Biol Blood Marrow Transplant 24 (2018) 930–936

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

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

Firoozeh Sahebi [1,*], Simona Iacobelli [2], Giulia Sbianchi [2], Linda Koster [3], Didier Blaise [4], Péter Reményi [5], Nigel H. Russell [6], Per Ljungman [7], Guido Kobbe [8], Jane Apperley [9], Marek Trneny [10], Marta Krejci [11], Wieslaw Wiktor-Jedrzejczak [12], James F. Sanchez [1], Nicolaas Schaap [13], Cecilia Isaksson [14], Stig Lenhoff [15], Paul Browne [16], Christof Scheid [17], Keith M.O. Wilson [18], Ibrahim Yakoub-Agha [19], Soledad González Muñiz [20], Stefan Schönland [21], Curly Morris [22], Laurent Garderet [23], Nicolaus Kröger [24]

[1] *Department of Hematology and Hematopoietic Cell Transplantation, City of Hope, Duarte, California*
[2] *Department of Biology, University of Rome Tor Vergata, Rome, Italy*
[3] *EBMT Data Office Leiden, Leiden, the Netherlands*
[4] *Institut Paoli Calmettes, Department of Hematology, Centre de Recherche en Cancérologie de Marseille, Marseille, France*
[5] *St. István & St. Laszlo Hospital, Budapest, Hungary*
[6] *Department of Haematology, Nottingham University Hospital, Nottingham, United Kingdom*
[7] *Division of Hematology, Department of Medicine, Karolinska University Hospital, Stockholm, Sweden*
[8] *Department of Hematology, Oncology and Clinical Immunology, Heinrich Heine Universität, Düsseldorf, Germany*
[9] *Department of Haematology, Imperial College, Hammersmith Hospital, London, United Kingdom*
[10] *Department of Hematology, Charles University Hospital, Prague, Czech Republic*
[11] *Department of Internal Medicine, Hematology and Oncology, University Hospital Brno, Brno, Czech Republic*
[12] *Department of Hematology, Oncology and Internal Medicine, Central Clinical Hospital, Warsaw, Poland*
[13] *Department of Hematology, Radboud University Medical Centre, Nijmegen, the Netherlands*
[14] *Department of Hematology, Umea University Hospital, Umeå, Sweden*
[15] *Department of Hematology, Skane University Hospital, Lund, Sweden*
[16] *Department of Haematology, St. James's Hospital, Dublin, Ireland*
[17] *Department of Internal Medicine I, University of Cologne, Cologne, Germany*
[18] *Department of Haematology, University Hospital of Wales, Cardiff, United Kingdom*
[19] *Department of Hematology, CHRU de Lille, Lille, France*
[20] *Department of Hematology, Hospital Universitario Central de Asturias, Oviedo, Spain*
[21] *Department of Internal Medicine V, University of Heidelberg, Heidelberg, Germany*
[22] *Center for Cancer Research & Cell Biology, Queens University of Belfast, Belfast, United Kingdom*
[23] *Department of Hematology and Cellular Therapy, Hospital Saint Antoine, Paris, France*
[24] *Department of Stem Cell Transplantation, University Hospital Eppendorf, Hamburg, Germany*

Article history:
Received 19 October 2017
Accepted 2 January 2018

Key Words:
Multiple myeloma
Second primary malignancies
Immunomodulatory drugs
Proteasome inhibitors
Plerixafor

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 SPMs, 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 SPMs. Only age

Financial disclosure: See Acknowledgments on page 935.
* Correspondence and reprint requests: Firoozeh Sahebi, MD, Department of Hematology and Hematopoietic Cell Transplantation, City of Hope, 1500 Duarte Road, Duarte, CA 91010.
E-mail address: fsahebi@coh.org (F. Sahebi).

https://doi.org/10.1016/j.bbmt.2018.01.006

over 65 years was statistically associated with an increased incidence. Overall, the incidence of SPMs was comparable to earlier estimations of SPMs 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 SPMs 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 SPMs. We examined the incidence of SPMs 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 SPMs in patients receiving plerixafor to overcome poor mobilization status. The secondary objectives were to evaluate the cumulative incidence of SPMs 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 SPMs. Patients who developed SPMs 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.

