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Increasing therapy-related myeloid neoplasms in multiple myeloma

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Abstract

Background: Despite the longer survival achieved in multiple myeloma (MM) patients due to new therapy strategies, a concern is emerging regarding an increased risk of secondary primary malignancies (SPMs) and how to characterize those patients at risk. We performed a retrospective study covering a 28-year follow-up period (1991-2018) in a tertiary single institution.

Material and Methods: Data of 403 MM patients were recorded and compared with the epidemiologic register of the population area covered by our centre, calculating the standardize incidence ratio (SIR) for the different types of SPMs diagnosed in the MM cohort. Fine and Gray regression models were used to identify risk factors for SPMs.

Results: Out of the 403 MM patients, 23 (5.7%) developed SPMs: 13 therapy-related myeloid (TRM) malignancies (10 of them (77%) myelodysplastic syndrome (MDS), 1 acute lymphoid leukaemia and 9 solid neoplasms. In the MM cohort, the relative risk of MDS was significantly higher than in the general population. Survival of patients with TRM malignancies was poor with a median of 4 months from the diagnosis, and most of them showed complex karyotype. Within the MM subset, multivariable analysis showed a higher risk of TRM malignancies in patients that previously received prolonged treatment with lenalidomide (>18 months).

Conclusions: Though the improvement in MM outcome during the last decades is an unprecedented achievement, it has been accompanied by the rise in TRM malignancies with complex cytogenetic profile and poor prognosis that are in the need of an improved biologic and therapeutic approach.

KEYWORDS
complex karyotype, multiple myeloma, myelodysplastic syndrome

1 | INTRODUCTION

Major advancements in the treatment of multiple myeloma (MM), such as high-dose melphalan followed by autologous stem cell transplant (ASCT), and the recent introduction of novel therapies as immunomodulatory drugs (IMIDs) or proteasome inhibitors (IPs) have notably improved the outcome of MM patients.[1] Despite this major achievement, a concern is emerging regarding the increased risk of secondary primary malignancies (SPMs) and how to characterize those patients at risk.

Fernández-Caballero and Salmerón authors contributed equally to this study

A raised rate of developing SPMs in MM patients has been reported previously, and the estimated incidence of SPMs in this setting ranged between 2 and 10%.[2–4]

Regarding therapy-related myeloid (TRM) neoplasms, a higher incidence of myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) has been described during prolonged treatment with melphalan.[5] Nilsson et al. reviewed previous published t-MDS/t-AML post-MM, finding that they were characterized by an alkylating agent–induced MDS/AML-cytogenetic profile: complex karyotypes, hypodiploidy, and certain genomic aberrations, standing out loss of chromosomes 5, 7, and 17, deletions of 12p, and monosomy 18.[6]

Recently, it has been suggested a relationship between SPMs and treatment with lenalidomide.[7–9] However, reports regarding TRM neoplasms in lenalidomide treated patients are uneven.[10–12] The aims of this study, performed in a well annotated series of MM patients, with a prolonged follow-up, were as follows: i) to analyse the incidence and characteristics of SPMs in the whole cohort comparing its data with a general population registry; ii) to determine differences in SPMs occurrence with the emergence of new therapies; iii) to test for SPMs risk factors within a competitive risk model.

2 | MATERIAL AND METHODS

2.1 | Patients and definitions

We retrospectively reviewed the medical records of patients with MM diagnosed in our institution between 1991 and 2015. In patients from whom written informed consent was not obtained, due to death or loss of follow-up, data were anonymised and de-identified prior to analysis, in agreement with our Institutional Review Board protocols.

We have recorded demographical data such as gender, age, smoking habit and obesity (defined as a body mass index (BMI) $\geq$30 kg/m^2). MM was diagnosed according to the International Myeloma Working Group guidelines.[13,14] Patients were studied from diagnosis until time of last visit, death or loss of follow-up. We have considered whether patients received treatment based on lenalidomide and its duration (less than 6 months, between 6 and 18 months or more than 18 months). Also, we have recorded if they received thalidomide-, bortezomib-, anthracyclines- or melphalan- based treatments, or in those eligible, bone marrow transplantation procedure. We also assessed whether patients received radiotherapy as supportive treatment for pain control or to prevent progression of localized or extramedullary disease. Haematological toxicity during the follow-up was classified according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), 3.0. version.[15]

Prior or synchronous neoplasms and SPMs were defined using the CIE-10 classification, excluding benign neoplasm and nonmelanoma skin cancer. Diagnosis of a solid neoplasm was verified by histology, and disease stages were classified according to TNM. Haematological SPMs were diagnosed according to the 2016 WHO classification.[16] Information about cytogenetic profile was also recorded.

