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Incidence of Second Primary Malignancies after Autologous Transplantation for Multiple Myeloma in the Era of Novel Agents

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A B S T R A C T

The advent of novel agents for multiple myeloma (MM) is cause for a re-examination of the incidence of second primary malignancies (SPMs). We examined the SPM rate in MM patients who were enrolled in the prospective observational CALM (Collaboration to Collect Autologous Transplant outcome in Lymphoma and Myeloma) study. Between 2008 and 2012, 3204 patients with MM underwent a first autologous hematopoietic stem cell transplantation. Plerixafor was used as a mobilizing agent for patients with poor (or potentially poor) stem cell mobilization as defined by the respective centers. A total of 135 patients developed SPM, with a cumulative incidence of 5.3% (95% confidence interval, 4.4 to 6.3) at 72 months. Ninety-four patients developed solid tumors, 30 developed hematologic malignancies, and 11 developed an SPM of an unknown type. The cumulative incidence of known hematologic and solid malignancies were 1.4% and 3.6%, respectively, at 72 months. In a univariate analysis, use of radiotherapy, type of induction regimen, hematopoietic stem cell dose, poor mobilizer status, plerixafor use, and sex did not influence the cumulative incidence of SPM. Only age

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over 65 years was statistically associated with an increased incidence. Overall, the incidence of SPM was comparable to earlier estimations of SPM in MM.

INTRODUCTION

Although multiple myeloma (MM) remains an incurable disease for the vast majority of patients, the introduction of novel agents including proteasome inhibitors (PIs) and immunomodulatory agents (IMiDs) has significantly improved patient outcomes, with median overall survival rising to 5 to 8 years over the last decade [1,2]. Further improvements in outcome are expected with the advent of new treatments such as monoclonal antibodies and rapidly expanding immune modulating therapeutic approaches. As patients live longer, the development of long-term complications, particularly second primary malignancies (SPMs) are emerging and gaining increased attention. Clinical trials have reported an incidence of SPMs of 1% to 12% [3-5]. Table 1 outlines selected population-based studies evaluating the incidence of SPMs in MM patients. Many of such studies included both transplanted and nontransplanted patients, and they extend from the years 1958 to 2012. In the most recent decade, a dramatic shift in treatment, from prolonged use of alkylating agents and anthracycline-based regimens to autologous hematopoietic stem cell transplantation (auto-HSCT) following IMiD- and PI-based regimens, has occurred. Therefore, the earlier results may not entirely illuminate the risk of SPM in the era of novel agents.

Well-designed prospective observational studies with a long follow-up are a relatively effective means to determine the true incidence of SPM. We examined the incidence of SPM in MM patients who were registered in the European Society for Blood and Marrow Transplantation (EBMT) registry, with data collected as part of a postmarketing (mandated by the European Medicines Agency) observational noninterventional study, the CALM (Collaboration to Collect Autologous Transplant outcome in Lymphoma and Myeloma) study, to review the relapse rates in patients with myeloma or lymphoma whose stem cells were mobilized using plerixafor (NCT01362972). There are limited data with respect to the use of plerixafor and development of SPMs, motivating our objective to gain more information on this subject. Furthermore, the CALM study supported a prospective observation data collection, an ideal method to capture SPM data in a registry database.

METHODS

The CALM study is a noninterventional prospective study of the EBMT registry enrolling patients with a diagnosis of lymphoma and MM who underwent their first auto-HSCT between 2008 and 2012. The details of the data collection and study design were reported previously (https://www.ebmt.org/Contents/Research/EBMTStudies/CurrentResearch). The data were collected in the EBMT registry database and the study conducted by the Plasma Cell Disorders subcommittee of the EBMT Chronic Malignancies Working Party. The current study is limited to patients with a new diagnosis of MM who underwent an upfront auto-HSCT between 2008 and 2012. Patients received an induction treatment per standard practice in Europe. Plerixafor was administered to those with poor mobilization (or potentially poor mobilization) as defined by the center. The primary objective of this study was to estimate the rate of SPM in patients receiving plerixafor to overcome poor mobilization status. The secondary objectives were to evaluate the cumulative incidence of SPM among all patients and according to age, sex, induction treatment, radiation use, and $CD34^+$ cell dose. We also analyzed the rate of overall survival in patients who developed SPM. Patients who developed SPM within 2 months of transplant were excluded to rule out the possibility of previous synchronous malignancies. The study was performed in accordance with the provisions of the Declaration of Helsinki.

Statistical Analysis

General patients' characteristics were shown using descriptive statistics. Frequencies and percentages were reported for categorical variables and the median with range for continuous variables. Overall survival (OS) was defined as the time from auto-HSCT to death from any cause, and patients who were still alive at the last follow-up were considered as censored observations. The probabilities of OS were computed using the Kaplan-Meier estimator, and the univariate comparisons were performed by applying the log-rank test. The same methods were used to determine the overall survival post-SPM. The incidence of SPMs was analyzed in the competing risk framework. SPM occurrence was considered as the event of interest, death without prior SPM was considered as the competing risk, and patients who did not develop an event were censored at their last follow-up. The probabilities of SPM occurrence and death without prior SPM were calculated using the proper nonparametric estimator for outcomes with competing risk and compared by Gray's test. These methods were applied to perform the analysis of the incidence of SPM by type, considering separately solid and hematological tumors. All *P* values shown were from 2-sided tests, and the reported confidence intervals (CIs) refer to 95% boundaries.

Patient Characteristics

A total of 3204 patients with MM were enrolled and underwent first auto-HSCT between 2008 and 2012. Patient characteristics are shown in Tables 2 and 3. The median age was 59 (range, 19 to 77) years, and the numbers of male and female patients were 1858 and 1346, respectively. The immunoglobulin subtypes were as follows for the 2409 patients with known data: IgG, 1749 (72.6%); IgA, 607 (25.2%); IgD, 31 (1.3%); IgM, 20 (.8%); and IgE, 2 (.1%). A total of 2567 (80.1%) patients underwent a first auto-HSCT within 12 months from the diagnosis, and 637 (19.9%) patients had their first transplant beyond 12 months. Among the 2714 patients with reported data, the induction regimen included a combination of PIs and IMiDs with no alkylating agents, in 445 (16.4%) patients; alkylating agents with no PIs or IMiDs in 275 (10.1%); alkylating agents in combination with PIs only in 413 (15.2%); alkylating agents with IMiDs only in 518 (19.1%); alkylating agents in combination with both IMiDs and PIs in 192 (7.1%); IMiDs only in 201 (7.4%); PIs only in 516 (19%); and other regimens in 154 (5%). A total of 1771 of 2717 patients with known data (65.2%) received their transplant after 1 line of therapy, 649 (23.9%) after 2 lines, and 297 (10.9%) after more than 2 lines

Table 1
SPM Incidence in MM Patients in Selected Population-Based Registry Studies

Period	Patients with SPM/total patients (%)	Hematological SPM (%)	Solid SPM (%)	Reference
1958-1996	475/8656 (5.5)	83 (1.0)	392 (4.5)	[6]
1982-2001	134/2174 (6.1)	NR	NR	[7]
1986-2005	577/8740 (6.6)	69 (.8)	508 (5.8)	[8]
1973-2008	2021/36,491 (5.5)	263 (.7)	1707 (4.7)	[9]
1997-2009	71/3970 (1.8)	35 (.9)	36 (.9)	[10]
1997-2011	49/744 (6.6)	17 (2.3)	32 (4.3)	[11]

NR, not reported.