Table 2
Patient Characteristics

Variable	
Age, y	59 (19-77)
Male/female	1858/1346
MM subtype	
IgG	1749 (72.6)
IgA	607 (25.2)
IgD	31 (1.3)
IgM	20 (.8)
IgE	2 (.1)
Interval from diagnosis	
<12	2567 (80.1)
>12	637 (19.9)
Induction regimen	
Alkylating alone	275 (10.1)
Alkylating + PI	413 (15.2)
Alkylating + IMiD	518 (19.1)
Alkylating + PI + IMiD	192 (7.1)
PI only	516 (19.0)
IMiD only	201 (7.4)
PI + IMiD	445 (16.4)
other	154 (5.7)
Line(s) of therapy before HSCT	
1	1771 (65.2)
2	649 (23.9)
>2	297 (10.9)
Prior radiation	
No	2180 (80.2)
Yes	537 (19.8)

Data are presented as median (range) or n (%). Percentages based on patients with available data in each category. Number of patients with MM subtype data available: n = 2409; number of patients with induction regimen data available: n = 2714; number of patients with line of therapy before HSCT data available: n = 2717; number of patients with prior radiation data available: n = 2717. Patient sex and interval from diagnosis data were available for all 3204 patients.

of treatment. A total of 537 of 2717 (19.8%) patients had radiation therapy for bone lesions before auto-HSCT. Poor stem cell mobilization as defined by the respective centers was reported in 507 out of 3204 (15.8%) patients, and 217 of those (42.8% of poor mobilizers) received plerixafor as a mobilizing agent. The conditioning regimen before stem cell transplant was high-dose melphalan in 3133 (97.9%) patients. Only 67 (2.1%) patients received melphalan with another chemotherapy agent. In 209 of 1806 (11.6%) patients the collected CD34+ cell dose was $<3 \times 10^6$, in 346 (19.2%) patients the dose was 3 to 5×10^6 cells, and in 1251 (69.3%) patients the dose was $>5 \times 10^6$ cells. $CD34^+$ cell infusions were $<3 \times 10^6$ cells in 678 of 2330 (29.1%) patients, 3 to 5×10^6 cells in 940 (40.3%) patients, and $>5 \times 10^6$ cells in 712 (30.6%) patients.

RESULTS

Incidence of Second Primary Malignancies

The median follow up for this study is 58.6 (range, .53 to 105) months. A total of 135 SPMs were identified, with a cumulative incidence of 4.3% (95% CI, 3.5% to 5.1%) at 60 months and 5.3% at 72 months (95% CI, 4.4% to 6.3%). Ninety-four patients developed solid SPMs, and 30 patients developed hematologic SPMs (Table 4). We observed a cumulative incidence of hematologic SPM of 1.4% and solid SPM of 3.6% at 72 months. The type of SPM is not documented in 11 patients. For all 135 patients, the median time to SPM was 33 (range, 2.1 to 86.5) months, with 75% occurring in the first 50 months. By Kaplan-Meier analysis the OS for the whole group was 65.3% (95% CI, 63.4% to 67.2%) at 60 months (Supplemental Figure S1). Overall survival post-development of SPM was 37.5% at 60 months (95% CI, 23.6% to 51.5%; Figure 1A), 15.2% (95% CI, 0% to 32.5%) for those who developed hematologic malignancies, and 58% at 36 months (95% CI, 46.8% to 70.0%) for those who developed solid SPMs (Figure 1B,C).

