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Late Mortality and Causes of Death among Long-Term Survivors after Allogeneic Stem Cell Transplantation

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A B S T R A C T

We sought to assess the late mortality risks and causes of death among long-term survivors of allogeneic hematopoietic stem cell transplantation (HCT). The cases of 11,047 relapse-free survivors of a first HCT at least 2 years after HCT were analyzed. Standardized mortality ratios (SMR) were calculated and specific causes of death were compared with those of the Japanese population. Among relapse-free survivors at 2 years, overall survival percentages at 10 and 15 years were 87% and 83%, respectively. The overall risk of mortality was significantly higher compared with that of the general population. The risk of mortality was significantly higher from infection (SMR = 57.0), new hematologic malignancies (SMR = 2.2), other new malignancies (SMR = 3.0), respiratory causes (SMR = 109.3), gastrointestinal causes (SMR = 3.8), liver dysfunction (SMR = 6.1), genitourinary dysfunction (SMR = 17.6), and external or accidental causes (SMR = 2.3). The overall annual mortality rate showed a steep decrease from 2 to 5 years after HCT; however, the decrease rate slowed after 10 years but was still higher than that of the general population at 20 years after HCT. SMRs in the earlier period of 2 to 4 years after HCT and 5 years or longer after HCT were 16.1 and 7.4, respectively. Long-term survivors after allogeneic HCT are at higher risk of mortality from various causes other than the underlying disease that led to HCT. Screening and preventive measures should be given a central role in reducing the morbidity and mortality of HCT recipients on long-term follow-up.

INTRODUCTION

Hematopoietic stem cell transplantation (HCT) is the curative treatment of choice for many malignant and nonmalignant hematologic disorders, such as leukemia, lymphoma, and bone marrow failure [1]. The annual number of allogeneic HCTs has increased steadily over the past

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3 decades worldwide [2-7]. Progress in HCT methodology has led to decreased early mortality which, combined with the steady increase in the number of HCT procedures worldwide, has resulted in a large population of long-term HCT survivors [8,9].

Several studies have shown that the mortality rate of long-term survivors is higher than that of the general population for at least 30 years after HCT in a recent study [10-14]. Long-term survivors are reported to be prone to developing various organ dysfunctions or other complications that result from the pre-HCT disease, its treatment before the HCT, or the HCT itself, including chronic graft-versus-host disease (GVHD) [15-22].

Here, we conducted a nationwide retrospective cohort study to evaluate late mortality and causes of late death.

MATERIALS AND METHODS

Data Source and Collection of data

HCT recipient clinical data were collected by the Japan Society for Hematopoietic Cell Transplantation using the Transplant Registry Unified Management Program (TRUMP), as described previously [23]. Information on survival, underlying disease status, and long-term complications including chronic GVHD (cGVHD) and second malignancies is renewed annually. Patient information is anonymized, so consent is not required. This study was approved by the data management committee of the Japan Society for Hematopoietic Cell Transplantation and by the institutional review board of Nagoya University Graduate School of Medicine.

HCT Recipients

A total of 23,824 first allogeneic HCTs for hematological diseases from 1974 to 2007 were recorded in the TRUMP database. Inclusion criteria for this study were relapse-free survival at least 2 years after a first allogeneic HCT from 1974 to 2007 (11,047 recipients). Exclusion criteria were death from any cause up to 2 years after HCT (n = 10,624), relapse of the underlying disease up to 2 years after HCT or no evidence of remission after HCT (n = 1270), need for a second HCT within 2 years of the first HCT (n = 237), absence of long-term follow-up more than 2 years after HCT (n = 536), and absent survival status information or date of last follow-up information (n = 110). The median follow-up period of survivors was 8.4 years (range, 2.0 to 30.5 years). A total of 8571 recipients were followed for more than 5 years after HCT and 3699 recipients were followed for more than 10 years.

