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Second Solid Cancers after Allogeneic Hematopoietic Cell Transplantation Using Reduced-Intensity Conditioning

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We examined risk of second solid cancers after allogeneic hematopoietic cell transplantation (AHCT) using reduced-intensity/nonmyeloablative conditioning (RIC/NMC). RIC/NMC recipients with leukemia/myelodysplastic syndrome (MDS) (n = 2833) and lymphoma (n = 1436) between 1995 and 2006 were included. In addition, RIC/NMC recipients 40 to 60 years of age (n = 2138) were compared with patients of the same age receiving myeloablative conditioning (MAC, n = 6428). The cumulative incidence of solid cancers was 3.35% at

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10 years. There was no increase in overall cancer risk compared with the general population (leukemia/MDS: standardized incidence ratio [SIR] .99, $P = 1.00$; lymphoma: SIR .92, $P = .75$). However, risks were significantly increased in leukemia/MDS patients for cancers of lip (SIR 14.28), tonsil (SIR 8.66), oropharynx (SIR 46.70), bone (SIR 23.53), soft tissue (SIR 12.92), and vulva (SIR 18.55) and skin melanoma (SIR 3.04). Lymphoma patients had significantly higher risks of oropharyngeal cancer (SIR 67.35) and skin melanoma (SIR 3.52). Among RIC/NMC recipients, age >50 years was the only independent risk factor for solid cancers (hazard ratio [HR] 3.02, $P < .001$). Among patients ages 40 to 60 years, when adjusted for other factors, there was no difference in cancer risks between RIC/NMC and MAC in leukemia/MDS patients (HR .98, $P = .905$). In lymphoma patients, risks were lower after RIC/NMC (HR .51, $P = .047$). In conclusion, the overall risks of second solid cancers in RIC/NMC recipients are similar to the general population, although there is an increased risk of cancer at some sites. Studies with longer follow-up are needed to realize the complete risks of solid cancers after RIC/NMC AHCT.

INTRODUCTION

It is well established that patients treated with allogeneic hematopoietic cell transplantation (AHCT) using myeloablative conditioning (MAC) are at increased lifelong risk for second solid cancers [1-8]. A latency period of 3 to 5 years occurs before second solid cancers start appearing after AHCT, and most recent large studies have reported cumulative incidence rates of 1% to 2% at 10 years and 3% to 5% at 20 years after transplantation. The incidence of solid malignancies continues to rise with increasing survival after transplantation, and lifelong surveillance is recommended for prevention in AHCT survivors [9]. Important risk factors for these cancers in MAC AHCT recipients include exposure to higher dose of total body irradiation (TBI), younger age at transplantation, use of HLA-mismatched donor, and chronic graft-versus-host disease (GVHD) [1,3,6,7].

The introduction of reduced-intensity conditioning (RIC) and nonmyeloablative conditioning (NMC) regimens over the last decade now allows AHCT to be offered as a treatment option for patients who are otherwise ineligible for transplantation using MAC based on age, performance status, or comorbidities [10-13]. AHCT using RIC/NMC regimens leads to long-term engraftment, exhibits graft-versus-malignancy effect, and results in significantly lower early transplant-related toxicity and mortality [14-18]. However, given the recent introduction of these conditioning regimens, the incidence and risk factors for late complications, including second solid cancers, have not been adequately characterized.

In patients with cancer, less chemotherapy is associated with a decreased probability of second malignancies [19-22]. It is therefore possible that RIC/NMC patients may have a lower probability of developing second solid malignancies compared with patients treated with MAC. On the other hand, lower doses of TBI and chemotherapy may be more carcinogenic than MAC regimens because cells may be damaged but not eliminated. Also, RIC/NMC regimens are typically used in older patients who have a higher baseline cancer risk compared with MAC recipients who tend to be younger in age. Recent data from a single-center study suggest that the risk of second cancers after RIC/NMC may not be diminished compared with MAC [23]. Given the paucity of studies characterizing second cancers in recipients of RIC/NMC transplantation, additional data using large samples are needed to better understand the impact of these potentially devastating late effects.

Using data from an international transplant outcomes registry, the Center for International Blood and Marrow Transplant Research (CIBMTR), we describe the incidence and risk factors for second solid cancers (excluding nonmelanoma skin cancers) after RIC/NMC AHCT for leukemia, myelodysplastic syndrome (MDS), and lymphoma. We also compare the risks of second solid cancers after RIC/NMC AHCT with general population control subjects. Finally, we compare the risks of solid cancers after RIC/NMC and MAC transplantation in a subgroup of patients with the same age at transplantation (40 to 60 years).

METHODS

Data Source

The CIBMTR is a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on HCTs to a Statistical Center at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program (NMDP) in Minneapolis. Participating centers are required to report all transplants consecutively; compliance is monitored by on-site audits. Patients are followed longitudinally. Computerized checks for discrepancies, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. Data are collected before transplant, 100 days, and 6 months after transplant and annually thereafter or until death. Among other data, all centers contribute data on the development of a new malignancy and causes of death. Observational studies conducted by the CIBMTR are performed under guidance of the Institutional Review Board of the NMDP and are in compliance with all applicable federal regulations pertaining to the protection of human research participants.

Patients

The study included all patients receiving AHCT for acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, MDS, and lymphoma between 1995 and 2006 that were reported to the CIBMTR. We limited our cohort to recipients of peripheral blood stem cell or bone marrow grafts from related or unrelated donors; umbilical cord blood transplant recipients were excluded. Also excluded were patients who had received syngeneic transplants. To avoid bias from inclusion of teams with incomplete follow-up and, consequently incomplete ascertainment of events in the late post-transplant period, we excluded patients from centers with completeness index of follow-up of <80% at 5 years post-transplantation (1179 patients from 68 centers) [24].

Study Definitions and Objectives

Conditioning regimens were defined as MAC, RIC, and NMC using previously defined guidelines [25]. Standard definitions were used for assigning disease status (early, intermediate, or advanced) for patients with acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, and MDS [26]. The NMDP classification of HLA-matching status was used for unrelated donor AHCT recipients (well matched, partially matched, or mismatched) [27]. Patients with leukemia/MDS and lymphoma were analyzed separately given the differences in their pretransplant and transplant treatment exposures. The CIBMTR routinely collects data on the occurrence of secondary cancers after AHCT. For this study, when necessary, pathology and physician reports of second cancers were requested from the transplant centers and reviewed centrally at the CIBMTR and tumors reclassified [28].

Statistical Analyses

For comparing groups, we used the chi-square or Fisher's test (as applicable) for categorical variables and Wilcoxon 2-sample test for continuous variables. The cumulative incidence of solid cancers was estimated taking into account the competing risk of death among patients who