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New Cancers after Autotransplantations for Multiple Myeloma

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A B S T R A C T

We describe baseline incidence and risk factors for new cancers in 4161 persons receiving autotransplants for multiple myeloma in the United States from 1990 to 2010. Observed incidence of invasive new cancers was compared with expected incidence relative to the US population. The cohort represented 13,387 person-years at-risk. In total, 163 new cancers were observed, for a crude incidence rate of 1.2 new cancers per 100 person-years and cumulative incidences of 2.6% (95% confidence interval [CI], 2.09 to 3.17), 4.2% (95% CI, 3.49 to 5.00), and 6.1% (95% CI, 5.08 to 7.24) at 3, 5, and 7 years, respectively. The incidence of new cancers in the auto-transplantation cohort was similar to age-, race-, and gender-adjusted comparison subjects with an observed/expected (O/E) ratio of 1.00 (99% CI, .81 to 1.22). However, acute myeloid leukemia and melanoma were observed at higher than expected rates with O/E ratios of 5.19 (99% CI, 1.67 to 12.04; $P = .0004$), and 3.58 (99% CI, 1.82 to 6.29; $P < .0001$), respectively. Obesity, older age, and male gender were associated with increased

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risks of new cancers in multivariate analyses. This large data set provides a baseline for comparison and defines the histologic type specific risk for new cancers in patients with MM receiving post-autotransplantation therapies, such as maintenance.

INTRODUCTION

Survival of persons with multiple myeloma (MM) has improved substantially because of new therapies, including autotransplantations and novel drugs, such as immune-modulating drugs and proteasome-inhibitors. Consequently, it is important to determine whether there is an increased risk of new cancers either because of the disease or its therapy. Several—but not all—studies report an increased risk of new cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) in persons with myeloma whether or not they receive autologous transplants [1-5].

Recent data from randomized trials of lenalidomide given after autotransplantation as maintenance therapy to prevent relapse indicate an increased risk of new cancers. Twenty-six of 307 in 1 study and 18 of 231 subjects in a second developed new cancers, with a significant higher incidence in subjects randomized to lenalidomide compared with those receiving placebo [6,7]. A recent meta-analysis reported a higher risk for new hematologic cancers in persons receiving lenalidomide and melphalan [8].

The purpose of our study was to determine the baseline incidence of new cancers after autologous transplantation in persons with MM in the United States and to compare this rate with those of an age-, gender-, and race-matched US population. We also wanted to identify factors associated with development of new cancers after autotransplantation using statistical models.

METHODS

Subjects

Subjects receiving a first autotransplant within 18 months of diagnosis in the United States for MM and reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) from 1990 to 2010 were included in the study. The CIBMTR is a voluntary group of more than 450 transplantation centers worldwide that contribute data on allogeneic and autologous transplantations to a statistical center at the Medical College of Wisconsin in Milwaukee or the National Marrow Donor Program coordinating center in Minneapolis, Minnesota. Participating centers are required to register all transplantations done consecutively and post-transplantation outcomes, including incidence of new cancer, are collected in prospective fashion. Compliance of the participating centers is monitored by periodic on-site audits. Subjects are followed up longitudinally, with yearly data update. Computerized checks for errors, physicians' review of submitted data, and on-site audits of participating centers are used to ensure data quality. Observational studies conducted by the CIBMTR are performed with a waiver of informed consent and in compliance with Health Insurance Portability and Accountability Act regulations as determined by the institutional review board and the privacy officer of the Medical College of Wisconsin.

Definition of Outcomes

A *new cancer* was defined as a previously unidentified invasive cancer occurring after transplantation. Carcinomas in situ and other precancerous abnormalities (eg, squamous intraepithelial neoplasia) were excluded. Pathology reports were obtained and reviewed centrally to confirm the diagnosis. Transplantation centers were contacted to resolve ambiguities. After confirmation, diagnoses of new cancers were coded by ICD-O-3 for comparison with the US National Cancer Institute's Surveillance, Epidemiology, and End Results program (SEER) [9]. SEER consists of high-quality, population-based cancer registries that are supported and sponsored by the National Cancer Institute. The SEER program is the authoritative source on invasive cancer incidence and survival in the United States.

Statistical Analyses

Summary statistics were used to describe the cohort. For each transplant recipient, person-years at risk were calculated from date of transplantation until the date of last contact, death, or diagnosis of a new cancer, whichever occurred first. Time to diagnosis of new cancer from transplantation was determined. Cumulative incidence of new cancers was computed at various time points by treating death as a competing risk. Recurrence or progression of MM was not considered a competing risk.

Age-, gender-, and race-specific cancer incidence rates derived from SEER for all cancers combined and for cancers at specific sites were applied to the appropriate person-years at-risk to compute the expected numbers of cancers. Observed/expected (O/E) ratios or standardized incidence ratios (SIRs) with 99% confidence intervals (CI) were calculated on the assumption that the observed number of cancers followed a Poisson distribution. Specific O/E ratios were not derived for nonmelanoma skin cancers and for MDS because nonmelanoma skin cancers cancers are not collected by SEER and MDS was not reportable to SEER until 2001. Also, there is ongoing concern that MDS may be under-reported to SEER [10]. However, the overall incidence estimates and multivariate analyses include all cancers confirmed in our study cohort.

Cox regression models were used to compare risks for various subgroups of transplant recipients and to identify risk factors for all new cancers and for AML and MDS separately. Variables analyzed in the Cox model were age at transplantation, gender, race, smoking history, Karnofsky performance score at transplantation, body mass index (BMI), number of lines and types of pretransplantation therapy, pretransplantation radiation, conditioning regimen, whether a second autotransplantation was done, post-transplantation maintenance therapy, and the year of transplantation.

In addition, a matched case–control analysis was done comparing autotransplantation recipients who developed a new cancer ($n = 163$) matched to a cohort of transplant recipients with similar follow-up who did not develop a new cancer. Controls were matched for gender, year of transplantation (± 3 years of cases), age (± 3 years), and follow-up interval (<1 year, 1 to 2 years, 3 to 5 years). Controls were selected to ensure post-transplantation follow-up time was similar and $\geq$ time to development of new cancer in the cases with the new cancer. Seven hundred seventy-six controls were generated from the database for the 163 new cancer cases. Separate multivariate analyses were then done to identify variables associated with development of all new cancers and of AML/MDS. Variables analyzed by conditional logistic regression included Karnofsky performance score, BMI, smoking history, pretransplantation therapy, radiation therapy before transplantation, and transplantation conditioning regimen.

RESULTS

Subjects

There were 4161 MM subjects from 164 US transplantation centers contributing 13,387 person-years follow-up (median, 2.5 years; range, .3 months to 16 years). Median post-transplantation survival was 63 months (95% CI, 60 to 67 months), with 70% (95% CI, 68% to 72%), 52% (95% CI, 50% to 54%), and 29% (95% CI, 26% to 31%) of subjects alive at 3, 5, and 10 years. Subject-, disease-, and treatment-related variables are summarized and described in Table 1. Median age at transplantation was 57 years (range, 22 to 80 years), with only 6% of subjects $>$ 70 years. High-dose melphalan as a single agent was the most common (81%) conditioning regimen. As expected for a cohort spanning from 1990 to 2010, novel MM drugs were used before transplantation in 69% of subjects, including thalidomide in 34%, lenalidomide in 14%, and bortezomib in 21%. Post-transplantation maintenance therapy included thalidomide (15%), lenalidomide (11%), bortezomib (9%), and interferon (6%). Most subjects (59%) underwent transplantation within 6 to 12 months of diagnosis, 27% within 6 months, and 14% between 12 and