2.2 | General population registry

Data available in the Servicio Murciano de Salud Healthcare System are routinely collected for administrative purposes. The Department of Epidemiology of the Región de Murcia Health Service is authorized to manage these databases within the rules of the Spanish Privacy Policy. An anonymous Unique Patient Number for every individual is used. Standardized protocols of deterministic record linkage are applied, to create and update the clinical history of patients for the evaluation of epidemiological studies.

2.3 | Statistics

To estimate an increase in SPMs occurrence in our patients, we compared the incidence rate found in our MM patients with the expected in the general population of the same area applying an age and sex standardization. Patient-years for age-stratification (5-year age-groups) was defined as the time in years from the diagnosis of MM to the date of death, date of diagnosis of SPMs, date of loss of follow-up or the end of study (1 May 2018), whichever came first. General population incidence rates from 2003 to 2007 for each stratum were multiplied by their respective accumulated patient-years-at-risk to estimate the overall expected cancer cases in that cohort of MM patients. We calculated the standardized incidence ratio (SIR) by dividing the observed number of SPMs cases by the expected number based on the general population rates.

Fine and Gray regression models were used to identify risk factors for SPMs. Subdistribution hazard ratios (SHRs), corresponding 95% confidence intervals (CI) and p-values were calculated. The SHRs was assessed considering either haematological malignance or solid neoplasm development as the dependent variable. We use a competitive risk model in order to considered the risk of death from other reasons different to SPMs,[17] and the following factors as covariates: gender, age at MM diagnosis ($\leq$ or $>$ 65 y.o.), smoking habit, obesity, prior or synchronous neoplasm, treatment with lenalidomide less than 6 months, during 6-18 months or more than 18 months, thalidomide, anthracyclines, melphalan, bortezomib, radiotherapy, bone marrow transplantation and haematological toxicities grade 3 or 4 as anaemia, neutropenia and thrombocytopenia

during treatment. Finally, we set up a multivariate model with all factors considered to be relevant (ie, sex, anti-myeloma-therapy, haematological toxicity). We favour a clinical-relevance approach by moving factors forward into the multivariate model. Finally, p-values < 0.05 were considered statistically significant. Statistical analyses were performed using SPSS of Windows software (Statistical Package for the Social Sciences version 15.0, SPSS Inc., Chicago, IL, USA) and Stata 14.2 for Windows (Stata Corporation, College Station, TX).

3 | RESULTS

3.1 | Incidence and characteristics of SPMs in the MM cohort in the context of a general population registry

With a median age at diagnosis of 66 years (range 24-90), four hundred and three MM patients were identified between 1991 and 2015 and included in the analysis. With a slight female predominance (53%) in the whole cohort, 31 patients (7,7%) reported a malignancy antecedent to MM diagnosis, and 2 patients (0,5%) a synchronous one. Baseline clinical characteristics and synchronous neoplasms are summarized in Table 1 and Supplementary Material Table S1**,** respectively.

Concerning treatment, 44% of patients received bone marrow transplantation as consolidation treatment. During the follow-up, 59% of patients received, at least, a second line of treatment at relapse or progression. The median number of lines of treatment was 2 (range 1-7), and the distribution of the different drugs received throughout the natural history of the disease and follow-up were as follows: thalidomide (16%), lenalidomide <6 months (14%), lenalidomide between 6-18 months (16%), lenalidomide >18 months (5%), anthracyclines (37%), melphalan (84%) and bortezomib (62%). Overall, 280 patients (69%) received novel therapies. In addition, radiotherapy was administered in 23% of the patients.

During the course of therapy, 48% of patients developed haematological grade 3 or 4 toxicities: anaemia (36%), thrombocytopenia (20%) and/or neutropenia (30%).

Median follow-up was 40 months (range 1-293). During this period, 23 patients developed SPMs (5.7%), including haematological SPMs, as therapy-related myeloid (TRM) malignancies, as follows: MDS (n = 10), myeloproliferative neoplasms (n = 1), and AML (n = 2) and ALL (n = 1). The origin of solid malignancies included: rectum (n = 2), kidney (n = 2), stomach (n = 1), colon (n = 1), gallbladder (n = 1), lung (n = 1) and metastases of unknown origin (n = 1). Gender distribution is provided in the Supplementary Material Table S2.

