after HSCT has reduced aGVHD and improved survival; this is now routine practice in patients living within 2 hours' driving distance of our hospital [28]. In more recent years, mesenchymal stem cells have been introduced by us and have been shown to have an effect in some patients with severe aGVHD that is otherwise refractory to therapy [29]. A randomized study showed that the use of ursodiol not only reduced liver toxicity, it also improved survival [30]. Because of these improvements, patients with higher age, with more resistant underlying disease, and those with comorbidities have been accepted for HSCT. The range of diagnoses in patients admitted for HSCT has also changed over the years. Because the proportion of patients admitted with more advanced disease has increased with time, there was no apparent improvement in patient survival for a long time. It was therefore of interest to determine whether or not outcome after HSCT has improved over the last 2 decades.

PATIENTS AND METHODS

Patients

From January 1992 until December 2009, 1013 patients underwent HSCT at Karolinska University Hospital, Huddinge, Sweden. Patients transplanted for a solid tumor (n = 60) were excluded, as this is an experimental treatment with poor outcome [31]. In total, 953 patients were included in the study. Patient and donor characteristics are listed in Table 1.

There were 275 patients with acute myeloid leukemia (AML), 176 with acute lymphoid leukemia (ALL), 161 with chronic myeloid leukemia (CML), 24 with chronic lymphoid leukemia (CLL), 60 with lymphoma, 86 with myelodysplastic syndrome or myeloproliferative syndrome (MDS/MPS), 27 with multiple myeloma (MM), and 6 with myelofibrosis (MF). One hundred thirty-eight other patients had a nonmalignant disorder: severe aplastic anemia (n = 38), Fanconi anemia (n = 13), inborn error of metabolism (n = 80), or another nonmalignant disease (n = 7). The median age of all patients was 34 years (0-69), and there were 545 males and 408 females. There were 293 children under the age of 18 years (31%). Almost one-half of the patients (46%) had a malignancy beyond first complete remission or first chronic phase (CR1/CP1), and were considered to have high-risk disease.

The study was approved by the Ethics Committee at Huddinge University Hospital. All patients included in the study gave informed consent.

Donors

Donors were an HLA-identical sibling in 406 cases, at least an HLA-A, -B and -DR matched unrelated donor (MUD) in 419 cases, an allele-mismatched unrelated donor in 56 cases, or an antigen-mismatched related or unrelated donor in 13 and 54 cases, respectively. Five patients were transplanted from a syngeneic twin. There were 531 male and 410 female donors with a median age of 35 years (range: 0-71).

HLA Typing

All patients and donors were typed using PCR-SSP high-resolution typing for both HLA class I and II antigens (at the 4-digit level) [18,32-34].

Stem Cell Source

Bone marrow (BM) was given to 480 patients, and 429 patients received peripheral blood stem cells (PBSCs) from a granulocyte-colony stimulating factor (G-CSF) stimulated donor. In 44 cases, 1 (n = 33) or 2 (n = 11) cord blood units were used as grafts, mainly for patients lacking an acceptable related or unrelated donor. Median nucleated cell dose was 4.8×10^8/kg (range: 0.03-81.3). The $CD34^+$ cell dose was known in 703 transplants and was median 6.3×10^6/kg (0.03-68).

Conditioning

Conventional myeloablative conditioning was given to 704 patients and consisted of cyclophosphamide (Cy) at 60 mg/kg for 2 days in combination with 7.5-10 Gy single-fraction total body irradiation (sTBI)