Biol Blood Marrow Transplant 19 (2013) 260–265

Second Primary Malignancies after Autologous Hematopoietic Cell Transplantation for Multiple Myeloma

Amrita Y. Krishnan [1,*], Matthew Mei [2], Can-Lan Sun [3], Sandra H. Thomas [1], Jennifer Berano Teh [3], Tongjun Kang [3], Myo Htut [1], George Somlo [2], Firoozeh Sahebi [1,4], Stephen J. Forman [1], Smita Bhatia [3]

[1] *Department of Hematology and Hematopoietic Cell Transplantation, City of Hope, Duarte, California*
[2] *Department of Medical Oncology, City of Hope, Duarte, California*
[3] *Department of Population Sciences, City of Hope, Duarte, California*
[4] *Southern California Kaiser Permanente Medical Group, Los Angeles, California*

Article history:
Received 6 July 2012
Accepted 27 September 2012

Key Words:
Treatment late effects
Immunomodulatory drugs
Age

A B S T R A C T

Recent studies demonstrate an increased risk of second primary malignancies (SPMs) in patients with multiple myeloma (MM) receiving maintenance lenalidomide after autologous stem cell transplantation (ASCT). We explored the possibility of other risk factors driving post-ASCT SPMs in patients with MM through analysis of our large transplantation database in conjunction with our Long-Term Follow-Up Program. We conducted a retrospective cohort study of 841 consecutive patients with MM who underwent ASCT at City of Hope between 1989 and 2009, as well as a nested case-control analysis evaluating the role of all therapeutic exposures before, during, and after ASCT. Median duration of follow-up for the entire cohort was 3.4 years (range, 0.3-19.9 years). Sixty cases with a total of 70 SPMs were identified. The overall cumulative incidence of SPMs was 7.4% at 5 years and 15.9% at 10 years when nonmelanoma skin cancers (NMSCs) were included and 5.3% at 5 years and 11.2% at 10 years when NMSCs were excluded. Multivariate analysis of the entire cohort revealed associations of both older age ($\geq$55 years; relative risk, 2.3; $P < .004$) and race (non-Hispanic white; relative risk, 2.4; $P = .01$) with an increased risk of SPM. Furthermore, thalidomide exposure demonstrated a trend toward increased risk (odds ratio, 3.5; $P = .15$); however, an insufficient number of patients were treated with lenalidomide to allow us to accurately assess the risk of this agent. Exclusion of NMSCs retained the association with these variables but was accompanied by loss of statistical significance. This large single-institution analysis identified associations between race and older age and increased risk of developing SPM. The trend toward increased risk with thalidomide exposure suggests a class effect from immunomodulatory drugs that might not be restricted to lenalidomide.

INTRODUCTION

High-dose therapy with autologous stem cell transplantation (ASCT) has been considered a standard of care for patients with multiple myeloma (MM) since the IFM2004 trial demonstrated an improved survival rate for patients treated with high-dose chemotherapy compared with conventional chemotherapy [1,2]. Over the ensuing years, MM has become a leading indication for ASCT in the United States. High-dose therapy in conjunction with induction and maintenance therapy with novel agents such as thalidomide, lenalidomide, and bortezomib has further improved survival in patients with MM. Ten-year survival in younger patients is approaching 50% [3].

As MM survival improves, the long-term impacts of novel therapies and ASCT are coming under investigation. Potential long-term adverse effects have led to a paradigm of intensive treatment for cytogenetically defined high-risk patients and toxicity-minimizing treatment in lower-risk patients. This approach may involve a choice of induction regimens and/or optimization of consolidation and maintenance therapy post-ASCT. Thalidomide maintenance has demonstrated improved progression-free survival in several randomized trials, as well as improved overall survival in some studies [4,5]. Lenalidomide, which has a more favorable toxicity profile with respect to peripheral neuropathy and sedation, has been used for maintenance therapy in more recent trials. Three randomized trials have reported a progression-free survival advantage for lenalidomide maintenance either with or without ASCT, and one group also reported an overall survival benefit [6-8]. However, both the IFM2005 trial [6] and the CALGB100104 trial [7] of maintenance lenalidomide versus observation post-ASCT reported an increased incidence of second primary malignancies (SPMs) in the maintenance arm compared with the control arm (8% vs 3%-4%).