TABLE 1 Baseline characteristics of the study patients

	n = 403
Male	190 (47%)
Median age (range), years	66 (24-90)
Median BMI kg/m2	28
Smoking habit	114 (28%)
Prior malignant neoplasm	31 (7.7%)
Synchronous malignant neoplasm	2 (0.5%)
Paraprotein subtype	
IgG	212 (52.6%)
IgA	111 (27.5%)
Immunoglobulin light chain	66 (16.3%)
No secretor	5 (1.2%)
IgD	1 (0.2%)
IgM	1 (0.2%)
Plasma cell myeloma	7 (2%)
Durie-Salmon staging	
I	61 (15.2%)
II	120 (29.8%)
III	213 (52.8%)
No data	9 (2.2%)
International Staging System	
1	95 (23.6%)
2	97 (24.1%)
3	111 (27.5%)
No data	100 (24.8%)

Abbreviations: BMI, body mass index.

Remarkably, one patient aggregated 3 tumors. She had an antecedent of breast cancer, developed a MM and, later on, a myelodysplastic syndrome with excess of blasts.

Compared to the general population, we observed a statistically significant increase in the risk of MDS, even when adjusting by gender: O/E (10/0.275); SIR = 36.29 (IC 95% 17.28-62.26). On the other hand, no differences have been found in other malignancies. Relative risks are reported in Table 3.

3.2 | Therapy-Related Myeloid Neoplasms in MM patients

Additional data from the TRM malignancies reported herein are described in Table 2. The median age at TRM diagnosis was 70 years (range 51-84), and the median time from MM diagnosis to develop a TRM neoplasm was 49

TABLE 2 Main features of patients with therapy-related myeloid malignancies

N° Patient	Sex	MM diagnosis date and Age (years)	Cytogenetics At MM diagnosis	5Previous treatment	Duration of treatment with lenalidomide (months)	Radiotherapy	TRM malignanciy Diagnosis
1	Female	12/12/1995 (39)	NA	VBMCP/VBAD, 2 ASCT, VAD, ASCT, TCD, VCD, LD, V	5	No	MDS with excess blasts
2	Male	15/09/1995 (52)	NA	VBMCP/VBAD, ASCT, IFN-α	No treatment with lenalidomide	Yes	MDS with excess blasts
3	Female	06/11/1998 (55)	NA	VBMCP/VBAD, IFN-α, VBMCP/ VBAD, ASCT	No treatment with lenalidomide	Yes	CMML
4	Male	10/03/1999 (60)	46,XY, del(20)(q12) [12]/46,XY[8]	MP, VAD, ASCT	No treatment with lenalidomide	No	MDS with excess blasts
5	Female	16/01/2004 (55)	NA	VBMCP/VBAD, ASCT, LD, VCD, Daratumumab	15	Yes	MDS with excess blasts
6	Female	06/08/2007 (61)	46, XX (20)	VBMCP/VBAD/V, ASCT	No treatment with lenalidomide	Yes	MDS with multilineage dysplasia
7	Male	09/05/2012 (63)	NA	BVP, ASCT, LD, VRD	28	Yes	MDS with excess blasts
8	Male	01/08/2010 (77)	NA	VMP, LD, VP, TD, VTD, MP, LD	27	No	Myelofibrosis
9	Female	02/02/2012 (67)	NA	BVP, LD	10	No	MDS with excess blasts
10	Male	01/02/2012 (71)	NA	VMP, LD	41	No	MDS with excess blasts
11	Male	02/11/2010 (69)	NA	PAD, LD, VMP	7	No	AML with myelodysplasia -related changes
12	Female	06/11/2015 (83)	46,XX[20]	MP	No treatment with lenalidomide	No	MDS-RS
13	Female	01/12/2012 (72)	NA	VMP, L	47	No	AML