Table 3
Transplantation Data

Variable	
Disease status at HSCT	
CR	1416 (45.0)
PR	1487 (47.2)
<PR	245 (7.8)
Poor mobilization	
Yes	507 (15.8)
No	2697 (84.2)
Plerixafor	
Yes	217 (6.8)
No	2987 (93.2)
Conditioning regimen	
Melphalan	3133 (97.9)
Melphalan + other	67 (2.1)
CD34 collected	
$<3 \times 10^6$	209 (11.6)
$3\text{-}5 \times 10^6$	346 (19.2)
$>5 \times 10^6$	1251 (69.3)
CD34 infused	
$<3 \times 10^6$	678 (29.1)
$3\text{-}5 \times 10^6$	940 (40.3)
$>5 \times 10^6$	712 (30.6)

Data are presented as n (%). *Percentages based on patients with available data in each category. Number of patients with disease status at HSCT data available: n = 3148; number of patients with conditioning regimen data available: n = 3200; number of patients with $CD34^+$ cell collection data available: n = 1806; number of patients with $CD34^+$ cell infusion data available: n = 2330. Poor mobilization status and plerixafor use data were available for all 3204 patients.
CR, complete response; PR, partial response.

We analyzed the impact of induction treatment (alkylating alone, IMiDs without alklyating or in combination with alkylating, proteasome inhibitors alone or combination regimens, or other treatments), radiation use, mobilization status, and $CD34^+$ cell dose on the incidence of SPM and of OS for the entire population. We also studied the effect of plerixafor use in patients who were considered to be poor mobilizers. A univariate analysis revealed a higher incidence of SPM in patients receiving alkylating agents alone or IMiDs alone as induction therapy, compared with the lower incidence with

Table 4
Second Primary Malignancy by Type

Variable	
Hematological malignancy	30
Lymphoma	11
MDS/MPN	10
Acute leukemia	8
Chronic leukemia	1
Solid tumor	94
Breast	15
Prostate	11
Nonmelanoma skin cancer	10
Gastrointestinal	9
Lung	5
Pancreas	4
Kidney tumor, including renal cell	4
Adenocarcinoma	4
Glioblastoma	1
Central nervous system	1
Melanoma	1
Angiosarcoma	1
Hepatobiliary	1
Uterine	1
Undifferentiated carcinoma	1
Other	17
Unknown solid	8
Type not reported	11

MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm.