The factors driving post-ASCT SPMs in patients with MM remain unclear, however, and lenalidomide may not be the sole putative contributor. The cause is likely multifactorial, involving host factors in addition to treatment. In fact, large epidemiologic studies have demonstrated that patients with monoclonal gammopathy of undetermined significance are at increased risk for additional malignancies [9]. Previous studies from our institution and others have shown an increased risk of SPMs after ASCT in patients with lymphoid neoplasms, suggesting that treatment-related factors independent of immunomodulatory drugs may also drive the risk of therapy-related malignancy [10-12]. In MM, the risk of post-ASCT SPMs may be mediated in part by the alkylator agents commonly used to treat MM before the advent of novel agents. A retrospective study evaluating exposure to alkylators before ASCT for MM demonstrated an increased incidence of

Financial disclosure: See Acknowledgments on page 264.

* Correspondence and reprint requests: Amrita Y. Krishnan, MD, Department of Hematology and Hematopoietic Cell Transplantation, City of Hope, 1500 E Duarte Rd, Duarte, CA 91010.
E-mail address: akrishnan@coh.org (A.Y. Krishnan).

1083-8791/$ – see front matter © 2013 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2012.09.023

myelodysplastic syndrome (MDS) in the group with prolonged chemotherapy exposure [13]. To better address the relationship of SPMs to treatment and demographic variables, we conducted an analysis of patients undergoing ASCT for MM at City of Hope over the past 20 years.

PATIENTS AND METHODS

The Long-Term Follow-Up Program supports complete follow-up of all patients undergoing ASCT at City of Hope. The protocol was approved by the City of Hope Institutional Review Board and conforms to the standards specified in the Declaration of Helsinki. A total of 869 patients underwent ASCT for MM at City of Hope between 1989 and 2009. Of these, 28 patients refused to participate in the Long-Term Follow-Up Program. This analysis includes the remaining 841 patients (participation rate, 96.8%).

Demographic Data and Clinical Characteristics

Demographic data (date of birth, sex, and race/ethnicity) and clinical characteristics (primary diagnosis, date of diagnosis, date of ASCT, disease status at ASCT, conditioning regimen, and stem cell source) were obtained from the ASCT database.

SPMs and Vital Status Information

Information regarding SPMs and vital status of the cohort was ascertained as of December 31, 2010. To ensure complete ascertainment of SPMs, institutional long-term follow-up data were combined with data from the California Cancer Registry and National Death Index Plus Program. For institutional long-term follow-up, medical records served as the primary source of data. If the date of the last medical visit at City of Hope was not recent, or if there were gaps in patients' history within the window of interest, a standard protocol was used to contact physicians outside City of Hope to obtain relevant details for the period of interest. If the physician was not available or able to provide recent information, the patient was contacted to obtain this information. Patient vital status was obtained through the following resources: National Death Index Plus, Social Security Death Index, medical records, and institutional long-term follow-up efforts.

Cohort Analysis

The cumulative incidence of SPMs was estimated by taking into consideration death from other causes as a competing risk [14]. Person-years at risk were computed from the date of ASCT to the date of death, date of SPM, or date of censoring (December 31, 2010, for those still alive without SPM), whichever occurred first. For multiple occurrences of non-melanoma skin cancers ([NMSCs] including basal cell carcinoma [BCC] and squamous cell carcinoma [SCC]), the date of first occurrence was considered the onset date. The proportional hazard regression method was used to examine the associations between demographic data (sex and race) and clinical characteristics (age at diagnosis of MM and year of ASCT) and the development of SPMs, measured by hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) and *P* values [15]. The analyses were conducted both with the entire cohort and with the exclusion of NMSCs.