Classification of Causes of Death

Primary and secondary causes of death were determined and reported by transplantation physicians and were collected in TRUMP. For causes of death listed as "other," detailed information was given by the transplantation physician. Cause of death information, including text comments, was reviewed by 6 transplantation physicians. Cause of death categories for TRUMP and cause of death classification algorithms are described in Supplemental Table 1. "Recurrent disease/death after relapse" was selected as the cause of death if the primary or secondary cause of death were relapse of underlying disease. In recipients with cGVHD specified as the primary cause of death, a secondary cause of death was selected for classification if other specific causes were identified, such as specific organ failure or infection. Patients who received a second HCT more than 2 years after the first HCT were censored, and therefore determined to be alive at the time of the second HCT (n = 351, of whom 224 died after the second HCT). Forty-eight recipients whose reported primary or secondary cause of death was other than recurrent disease were classified as "recurrent disease/death after relapse" because they had experienced relapse of the underlying disease (reported primary causes were cGVHD, n = 1; infection, n = 18; new malignancy, n = 9; cardiovascular, n = 4; neurologic, n = 1; genitourinary, n = 1; other, n = 3; and unknown, n = 3) Nine recipients whose reported primary or secondary cause of death was rejection/graft failure or acute GVHD without any information on a second HCT were classified as "recurrent disease/death after relapse" (acute GVHD, n = 7; rejection/graft failure, n = 2). Cause of death classifications for general data are defined in Supplemental Table 2. Estimating the expected number of deaths is described in the Statistical Analysis section.

Statistical Analysis

Standardized mortality ratios (SMRs) were calculated to determine whether the number of deaths in the cohort of long-term survivors who lived at least 2 years after HCT was excessive compared with that in the general population. The calculations are based on the ratio of the number of patients dying (observed number) to the number in the general population who would be expected to die from any or specific causes (expected number). The expected number was determined as follows: for each patient, the number of person-years at risk was calculated from 2 years (730.5 days) after the date of HCT until the date of death or the date of last contact. Age (5-year strata)-, sex-, and calendar year (5-year strata)–specific mortality rates for overall or specific causes of death of Japanese general population were applied to the appropriate person-years at risk to compute the expected numbers of deaths. The median year of each 5-year period was chosen to represent the mortality rate of that period. Mortality rates for overall or specific causes of death of Japanese general population were obtained from the database of the Health, Labour and Welfare Statistics Association. The 95% confidence intervals (CIs) for the SMRs were calculated based on the assumption that the observed number of deaths followed a Poisson distribution.

Overall survival was defined as time from HCT to death from any cause, whose probabilities were estimated using the Kaplan-Meier method. The log-rank test was used to compare the survival curves among groups. Cumulative incidence curves were used in a competing-risks setting to calculate the probability of cause-specific mortality, treating death from other causes as a competing risk [24]. The influence of potential prognostic factors was estimated using the Cox proportional hazard model [25]. A stepwise multivariate approach was used to identify the most important prognostic factors with a variable retention criterion of $P < .05$. The variables considered were HCT year, age at HCT, patient sex, donor source type (related bone marrow transplant, related peripheral stem cell transplant, unrelated bone marrow transplant, and unrelated cord blood transplant), whether total body irradiation was part of the conditioning regimen, reduced-intensity conditioning, and cGVHD. cGVHD was considered to be a time-dependent covariate. In addition, mortality rates during the 2 decades from the HCT were smoothed by the smoothing spline Poisson regression using an R package (gss, R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria). All other analyses were performed using commercial software (Stata version 13.0, Stata Corporation, College Station TX). All *P* values are 2-sided.

RESULTS

Patient and HCT Characteristics

Table 1 shows patient characteristics, diseases, and HCT regimens for 11,047 relapse-free survivors at 2 years after first HCT. Among these survivors at 2 years, 47% had undergone HCT before 2000, the percentage of male recipients was 57%, and the median age at HCT was 29 years (range, 0 to 76). Among recipients whose racial information was available, more than 99% were Japanese. Seventy-nine percent of recipients were diagnosed with leukemia and 10% were diagnosed with aplastic anemia. Forty-two percent received HCT from an unrelated donor. The percentages of patients who received bone marrow, peripheral blood, and cord blood were 76%, 15%, and 9%, respectively. Myeloablative conditioning was given to 77% of recipients before HCT, and total body irradiation was included in the myeloablative conditioning of 73% of the recipients. Cyclosporine or tacrolimus with short-term methotrexate was used for GVHD prophylaxis in most recipients. The median follow-up after HCT of the 11,047 2-year relapse-free survivors was 7.9 years (range, 2.0 to 30.5 years). The observation period totaled 74,079 person-years.

Overall Survival

The probability of overall survival among relapse-free survivors at 2 years after HCT was 93% at 5 years, 87% at 10 years, and 83% at 15 years (Figure 1A). Survival probability at 10 years was 86% for leukemia, 86% for lymphoma, and 95% for aplastic anemia patients, with significant differences among their survival curves ($P < .001$). The survival curves also varied by recipient age at HCT ($P < .001$), with a 10-year survival probability of 95% for those whose age at HCT was 0 to 15 years, 90% for 16 to 30 years, 85% for 31 to 45 years, and 73% for 46 years or older (Supplemental Figure 1).