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Second Cancer Risk and Late Mortality in Adult Australians Receiving Allogeneic Hematopoietic Stem Cell Transplantation: A Population-Based Cohort Study

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A B S T R A C T

We quantified the risk of second cancer and late mortality in a population-based Australian cohort of 3273 adult (≥15 years) allogeneic hematopoietic stem cell transplant recipients (1992 to 2007). Most recipients received nonradiation-based conditioning and a peripheral blood graft from a matched related donor. Using record linkage with death and cancer registries, 79 second cancers were identified a median of 3.5 years after transplantation. The competing-risk adjusted cumulative incidence of second cancers was 3.35% (95% CI, 2.59 to 4.24) at 10 years, and the cancer risk relative to the matched general population was 2.10 (95% CI, 1.65 to 2.56). We observed an excess risk of melanoma and lip, tongue, esophagus, and soft tissue cancers. Cancer risk relative to the general population was elevated for those transplanted for lymphoma, some leukemia subtypes, and severe aplastic anemia, recipients who developed chronic graft-versus-host disease (cGVHD) and irrespective of radiation-based conditioning or stem cell source. In those alive 2 years after transplantation (n = 1463), the cumulative incidence of late mortality was 22.2% (95% CI, 19.7 to 24.9) at 10 years, and the risk of death relative to the matched general population was 13.8 (95% CI, 12.2 to 15.6). In multivariable modeling, risk of late death was reduced for females compared with males and those transplanted for chronic myeloid leukemia compared with acute myeloid leukemia; risk was increased for recipients with discordant sex donors, cGVHD, those undergoing second transplants, and disease relapse. Adults undergoing allogeneic transplantation have unique cancer and mortality risk profiles that continue to warrant prevention and surveillance activities targeted at high-risk subgroups.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is now standard of care for the treatment of certain patients with hematologic malignancies and nonmalignant disorders [1]. Patient outcomes have improved dramatically over time, but the long-recognized increased risk of second cancers [2] and late mortality [3] remains. The most common incident cancers after allogeneic HSCT are oral cavity, esophageal, and skin cancers [4-6]. Consistently observed risk factors for second cancer are pretransplant high-dose total body irradiation (TBI) and post-transplant chronic graft-versus-host disease (cGVHD) and its therapy [4,7]. Late deaths are common and predominantly attributed to malignancy relapse, second cancers, infections, cGVHD, and organ dysfunction [8,9].

Several studies have quantified the risk of second cancer and late mortality after transplantation, but none has been population-based, incorporating consecutive HSCT recipients and ascertaining and standardizing the classification of outcomes from statutory registers. Studies that identify incident cancers in the cohort and the general population using identical sources, population-based cancer registries,

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reduce the risk of under-ascertainment and misclassification error. Furthermore, some prior studies combined allogeneic and autologous cohorts and pediatric and adult recipients, potentially masking clinically important differences among recipient subpopulations. Allogeneic transplant recipients are subject to more profound and longer-lasting immunosuppression and immune reconstitution than their autologous counterparts [10,11]. Accurate risk estimates are required to inform allogeneic HSCT protocols and survivorship care programs [7]. Risk estimates from different countries are needed because of heterogeneity in transplanted populations, HSCT protocols, and underlying lifestyle and environmental risk factors. Therefore, we quantified the risk of second cancers (excluding nonmelanoma skin cancers) and late mortality in a retrospective population-based cohort of adult Australian allogeneic HSCT recipients from 1992 to 2007.

METHODS

Study Population

The Australasian Bone Marrow Transplant Recipient Registry (ABMTRR) records up to 99.5% of HSCTs performed in Australia since 1992 [12]. Our cohort included all adult (≥15 years) allogeneic HSCT recipients recorded on the ABMTRR between 1992 and 2007, the latest date for which cancer registrations were available (n = 3273).

We ascertained deaths and incident cancers by record linkage with population-based datasets: the National Death Index (1980 to 2007) and the Australian Cancer Database (1982 to 2007). Patient name code (first 2 letters of given name and first 4 letters of surname), sex, date of birth, date of death, and state of residence were used during record linkage that was performed using an established probabilistic algorithm. A linkage probability or weight was given to each potential matching record pair and a subset of paired records underwent clerical review [13].

The Australian Cancer Database is a register of incident primary invasive neoplasms other than basal and squamous cell carcinoma of the skin. The Australian cancer registries apply international rules when registering multiple primary cancers. Cancer incidence rates for the Australian general population were obtained from the Australian Cancer Database and recipient demographic and clinical characteristics from the ABMTRR. We received ethical approval from all relevant institutional review boards; the requirement for informed consent was waived.