Nested Case-Control Analysis

A nested case-control study was also conducted to examine the role of pre-ASCT, peri-ASCT, and post-ASCT therapeutic exposures associated with SPMs. Controls were patients with MM without post-ASCT SPMs, matched to index case by year of ASCT (±5 years). In addition, each control was required to have longer post-ASCT follow-up than its associated case. The conditional logistic regression method was used for the case-control analysis; odds ratios (ORs) and their corresponding 95% CIs and *P* values are presented. Statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC). All *P* values are 2-sided.

RESULTS

Cohort Study

Patient demographic and clinical characteristics are detailed in Table 1. The median duration of follow-up was 3.4 years (range, 0.3-19.9 years). The median age at diagnosis of MM was 55 years (range, 18-76 years) and that at ASCT was 56 years (range, 18-77 years). There was a male predominance (61%), and the racial/ethnic distribution was 61% non-Hispanic white, 18% Hispanic, and 13% African American. Almost two-thirds (62%) of the patients received a single ASCT, 27% received tandem ASCT, and the remaining 11% received multiple ASCTs (72 of whom received an allogeneic transplantion after an ASCT).

Table 1
Demographic and Clinical Characteristics of the Cohort

Characteristic	Entire Cohort	Patients with SPMs Including NMSCs*	Patients with SPMs Excluding NMSCs†
Number of patients	841	60	42
Sex, n (%)			
Female	330 (39)	17 (28)	12 (29)
Male	511 (61)	43 (72)	30 (71)
Race/ethnicity, n (%)			
Non-Hispanic Caucasian	511 (61)	49 (82)	31 (74)
Hispanic	151 (18)	5 (8)	5 (12)
African American	107 (13)	4 (7)	4 (9)
Other	72 (9)	2 (3)	2 (5)
Age at ASCT, y			
Median (range)	56 (18-77)	59 (32-77)	56 (32-69)
Mean (standard deviation)	55 (8.9)	57 (9.4)	55 (9.5)
Age at diagnosis of MM, y			
Median (range)	55 (18-76)	57 (31-76)	54 (31-68)
Mean (standard deviation)	54 (8.9)	55 (9.4)	53 (9.3)
Year of diagnosis of MM, n (%)			
1983-1999	206 (24)	30 (50)	25 (60)
2000-2004	301 (36)	20 (33)	11 (26)
2005-2009	334 (40)	10 (17)	6 (14)
Year of ASCT, n (%)			
1989-1999	133 (16)	22 (37)	18 (43)
2000-2004	278 (33)	22 (37)	15 (36)
2005-2009	430 (51)	16 (27)	9 (21)
Stem cell source, n (%)			
Peripheral blood	841 (100)	60 (100)	42 (100)
Disease status at ASCT, n (%)			
Partial remission	578 (69)	44 (73)	33 (79)
Stable disease	115 (14)	9 (15)	4 (9)
Complete remission	111 (13)	7 (12)	5 (12)
Progressive disease	31 (4)	0 (0)	0 (0)
Unknown	6 (0.7)	0 (0)	0 (0)
Transplantation type, n (%)			
Single autologous	527 (63)	32 (53)	22 (55)
Tandem autologous	229 (27)	18 (30)	12 (29)
Multiple	85 (10)	10 (17)	7 (17)

* Including non-melanoma skin cancers.
† Excluding non-melanoma skin cancers.

As of December 31, 2010, 60 patients had developed a total of 70 SPMs. The SPMs included 27 NMSCs (13 BCC and 14 SCC), 4 melanomas, 9 therapy-related MDS/acute myelogenous leukemias (t-MDS/AML), 5 prostate cancers, 4 colorectal cancers, 4 oropharyngeal cancers, 3 breast cancers, 2 acute lymphoblastic leukemias, 2 bladder cancers, and 1 case each of adrenocortical carcinoma, esophageal carcinoma, gastric carcinoma, germ cell tumor, non-Hodgkin lymphoma, pancreatic carcinoma, renal cell carcinoma, thyroid cancer, uterine cancer, and site unknown. The overall cumulative incidence was 7.4% at 5 years and 15.9% at 10 years (Figure 1). After excluding NMSCs, the overall cumulative incidence was 5.3% at 5 years and 11.2% at 10 years (Figure 1). The cumulative incidence of t-MDS/AML for the entire cohort was 1.0% at 5 years and 2.0% at 10 years, whereas for patients with solid tumors (excluding NMSCs), it was 3.7% at 5 years and 8.2% at 10 years (Figure 1).