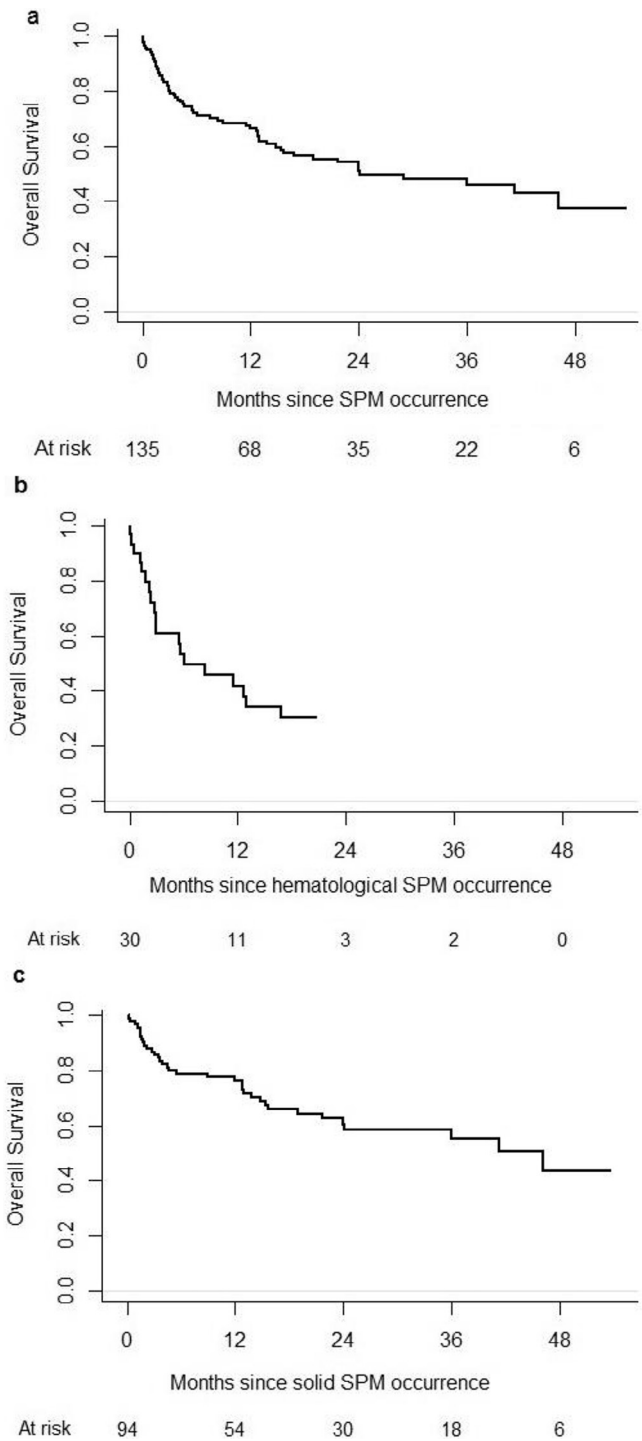

Figure 1. (A) Overall survival post-SPM, (B) overall survival post–hematological SPM, and (C) overall survival post–solid SPM.

proteasome inhibitor therapy; however, these values did not reach statistical significance (Gray test $P = .621$; Supplemental Figure S2A). The use of prior radiotherapy, $CD34^+$ cell dose collected or infused, Karnofsky score, disease status at transplantation, mobilization status, and use of plerixafor did not have any statistically significant influence on the incidence of SPM (Figure 2A and Supplemental Figures S2B and S3). Only age >65 years was associated with a higher incidence of SPM (Gray test $P = .012$; Figure 2B); no association by sex was noted (Supplemental Figure S4). In a univariate analysis, prior radiation ($P = .022$), poor Karnofsky score ($P = .01$), disease status less than partial response at transplant, and age over 65 years ($P = .005$) were associated with lower overall survival. The type of induction regimen, $CD34^+$ cell dose, poor mobilization status, and use of plerixafor did not have any impact on OS. We also analyzed the probability of developing SPMs, which is 7.0%. By contrast, there was a 61.0% probability of death from causes other than SPM in this study, indicating the risk of SPM is small compared with other causes of death (Figure 3).