Abbreviations: AML, acute myeloid leukaemia; ASCT, autologous stem cell transplant; BVP, bendamustine, bortezomib, prednisone; CMML, chronic myelomonocytic leukaemia; CR, complete remission; IFN-α interferon alpha; L, lenalidomida; LD, lenalidomida, dexamethasone; MDS, myelodysplastic syndrome; MDS-RS, myelodysplastic syndrome with ring sideroblasts SC, supportive care; MP, melphalan, prednisone; NA, non available; PAD, bortezomib, doxorubicin, dexamethasone ; PR, parcial remission; RIC-Allo HCT, reduced intensity conditioning allogeneic hematopoietic stem cell transplantation; SC, supportive care; SD, stable disease; TCD, thalidomide, cyclophosphamide, dexamethasone ; TD, thalidomide, dexamethasone; TRM, therapy-related myeloid; V, bortezomib; VAD, vincristine, adriamycin, dexamethasone ; VBMCP/ VBAD, vincristine, carmustine (BCNU), cyclophosphamide, melphalan, prednisone/vincristine, carmustine (BCNU), adriamycin, dexamethasone; VBMCP/ VBAD/V, vincristine, carmustine (BCNU), cyclophosphamide, melphalan, prednisone/vincristine, carmustine (BCNU), adriamycin, dexamethasone/ velcade; VCD, bortezomib, cyclophosphamide, dexamethasone; VMP, bortezomib, melphalan, prednisone; VP, bortezomib, prednisone; VRD, bortezomib, lenalidomida, dexamethasone; VTD, bortezomib, thalidomide, dexamethasone; 5-Aza, 5-Azacitidine

Date of TRM Malignancy and Age (years)	Cytogenetics At TRM Malignancy diagnosis	MM Status At TRM diagnosis	Time from MM diagnosis (months)	TRM malignancy Treatment	Survival from TRM malignancy diagnosis (months)	Cause of Death
08/10/2008 (51)	46,XX,-4,-5,+11, del(11)(q22), der (18),+mar (20)	Progression	154	SC	1	Infection
06/07/2003 (60)	44 (XY) -3,-4,-4,-5, -7,-10,-20,-21+5 mar [18]/46(XY) [2]	CR	94	RIC-Allo HCT	4	Acute Pulmonary Embolism
01/09/2009 (66)	52,XX, del(5)(q13q33), add(6) (p22),+8, +8,+8,+11,+11, +21,+mar (20)	PR	130	Hydrea	7	Infection
15/01/2003 (64)	46,XY,-5,del(5)(q13q33),+8,add(11) (pter),-15,+mar[15]/46,XY[5]	CR	46	SC	4	Infection
01/02/2018 (69)	44,XX,- 3 der(3;7)(q12;p10),der(5)t (3;5)(p13;q14),add(12)(p11.2),-20 [9]/45,idem, +mar[3]/44,ídem,dic (12;20)(p11.2;q13)[6]/46,XX[3]	CR	168	SC	2	Infection
12/05/2016 (70)	46,XX (20)	CR	105	5-Aza	34	AML Progression
10/10/2015 (67)	43,XY,-1,-5,-12, -13,-17,+3mar[11]/46,XY[9]	CR	41	5 Aza/RIC-Allo HCT	15	Infection
10/04/2014 (81)	46,XY, (20)	SD	44	SC	4	Infection
05/03/2016 (71)	48,XX(del5)(q13q33),del(7) (q22),+8,+mar[21]/46 XX[4]	PR	49	SC	4	AML Progression
23/03/2016 (76)	46,XY,-3,-5,-7,-10, -18,-22,+6mar[18]/46,XY[2]	CR	49	5-Aza	5	AML Progression
10/03/2014 (73)	43, X, -Y, der(1)del (1)(q23)t(1;9) (q23;p23), del(5)(q14q33), -7, der (9)t(1,9), del(10)8q23)(15)/46,XY (5)	PR	40	SC	1	Infection
11/04/2017 (84)	46,XX[20]	CR	17	SC	9	Alive
01/04/2018 (78)	47,XX,del(5)(q31q35),-6,-21,+mar1,+mar2,+mar3[20]	CR	64	5-Aza	1	Alive

TABLE 3 Relative risk for each neoplasm by gender

	Male	Female	Both sexes
Haematological malignancies			
Myelodysplastic Syndrome (n = 10)	34.26 (IC 95% 10.81-70.87)	38.56 (IC 95% 12.17-79.77)	36.29 (IC 95% 17.28-62.26)
Myeloproliferative neoplasms (n = 1)	15.93 (IC 95% 0.01-62.44)		
Acute leukaemia (n = 3)	7.82 (IC 95% 0.74-22.43)	5.06 (IC 95% 0-19.83)	
Solid neoplasms			
Stomach (n = 1)	2.73 (IC 95% 0-10.69)		
Colon (n = 1)	0.99 (IC 95% 0-3.89)		
Rectum (n = 2)		5.53 (IC 95% 0.52-15.84)	
Gallbladder (n = 1)		9.65 (IC 95% 0-37.82)	
Lung/bronchus (n = 1)	0.55 (IC 95% 0-2.17)		
Kidney (n = 2)	8.01 (IC 95% 0.76-22.97)		

months (range 17-168). Ten patients (77%) presented with complex karyotype at diagnosis. The prognostic was poor, with a median time of survival from diagnosis of 4 months (range 1-34). The two main causes of death were infection (64%) or AML progression (27%).