Cohort Risk Factor Analysis

Table 2 presents the results of the multivariate analysis including and excluding NMSCs. With the inclusion of

NMSCs, multivariate Cox regression analysis revealed that non-Hispanic white race (relative risk [RR], 2.4; 95% CI, 1.2-4.6: $P = .01$) and older age (≥55 years) at diagnosis of MM (RR, 2.3; 95% CI, 1.3-4.1; $P = .004$) were associated with an increased risk of developing SPMs, after adjustment for sex and year of ASCT. However, after excluding NMSCs, the magnitude of these associations was mitigated, and the associations became nonsignificant.

Case-Control Study

Table 3 presents demographic characteristics and therapeutic exposures for the cases (including and excluding NMSCs) and matched controls. Table 4 summarizes results for the variables that were retained in the multivariate analysis of the case-control study. Similar to the cohort analysis results, older age at diagnosis of MM and non-Hispanic white ethnicity were associated with an increased risk of developing SPMs after ASCT when NMSCs were included. Individually, none of the therapeutic agents used in the pre-ASCT, peri-ASCT, or post-ASCT periods was associated with development of SPMs after ASCT (Table 3). However, exposure to thalidomide either pre-ASCT or post-ASCT demonstrated a trend toward positive association when NMSCs were included in the analysis (OR, 3.5; 95% CI, 0.6-19.4; $P = .15$) (Table 4). Only 6 patients (3 cases and 3 controls) were exposed to lenalidomide before the development of SPMs, and exposure to this agent was not associated with an increased risk of SPMs (OR, 1.0; 95% CI, 0.14-7.1). Data on total $CD34^+$ cell yields were available for 55 of the 60 cases and for 52 of the 60 controls. The mean $CD34^+$ cell yield was slightly lower in the cases compared with the controls (7.8×10^6 cells vs 9.5×10^6 cells; $P = .08$). The median $CD34^+$ cell yield was 7.4×10^6 cells (range, $1.8\text{-}24.5 \times 10^6$) for cases and 8.6×10^6 cells (range, $1.7\text{-}32.4 \times 10^6$ cells) for controls. Five of the cases had poor-risk cytogenetics (deletion 13 by metaphase karytoyping or deletion 17p by FISH), as did 5 controls (deletion 13 by metaphase karyotyping or deletion 17p, t[14,16]). Similar to the cohort analysis results, exclusion of the NMSCs resulted in some mitigation of the magnitude of risk with these variables, with the associations no longer statistically significant.

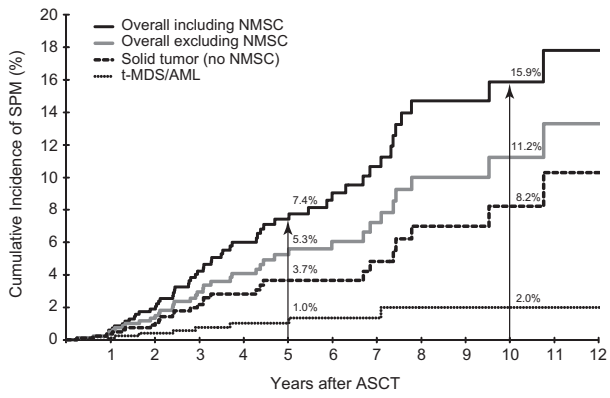

Figure 1. Cumulative incidence of SPMs in the cohort. The cumulative incidence of SPMs (%) from the date of ASCT (years) was calculated using death from other causes as a competing risk. Number at risk was 841 at ASCT (time 0), 378 at 5 years post-ASCT, and 82 at 10 years post-ASCT. The solid black line represents overall cumulative incidence (all types of SPMs), the gray line represents overall cumulative incidence (SPMs excluding NMSCs), the dashed line represents solid tumors (SPMs excluding NMSCs), and the dotted line represents t-MDS/AML.