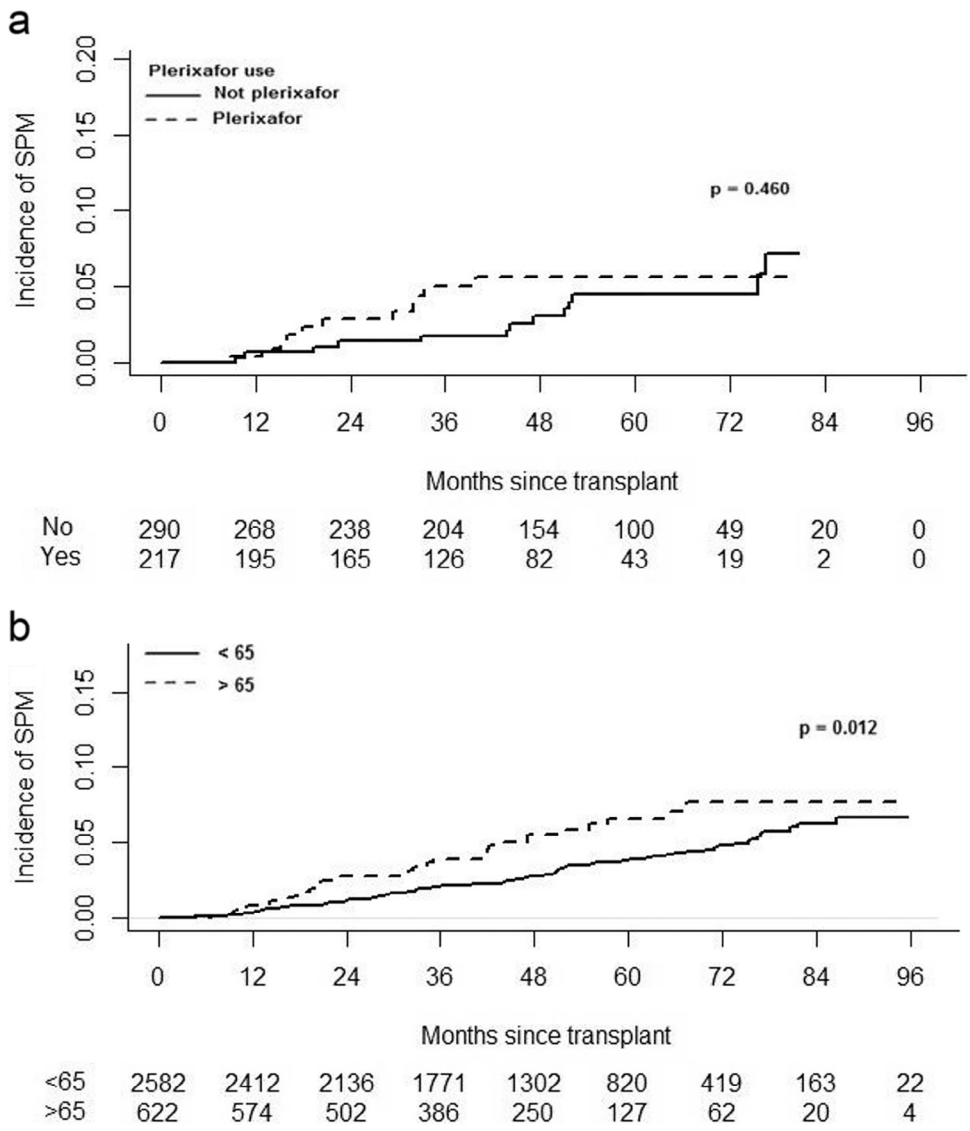

Figure 2. (A) SPM incidence by plerixafor use and (B) SPM incidence by age.

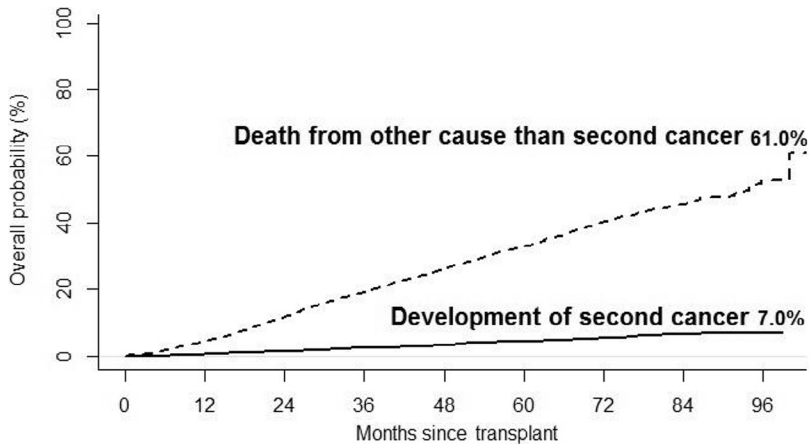

Figure 3. Cumulative incidence rate of developing SPM versus death from all causes without occurrence of SPM.

DISCUSSION

Although patients with MM live longer, the risk of late complications including second malignancies are becoming more apparent. Data from the Surveillance, Epidemiology, and End Results Program reported a cumulative SPM incidence of 1% to 10% in MM, comparable to the incidence of cancer per life-year in the general population [5]. Other large population-based studies have reported incidence rates in the range of 1.9% to 12% (Table 1). Our results align well with earlier investigations of SPM incidence in MM patients [6-13] and indicate that shifts in treatment practice, although extending survival, have not increased the risk of developing SPMs. Furthermore, as shown in Figure 2, the cumulative probability of SPM is markedly lower than the probability of death from any other cause than second cancer. A similar observation was reported by other groups [5,11]. This finding is indicative that although SPM is of a concern requiring attention, controlling disease should remain a priority.