Among the 280 patients that received novel therapies during the course of the disease, 10 (3.6%) developed TRM malignancies. Three (2.4%) out of 123 patients who did not receive novel therapies, developed a TRM malignancy.

3.3 | TRM neoplasm development risk factors within a competitive risk model

Fine and Gray multivariate regression analysis showed a significant increase of risk for developing TRM malignancies in patients who received prolonged treatment with lenalidomide (>18 months) (SHRs 10.499 (95% CI 1.503-73.318); $P = 0.018$). The results of the multivariate analysis are shown in Table 4.

TABLE 4 Fine and Gray multivariate regression analysis of risk factors associated to the development of Therapy-Related Myeloid Neoplasms

	Multivariate Analysis HR (IC 95%); *P*
Gender (female)	2.856 (0.346-23.578); 0.330
Bone marrow transplantation	2.427 (0.261-22.529); 0.435
Anthracyclines	0.149 (0.109-2.028); 0.153
Radiotherapy	2.677 (0.751-9.539); 0.129
Melphalan	0.310 (0.020-4.672); 0.398
Bortezomib	0.986 (0.949-10.253); 0.991
Lenalidomide >18 months	10.499 (1.503-73.318); 0.018
Thrombocytopenia grade 3-4	0.857 (0.372-19.737); 0.923
Neutropenia grade 3-4	1.175 (0.037-36.471); 0.927
Anaemia grade 3-4	8.223 (0.872-77.505); 0.066

4 | DISCUSSION

The data obtained within this study reflect the incidence of SPMs in patients with MM during a long period of follow-up, including a comparison of the incidence rates with the registered data in our general population. Interestingly, the long follow-up allowed us to characterize, clinically and cytogenetically, the TRM incidence attributed to the relatively recent introduction of new agents. Of note, we found an approximately 4 years latency from diagnosis. On the other hand, complex cytogenetics and poor outcomes were the most common features within this subset. That latency period explains why 9 out of 13 TRM neoplasms were diagnosed in the last period of follow-up: from 2014 to 2018. In other words, 69% of the TRM neoplasms diagnosed during a 28-year follow-up, were diagnosed in the last 4 years, raising a clear need to confirm and address this particular issue in MM patients.

Previous studies have described an increased risk of SMPs in MM patients, notably the development of MDS/AML.[18,19] The association between the development of TRM neoplasms and the treatment with lenalidomide in patients with MM is a matter of debate, with contradictory results reported.[10–12,20] Differences in the design of these studies might account for those discrepancies, with the lack of SPMs incidence/follow-up in those cases in which lenalidomide was discontinued, as the major limitation in the clinical trial setting. In our study, long-term lenalidomide treatment (for more than 18 months) demonstrated to increase the risk of developing TRM malignancies with a statistically and independent significance within a competitive risk multivariate model. It is remarkable that in our study no patients were treated with lenalidomide plus

melphalan at the same time. Moreover, most of the patients were treated with lenalidomide for less than 6 months (n = 55, 14%) or between 6 and 18 months (n = 64, 16%). Only 21 patients (5.2%) were treated with lenalidomide for more than 18 months; however, 4 out of those 21 patients (19%) developed a therapy-related myeloid neoplasms. A significant association does not imply causation. Whether the prolonged treatment with lenalidomide favours the emergence of TRM neoplasms due to achieving a longer survival or a direct carcinogenetic effect is still unresolved. The similarities of the cytogenetic profile of TRM neoplasms after lenalidomide with those described after the use of alkylating agents would support the first hypothesis. On the other hand, we and others did not find bortezomib-based regimens to be associated with a higher rate of TRM neoplasms, a fact favouring the second scenario.[21]

According to our data, complex karyotype is the most frequently alteration in TRM malignancies in patients treated for a previous MM. In another population-based study focused on SPMs during the lenalidomide-dexamethasone regimen in relapsed/refractory MM patients 5 out of 6 patients who developed a therapy related AML/MDS had complex cytogenetics.[10] With regard to survival, in a previous large population-base study of MM patients the median time of survival after diagnosed AML/MDS was 2.4 months.[22], even shorter than that of 4 months found in our cohort.