DISCUSSION

Patients with MM are surviving longer with the use of novel agents and ASCT. Approaches to further decreasing post-ASCT relapse rates include maintenance therapy with combinations of novel agents. Much controversy has surrounded the optimal maintenance regimen and duration of maintenance therapy. This debate intensified with the initial reports of increased incidence of SPMs in patients receiving lenalidomide maintenance in the CALGB100104 and IFM2005 trials [16,17]. In addition, a pooled analysis of 9 European trials demonstrated an increased incidence of SPMs in patients receiving lenalidomide maintenance after melphalan therapy, as well as in patients receiving thalidomide after melphalan [18]. In all series, the SPMs were a combination of solid tumors and hematologic malignancies.

The increased incidence of SPMs in patients with MM is a complex story and likely represents an interplay of host and genetic factors in addition to treatment-related risks. We have analyzed the effects of multiple host demographic, disease, and treatment variables to determine their relevance to the later development of SPMs in our cohort of 841 patients. Our cohort analysis confirms that SPM remains an issue in patients with MM, especially those aged ≥55 years. Our overall cumulative incidence of 15.9% is consistent with the findings of the German group that reported a cumulative incidence of 15.7% at 10 years in a retrospective study of post-ASCT SPM incidence (including NMSCs) in patients with MM [19]. An Arkansas group also identified an association between older age (≥65 years) and SPM onset [20]. The high rate of SPMs in our cohort likely reflects the combined expected increase in malignancy in older adults in the general population, as well as the increased risk of malignancy in patients with MM. However, these data must be considered in the context of the increased survival of patients with MM owing to more effective therapies. The overall survival rate at 5 years was 60% in our entire cohort and 58% in patients aged ≥55 years.

Host characteristics beyond age may also play roles in the risk of developing SPMs. Analysis of our cohort identified race/ethnicity as a risk factor, with a higher incidence in non-Hispanic white patients. Slightly more than half (52%) of the SPMs in our cohort were skin cancers, which typically are more prevalent in non-Hispanic whites. We analyzed the incidence of SPMs with both the inclusion and the exclusion of NMSCs, because, of the 4 major studies analyzing SPM outcomes after lenalidomide or thalidomide maintenance therapy reported in 2012, 2 included NMSCs [6,20] and 2 excluded NMSCs [7,8]. Given our institution's location in southern California, where the population has relatively high sun exposure, we felt it important to include all skin cancers. We also considered previous chemotherapy exposures, given that several drug classes have been implicated in t-MDS/AML. Cyclophosphamide and busulfan as part of pre-ASCT therapy, cyclophosphamide mobilization therapy, and epipodophyllotoxin therapy did not attain statistical significance as risk factors in our analysis; however, a previous study reported such associations with alkylator therapy in patients with MM [21]. The risks are likely related in part to dosage and to duration of exposure [22], and the lack of association in the present study may be linked in part to the shorter-term and lower-dose alkylators used in more modern regimens.

Immunomodulatory agents in modern regimens have been combined with alkylators as the backbone of therapy or

Table 2
Cohort Multivariate Analysis of Risk Factors Associated with SPMs

Characteristic	Including NMSCs			Excluding NMSCs		
	Cohort/SPMs, n	HR (95% CI)	*P* Value	Cohort/SPMs, n	HR (95% CI)	*P* Value
Number of patients	841/60			841/42		
Sex						
Female	330/17	1.0		330/12	1.0	
Male	511/43	1.44 (0.82-2.53)	.21	511/30	1.42 (0.72-0.78)	.31
Race/ethnicity						
Other		1.0		330/11	1.0	
Non-Hispanic Caucasian	511/49	2.37 (1.22-4.61)	.01	511/31	1.53 (0.76-0.09)	.16
Age at diagnosis of MM						
<55 years	408/24	1.0		408/21	1.0	
≥55 years	433/36	2.32 (1.30-4.14)	.004	433/21	1.64 (0.84-0.23)	.15
Year of ASCT						
1989-1999	133/22	1.0		133/18	1.0	
2000-2004	278/22	0.65 (0.33-1.25)	.20	278/15	0.58 (0.27-0.25)	.17
2005-2009	430/16	0.56 (0.26-1.22)	.14	430/9	0.42 (0.17-0.07)	.07