Data Analysis

We excluded recipients whose malignant indication for transplantation was not identified in linkage with the Australian Cancer Database (n = 174) and non-Australian residents (n = 5) from the second cancer analyses. Solid cancers diagnosed at least 30 days after HSCT and hematologic malignancies diagnosed any time after HSCT were counted as second cancers. We assessed and excluded potential progressed malignant indications for transplantation. We estimated the probability of second cancer by computing the cumulative incidence, treating death from other causes as a competing risk [14]. Probabilities were calculated from the date of HSCT to the date of second cancer diagnosis, death, or censoring (December 31, 2007).

Person-years follow-up was accrued from transplantation (or day 31) until the date of second cancer diagnosis, death, or December 31, 2007, whichever occurred first. Standardized incidence ratios, the ratio of observed and expected numbers of cancers, were computed for all cancers and for specific cancers. We calculated the expected numbers of incident cancers by multiplying the number of person-years at risk by the corresponding 5-year age-, sex-, state- and calendar year–specific cancer incidence rates for the Australian population. All higher-order cancers were counted, and recipients did not contribute person-years at risk for their pre-HSCT cancer type.

Patients who did not link with the National Death Index but who were recorded as deceased in medical records or the ABMTRR were classified as deceased in our analyses (n = 173, 10.1% of all deaths). We examined late mortality for recipients (1980 to 2005) who were alive 2 years after transplantation. Overall survival probabilities were estimated by the Kaplan-Meier method from the date of HSCT to the date of death or December 31, 2007 for those who remained alive. We computed standardized mortality ratios, the ratio of deaths observed in the study population to deaths expected in the Australian general population, for deaths from any cause. Expected deaths were calculated by multiplying the number of person-years at risk in each age, sex, state, and calendar year band by the corresponding Australian mortality rates reported by the National Death Index. Person-years at risk were computed from 2 years after the date of HSCT to the date of death or December 31, 2007.

Risk factor analysis for all-cause mortality used multivariate Cox regression modeling and proportional hazards assumption testing for each covariate. Because some clinical data were missing for some patients, multiple imputation was used. Imputation allowed all patients to be included in the analyses, not just those with complete data. We imputed missing values for the following variables using chained equations [15,16], T cell depletion, acute GVHD, cGVHD, and donor–patient sex concordance. Variables used for imputations were age, sex, era of HSCT, donor type, donor source, relapse or persistent disease within 2 years of HSCT, and death. All analyses were performed using STATA, version 12 (StataCorp, College Station, TX).

RESULTS

The median age at HSCT was 40.4 years (range, 15.5 to 59.2), with the largest subgroup (34%) transplanted for acute myeloid leukemia (AML), a minority for nonmalignancy (4%), and very few for solid malignancy (1%; Table 1). At least 56% of recipients received chemotherapy only before HSCT; 7% received both chemotherapy and radiotherapy.

Most transplants were from matched related donors (66%), and similar proportions received radiation-based (TBI; 46%) and nonradiation based conditioning (45%; Table 1). Of those who received TBI, 51% were known to have received low-dose conditioning (single < 10 Gy or fractionated < 13 Gy). Peripheral blood was the sole source of hematopoietic stem cells for 54% of the cohort. After transplantation, 30% were known to have developed grade II or higher acute GVHD, 48% were known to have developed cGVHD, and 28% experienced relapse of their primary disease.

The median follow-up for the cohort of 3094 recipients was 2.81 person-years (interquartile range, .36 to not reached); 897 and 374 patients were alive 5 and 10 years after transplantation, respectively. The median follow-up for the 1463 recipients who survived at least 2 years was 6.74 person years (interquartile range, 3.96 to 10.5). Fifty-three percent (n = 1751) of recipients died during follow-up, 85% within 2 years of transplantation.

Cancer Incidence

We observed 79 second primary cancers in 76 patients (Supplementary Table 1) a median of 3.54 years after HSCT (range, .13 to 13.5). Most were solid tumors (n = 76, 96%) with melanoma the most common (n = 19), followed by oral cavity cancers (n = 15). All incident melanomas were located on the limbs (n = 12) or trunk (n = 7).

The cumulative incidence of all second cancers adjusting for competing risk of death was 4.44% (95% confidence interval [CI], 3.38 to 5.70): .43% (95% CI, .25 to .73) at 1 year after HSCT, 1.98% (95% CI, 1.48 to 2.59) at 5 years, and 3.35% (95% CI, 2.59 to 4.24) at 10 years (Figure 1). The overall risk of cancer relative to the age-, sex-, state-, and calendar year–matched general population was modestly elevated (standardized incidence ratio, 2.10; 95% CI, 1.65 to 2.56; Table 2). In stratified analyses, risk was significantly elevated for all age groups and for males but not females (Table 2). Excess risk was observed for recipients whose indication for HSCT was AML, acute lymphoblastic leukemia, lymphoma, another leukemia subtype, or severe aplastic anemia (Table 2). Cancer risk was significantly increased irrespective of the source of stem cells and whether radiation-based conditioning was received but was only elevated in those known to have developed cGVHD (Table 2).