The association between alkylating agents and development of myelodysplastic syndrome and acute myeloid leukemia has long been known [14-17]. Among the new antimyeloma therapies, immunomodulatory agents, especially lenalidomide, have been linked to the development of SPM. The association was particularly observed when a prolonged course of lenalidomide was used as a maintenance therapy. Two maintenance studies using lenalidomide post single auto-HSCT reported an increased incidence of SPM as compared with placebo [18,19]. In a randomized study of nontransplanted patients, an increased SPM rate in the maintenance lenalidomide arm was observed in transplant noneligible patients over 74 years of age, but there was no significant difference among younger noneligible patients [20]. Furthermore, a meta-analysis of randomized controlled trials using lenalidomide as first line therapy reported an increased SPM ratin newly diagnosed patients given lenalidomide; however, the difference in study groups was mainly driven by treatment regimens comprising lenalidomide and oral melphalan [21]. A more recent meta-analysis similarly found that with lenalidomide maintenance the incidences of both hematologic and solid SPMs were higher (5.3% and 5.8%, respectively; median follow-up of 79.5 months) in comparison with placebo or control [22]. In this study, we observed a trend toward a higher incidence of SPMs in patients using induction therapy that included alkylating agents and IMiDs compared with the relatively lower risk with proteasome inhibitors without the co-use of IMiDs and alkylating agents. However, these differences did not reach statistical significance. A limitation of our study is that assessing the effect of maintenance therapy is not possible, as the registry cannot collect the data prospectively as would be necessary. Nevertheless, maintenance lenalidomide did not become standard practice in Europe outside clinical trials until very recently. Another limitation is that all patients studied underwent high-dose chemotherapy and auto-HSCT and therefore are not a complete representation of the entire MM population. Finally, this study did not collect SPM data before auto-HSCT; it would be interesting to compare SPM incidence prior to and post-transplantation.

We did not find any association between the use of radiotherapy and development of SPMs, in accordance with the U.S. Connect MM registry data [13]. This finding may be related to the relatively lower dose of palliative radiation used for pain control in myeloma patients. Use of plerixafor for poor mobilizers, poor mobilizer status, and $CD34^+$ cell dose collected did not have any statistical influence in SPM risk. Although we did not observe any relationship between use of plerixafor and incidence of SPMs, further validation is required with a larger set of patients. Unlike previous reports in which an association between male sex and malignancies was reported, we did not find a similar correlation. Only age older than 65 years was associated with a significant increased risk of SPMs. This finding is consistent with previous observations of increasing risk of malignancies in older age [23-25]. Last, we observed an early onset of SPMs in this study, with 75% of cancer occurring within the first 50 months.

In conclusion, this large observational study highlights that the incidence of SPMs remains low in MM patients receiving high-dose chemotherapy and auto-HSCT in the current era. This information may be useful for clinicians counseling patients who are candidates for auto-HSCT. As the number of durably surviving patients with myeloma rises, early detection and intervention for SPMs should become part of long-term care for such patients.

ACKNOWLEDGMENTS

Financial disclosure: This work was supported by Genzyme Corporation.

Conflict of interest statement: There are no conflicts of interest to report.

Authorship statement: F.S., S.I., L.G., and N.K. designed the study. All authors analyzed data. F.S. and J.F.S. wrote the manuscript. All authors reviewed the manuscript.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2018.01.006.