in some cases have supplanted alkylators entirely. Concerns regarding this class of agents as risk factors for SPMs first arose in studies of patients treated with lenalidomide as maintenance therapy post-ASCT. Interestingly, in those studies, the SPMs included both hematologic malignancies and solid tumors. Our cohort contained too few patients receiving lenalidomide therapy either before or after ASCT to meaningfully examine this exposure, but thalidomide exposure was common. Thus, we included thalidomide exposure in the case-control analysis, which revealed a nonsignificant trend toward increased risk with thalidomide use both before and after ASCT. The large European trial series reviewed by Palumbo et al. [18] demonstrated an annual incidence of SPMs of approximately 1% in the

Table 3
Demographic and Therapeutic Exposure in Cases and Controls

Characteristics	Including NMSCs			Excluding NMSCs		
	Cases, n (%)	Controls, n (%)	*P* Value	Cases, n (%)	Controls, n (%)	*P* Value
Number of patients	60	60		42	42	
Sex						
Female	17 (28)	26 (43)		12 (29)	18 (43)	
Male	43 (72)	34 (57)	.09	30 (71)	24 (57)	.19
Race/ethnicity						
Others	11 (18)	22 (37)		11 (26)	16 (38)	
Non-Hispanic Caucasian	49 (82)	38 (63)	.02	31 (74)	26 (62)	.15
Age at diagnosis of MM						
<55 years	24 (40)	38 (63)		21 (50)	27 (64)	
≥55 years	36 (60)	22 (37)	.01	21 (50)	15 (36)	.14
Pre-ASCT exposure						
Irradiation	20 (33)	17 (28)	.51	14 (33)	12 (29)	.59
Cyclophosphamide	7 (12)	12 (20)	.23	6 (14)	9 (21)	.41
Doxorubicin	42 (70)	47 (78)	.18	32 (76)	34 (81)	.53
Etoposide	7 (12)	5 (8)	.48	6 (14)	3 (7)	.27
Prednisone	19 (32)	15 (25)	.40	15 (36)	14 (33)	.81
Thalidomide	22 (37)	19 (32)	.29	14 (33)	11 (26)	.27
Vincristine	40 (67)	48 (80)	.04	30 (71)	35 (83)	.12
Priming agents*						
Cyclophosphamide	40 (70)	38 (69)	1.00	23 (59)	25 (66)	.18
Paclitaxel	9 (16)	12 (22)	.37	6 (15)	10 (26)	.14
Conditioning agents†						
Total-body irradiation	9 (16)	10 (18)	.74	7 (18)	9 (24)	.42
Busulfan	16 (29)	18 (33)	.53	10 (26)	11 (29)	.71
Cyclophosphamide	19 (35)	22 (40)	.37	13 (34)	15 (39)	.48
Etoposide	3 (5)	4 (7)	.57	3 (8)	4 (11)	.57
Melphalan	50 (90)	49 (89)	.57	34 (89)	33 (87)	.57
Post-ASCT exposure						
Dexamethazone	19 (35)	14 (25)	.28	12 (35)	10 (25)	.59
Interferon-α	18 (33)	16 (29)	.59	12 (33)	12 (29)	1.00
Prednisone	5 (10)	3 (5)	.42	5 (10)	3 (5)	.42
Thalidomide	30 (50)	26 (47)	.29	19 (50)	18 (47)	.74
Timing of thalidomide exposure						
None	21 (35)	26 (44)		16 (38)	19 (45)	
Pre-ASCT	9 (15)	8 (13)	.19	7 (17)	5 (12)	.17
Post-ASCT	17 (28)	15 (25)	.15	12 (28)	12 (29)	.42
Both pre- and post-ASCT	13 (22)	11 (18)	.12	7 (17)	6 (14)	.26
Either pre- or post-ASCT	39 (65)	34 (56)	.12	26 (62)	23 (55)	.27

* Includes 3 cases and 5 controls without information on priming agents.
† Includes 5 cases and 5 controls without information on conditioning.