Population-based studies are necessary to estimate the incidence, characteristics and risks factors associated to TRM malignancies in the setting of MM patients. Long term follow-up, a large well-annotated series of patients and comparing incidence rates of cancer with a same area general population registry are the strengths of our study. We acknowledge that the main caveat is the lack of cytogenetics at MM diagnosis in 10 out of 13 patients who developed TRM neoplasms in the follow-up. In this regard, Mitelman et al., showed that the distribution of the number of anomalies and ploidy levels, as well as the frequency of most of the investigated aberrations differed significantly, and that these features often could be used to distinguish between MM and t-MDS/t-AML.[6,23] However, the MM CR status at TRM neoplasm diagnosis in 6/10 of the complex karyotype cases, and the expansion of those exact altered metaphases in the 2 MDS cases when progressed to AML are strong arguments to countermeasure that study weakness.

In summary, although the improvement in the survival of the MM during the last decades is an unprecedented achievement, the introduction of those new procedures and therapies has lead to the emergence of new health-relates issues, such as the development of TRM malignancies with poor cytogenetic profile that at the present moment lack a satisfactory approach.

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REFERENCES

1. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood*. 2008;111(5):2516-2520.
2. 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(10):1340-1349.
3. Bergsagel DE, Bailey AJ, Langley GR, MacDonald RN, White DF, Miller AB. The Chemotherapy of Plasma-Cell Myeloma and the Incidence of Acute Leukemia. *N Engl J Med*. 1979;301(14):743-748.
4. Kyle RA, Pierre RV, Bayrd ED. Multiple myeloma and acute myelomonocytic leukemia. *N Engl J Med*. 1970;283(21):1121-1125.
5. 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(5):523-529.
6. Nilsson T, Nilsson L, Lenhoff S, et al. MDS/AML-associated cytogenetic abnormalities in multiple myeloma and monoclonal gammopathy of undetermined significance: Evidence for frequent de novo occurrence and multipotent stem cell involvement of del (20q). *Genes Chromosom Cancer*. 2004;41(3):223-231.
7. Palumbo A, Hajek R, Delforge M, et al. Continuous Lenalidomide Treatment for Newly Diagnosed Multiple Myeloma. *N Engl J Med*. 2012;366(19):1759-1769.
8. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide Maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366(19):1782-1791.
9. 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(3):333-342.
10. Kotchetkov R, Masih-Khan E, Chu C-M, et al. Secondary primary malignancies during the lenalidomide-dexamethasone regimen in relapsed/refractory multiple myeloma patients. *Cancer Med*. 2017;6(1):3-11.
11. Rossi AC, Mark TM, Jayabalan D, et al. Incidence of second primary malignancies (SPM) after 6-years follow-up of continuous lenalidomide in first-line treatment of multiple myeloma (MM). *J Clin Oncol*. 2011;29(15_suppl):8008-8008.
12. Dimopoulos MA, Richardson PG, Brandenburg N, et al. A review of second primary malignancy in patients with relapsed or refractory multiple myeloma treated with lenalidomide. *Blood*. 2012;119(12):2764-2767.
13. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15(12):e538-e548.
14. International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *Br J Haematol*. 2003;121(5):749-757.

15. Terminology C. Criteria for adverse events v3.0 (CTCAE). *Quick Reference*. 2003.
16. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391-2405.
17. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. *Stat Med*. 2007;26(11):2389-2430.
18. 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(6):e121.
19. Tzeng H-E, Lin C-L, Tsai C-H, et al. Time trend of multiple myeloma and associated secondary primary malignancies in Asian patients: a Taiwan population-based study. Hills RK, ed. *PLoS ONE*. 2013;3(6):e121.
20. Dimopoulos MA, Swern AS, Li JS, et al. Efficacy and safety of long-term treatment with lenalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma. *Blood Cancer J*. 2014;4(11):e257.
21. San Miguel JF, Schlag R, Khuageva NK, et al. Persistent overall survival benefit and no increased risk of second malignancies with bortezomib-melphalan-prednisone versus melphalan-prednisone in patients with previously untreated multiple myeloma. *J Clin Oncol*. 2013;31(4):448-455.
22. Jonsdottir G, Lund SH, Bjorkholm M, et al. Survival in multiple myeloma patients who develop second malignancies: A population-based cohort study. *Haematologica*. 2016;101(4):e145-e148.
23. Haas O. Felix Mitelman: database of chromosome aberrations in cancer. *Hum Genet*. 2002;110(5):524-525.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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