REFERENCES

1. Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia*. 2014;28:1122-1128.
2. Pulte D, Gondos A, Brenner H. Improvement in survival of older adults with multiple myeloma: results of an updated period analysis of SEER data. *Oncologist*. 2011;16:1600-1603.
3. Pratt G. Lenalidomide and second malignancies in myeloma patients. *Lancet Oncol*. 2014;15:253-254.
4. Thomas A, Mailankody S, Korde N, Kristinsson SY, Turesson I, Landgren O. Second malignancies after multiple myeloma: from 1960s to 2010s. *Blood*. 2012;119:2731-2737.
5. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Bethesda, MD. Available at: http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site, April 2016. Accessed February 15, 2017.
6. Dong C, Hemminki K. Second primary neoplasms among 53 159 haematolymphoproliferative malignancy patients in Sweden, 1958-1996: a search for common mechanisms. *Br J Cancer*. 2001;85:997-1005.
7. Youlden DR, Baade PD. The relative risk of second primary cancers in Queensland, Australia: a retrospective cohort study. *BMC Cancer*. 2011;11:83.
8. Mailankody S, Pfeiffer RM, Kristinsson SY, et al. Risk of acute myeloid leukemia and myelodysplastic syndromes after multiple myeloma and its precursor disease (MGUS). *Blood*. 2011;118:4086-4092.
9. Razavi P, Rand KA, Cozen W, Chanan-Khan A, Usmani S, Ailawadhi S. Patterns of second primary malignancy risk in multiple myeloma patients before and after the introduction of novel therapeutics. *Blood Cancer J*. 2013;3:e121.
10. Tzeng HE, Lin CL, Tsai CH, et al. Time trend of multiple myeloma and associated secondary primary malignancies in Asian patients: a Taiwan population-based study. *PLoS ONE*. 2013;8:e68041.
11. Engelhardt M, Ihorst G, Landgren O, et al. Large registry analysis to accurately define second malignancy rates and risks in a well-characterized cohort of 744 consecutive multiple myeloma patients followed-up for 25 years. *Haematologica*. 2015;100:1340-1349.
12. Chakraborty S, Hauke RJ, Bonthu N, Tarantolo SR. Increased incidence of a second lymphoproliferative malignancy in patients with multiple myeloma–a SEER based study. *Anticancer Res*. 2012;32:4507-4515.

13. Rifkin RM, Abonour R, Shah JJ, et al. Connect MM(R)—the Multiple Myeloma Disease Registry: incidence of second primary malignancies in patients treated with lenalidomide. *Leuk Lymphoma*. 2016;57:2228-2231.
14. Bergsagel DE, Bailey AJ, Langley GR, MacDonald RN, White DF, Miller AB. The chemotherapy on plasma-cell myeloma and the incidence of acute leukemia. *N Engl J Med*. 1979;301:743-748.
15. Cuzick J, Erskine S, Edelman D, Galton DA. A comparison of the incidence of the myelodysplastic syndrome and acute myeloid leukaemia following melphalan and cyclophosphamide treatment for myelomatosis. A report to the Medical Research Council's working party on leukaemia in adults. *Br J Cancer*. 1987;55:523-529.
16. Reddi DM, Lu CM, Fedoriw G, et al. Myeloid neoplasms secondary to plasma cell myeloma: an intrinsic predisposition or therapy-related phenomenon? A clinicopathologic study of 41 cases and correlation of cytogenetic features with treatment regimens. *Am J Clin Pathol*. 2012;138:855-866.
17. Areethamsirikul N, Reece DE. The risk of secondary primary malignancies after therapy for multiple myeloma. *Leuk Lymphoma*. 2015;56:3012-3021.
18. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366:1782-1791.
19. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366:1770-1781.
20. Jones JR, Cairns DA, Gregory WM, et al. Second malignancies in the context of lenalidomide treatment: an analysis of 2732 myeloma patients enrolled to the Myeloma XI trial. *Blood Cancer J*. 2016;6:e506.
21. Palumbo A, Bringhen S, Kumar SK, et al. Second primary malignancies with lenalidomide therapy for newly diagnosed myeloma: a meta-analysis of individual patient data. *Lancet Oncol*. 2014;15:333-342.
22. McCarthy PL, Holstein SA, Petrucci MT, et al. Lenalidomide maintenance after autologous stem-cell transplantation in newly diagnosed multiple myeloma: a meta-analysis. *J Clin Oncol*. 2017;35:3279-3289.
23. Miller JS, Arthur DC, Litz CE, Neglia JP, Miller WJ, Weisdorf DJ. Myelodysplastic syndrome after autologous bone marrow transplantation: an additional late complication of curative cancer therapy. *Blood*. 1994;83:3780-3786.
24. Pedersen-Bjergaard J, Andersen MK, Christiansen DH. Therapy-related acute myeloid leukemia and myelodysplasia after high-dose chemotherapy and autologous stem cell transplantation. *Blood*. 2000;95:3273-3279.
25. Mahindra A, Raval G, Mehta P, et al. New cancers after autotransplantations for multiple myeloma. *Biol Blood Marrow Transplant*. 2015;21:738-745.