Table 4
Case-Control Multivariate Analysis of Risk Factors Associated with SPMs

	Including NMSCs			Excluding NMSCs		
	Cases/Controls, n	OR (95% CI)	*P* Value	Cases/Controls, n	OR (95% CI)	*P* Value
Number of patients	60/60			42/42		
Sex*						
Female	17/26	1.0		12/18	1.0	
Male	43/34	1.55 (0.63-3.84)	.34	30/24	1.76 (0.60-5.12)	.30
Race/ethnicity*						
Other	11/22	1.0		11/16	1.0	
Non-Hispanic Caucasian	49/38	2.90 (0.76-11.13)	.12	21/26	1.82 0.41-8.13)	.44
Age at diagnosis of MM*						
<55 years	24/38	1.0		21/27	1.0	
≥55 years	36/22	3.14 (1.15-8.57)	.03	21/15	2.43 (0.75-7.85)	.14
Timing of thalidomide exposure*						
None	21/26	1.0		16/19	1.0	
Pre-ASCT	9/8	4.70 (0.50-44.30)	.18	7/5	8.55 (0.38-190)	.18
Post-ASCT	17/15	3.31 (0.54-20.30)	.20	12/12	2.29 (0.34-15.5)	.39
Both pre- and post-ASCT	13/11	2.63 (0.30-22.75)	.38	7/6	1.71 (0.12-24.2)	.69
Any thalidomide exposure†						
None	21/26	1.0		16/19	1.0	
Either pre- or post-ASCT	39/34	3.48 (0.62-19.40)	.15	26/23	2.59 (0.42-15.9)	.30

* All of the variables were included in the multivariate conditional logistic regression model.
† ORs obtained from a multivariate conditional logistic regression model including sex, race/ethnicity, and age at diagnosis of MM.

melphalan and thalidomide group. Thus, although the association between thalidomide exposure and SPMs did not reach statistical significance in our cohort, the trend that we observed has potential implications. It raises the question of whether the risk of SPMs with immunomodulatory therapy has more to do with the immunomodulatory class of drugs than with lenalidomide specifically.

In conclusion, our findings in this large, single-institution series confirm that the risk of SPMs remains a concern after ASCT for MM. We were able to identify patients at greater risk for SPMs based on age and race/ethnicity. Previously identified risk factors for SPMs include lenalidomide therapy, low $CD34^+$ cell dose, chemotherapy with alkylators and epipodophyllotoxins, and radiation exposure. Lenalidomide has known effects on the bone marrow microenvironment, as evidenced by poor stem cell mobilization with long-term lenalidomide exposure. In turn, low $CD34^+$ stem cell yields have been associated with t-MDS/AML. However, our cohort included few cases of lenalidomide exposure, and all cases of t-MDS/AML occurred prior to the year 2000, before the use of lenalidomide became widespread. The trend in our case-control analysis toward an association between thalidomide exposure and post-ASCT SPMs in patients with MM may point to a class effect rather than a lenalidomide-specific effect. This potential class effect is consistent with data showing similar but slightly lower rates of SPMs in thalidomide-exposed patients compared with lenalidomide-exposed patients [20]; however, the possible mechanism of action remains unclear, especially because thalidomide does not affect stem cell yields. As we enter an era of personalized medicine in the treatment of MM in the context of improved survival with novel drugs, the risks and benefits of exposure to these drugs must be weighed. Ultimately, we envision the development of an algorithm incorporating host factors, disease-related factors, and SPM risk factors to better tailor therapy for patients with multiple myeloma.

ACKNOWLEDGMENTS

Financial disclosure: This work was supported in part by funding from the Kennedy Klemens Fund (to A.Y.K); National Institutes of Health grants P30 CA33572 (to the Cancer Center), R01 CA078938 (to S.B.), and P01 CA30206 (to S.J.F.); and Leukemia Lymphoma Society grant 2192 (to S.B.). Amrita Krishnan serves on the speaker's bureau for Celgene and Millenium, owns Celgene stock, and is a consultant for Celgene and Merck. George Somlo serves as a consultant and speaker for Celgene and as a speaker for Millenium. Firoozeh Sahebi received research funds from Millenium. The other authors have no conflicts of interest to disclose.

REFERENCES

1. Attal M, Harousseau JL, Stoppa AM, et al. Intergroupe Francais du Myelome. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. *N Engl J Med*. 1996;335:91-97.
2. Turesson I, Velez R, Kristinsson SY, et al. Patterns of improved survival in patients with multiple myeloma in the twenty-first century: a population-based study. *J Clin Oncol*. 2010;28:830-834.
3. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood*. 2008;111:2516-2520.
4. Barlogie B, Pineda-Roman M, van Rhee F, et al. Thalidomide arm of total therapy 2 improves complete remission duration and survival in myeloma patients with metaphase cytogenetic abnormalities. *Blood*. 2008;112:3115-3121.
5. Spencer A, Prince HM, Roberts AW, et al. Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure. *J Clin Oncol*. 2009;27:1788-1793.
6. 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.
7. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366:1770-1781.
8. Palumbo A, Hajek R, Delforge M, et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. *N Engl J Med*. 2012;366:1759-1769.
9. 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.
10. Bhatia S, Ramsay NK, Steinbuch M, et al. Malignant neoplasms following bone marrow transplantation. *Blood*. 1996;87:3633-3639.
11. Micallef IN, Lillington DM, Apostolidis J, et al. Therapy-related myelodysplasia and secondary acute myelogenous leukemia after high-dose therapy with autologous hematopoietic progenitor-cell support for lymphoid malignancies. *J Clin Oncol*. 2000;18:947-955.
12. Darrington DL, Vose JM, Anderson JR, et al. Incidence and characterization of secondary myelodysplastic syndrome and acute myelogenous leukemia following high-dose chemoradiotherapy and autologous stem-cell transplantation for lymphoid malignancies. *J Clin Oncol*. 1994;12:2527-2534.

13. Govindarajan R, Jagannath S, Flick JT, et al. Preceding standard therapy is the likely cause of MDS after autotransplants for multiple myeloma. *Br J Haematol*. 1996;95:349-353.
14. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat*. 1988;16:1140-1154.
15. Cox DR. Regression models and life tables. *J R Stat Soc*. 1972;B34: 187-220.
16. Attal M, Lauwers V, Marit G, et al. Maintenance treatment with lenalidomide after transplantation for myeloma: final analysis of the IFM 2005-02. *ASH Annual Meeting Abstracts*. 2010;116:310. Available from: http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;116/21/310. Accessed March 13, 2012.
17. McCarthy PL, Owzar K, Anderson KC, et al. Phase III Intergroup Study of lenalidomide versus placebo maintenance therapy following single autologous hematopoietic stem cell transplantation (AHSCT) for multiple myeloma: CALGB 100104. *ASH Annual Meeting Abstracts*. 2010;116:37. Available from: http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;116/21/37. Accessed March 13, 2012.
18. Palumbo A, Larocca A, Zweegman S, et al. Second primary malignancies in newly diagnosed multiple myeloma patients treated with lenalidomide: analysis of pooled data in 2459 patients. *ASH Annual Meeting Abstracts*. 2011;118:996. Available from: http://abstracts.hematologylibrary.org/cgi/content/abstract/118/21/996. Accessed June 5, 2012.
19. Fenk R, Neubauer F, Bruns I, et al. Secondary primary malignancies in patients with multiple myeloma treated with high-dose chemotherapy and autologous blood stem cell transplantation. *Br J Haematol*. 2012; 156:683-686.
20. Usmani SZ, Sexton R, Hoering A, et al. Second malignancies in total therapy 2 and 3 for newly diagnosed multiple myeloma: influence of thalidomide and lenalidomide during maintenance. *Blood*. 2012;120: 1597-1600.
21. Bergsagel DE, Bailey AJ, Langley GR, et al. The chemotherapy on plasma-cell myeloma and the incidence of acute leukemia. *N Engl J Med*. 1979;301:743-748.
22. Kaldor JM, Day NE, Clarke EA, et al. Leukemia following Hodgkin's disease. *N Engl J Med*. 1990;322:7-13.