Second primary malignancies with lenalidomide therapy for newly diagnosed myeloma: a meta-analysis of individual patient data.

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Summary

Background

Lenalidomide has been linked to second primary malignancies in myeloma. We aimed to pool and analyse available data to compare the incidence of second primary malignancies in patients with and without lenalidomide exposure.

Methods

We identified relevant studies through a search of PubMed and abstracts from the American Society of Clinical Oncology, American Society of Hematology, and the International Myeloma Workshop. Randomised, controlled, phase 3 trials that recruited patients with newly diagnosed multiple myeloma between Jan 1, 2000, and Dec 15, 2012, and in which at least one group received lenalidomide were eligible for inclusion. We obtained individual patient data (age, sex, date of diagnosis, allocated treatment and received treatment, duration of treatment and cause of discontinuation, maintenance treatment, date of first relapse, date of second primary malignancy diagnosis, type of second primary malignancy, date of death or last contact, and cause of death) by direct collaboration with the principal investigators of eligible trials. Primary outcomes of interest were cumulative incidence of all second primary malignancies, solid second primary malignancies, and haematological second primary malignancies, and were analysed by a one-step meta-analysis.

Findings

We found nine eligible trials, of which seven had available data for 3254 patients. 3218 of these patients received treatment (2620 had received lenalidomide and 598 had not), and were included in our analyses. Cumulative incidences of all second primary malignancies at 5 years were 6·9% (95% CI 5·3–8·5) in patients who received lenalidomide and 4·8% (2·0–7·6) in those who did not (hazard ratio [HR] 1·55 [95% CI 1·03–2·34]; p=0·037). Cumulative 5-year incidences of solid second primary malignancies were 3·8% (95% CI 2·7–4·9) in patients who received lenalidomide and 3·4% (1·6–5·2) in those that did not (HR 1·1 [95% CI 0·62–2·00]; p=0·72), and of haematological second primary malignancies were 3·1% (95% CI 1·9–4·3) and 1·4% (0·0–3·6), respectively (HR 3·8 [95% CI 1·15–12·62]; p=0·029). Exposure to lenalidomide plus oral melphalan significantly increased haematological second primary malignancy risk versus melphalan alone (HR 4·86 [95% CI 2·79–8·46]; p<0·0001). Exposure to lenalidomide plus cyclophosphamide (HR 1·26 [95% CI 0·30–5·38];

p=0·75) or lenalidomide plus dexamethasone (HR 0·86 [95% CI 0·33–2·24]; p=0·76) did not increase haematological second primary malignancy risk versus melphalan alone.

Interpretation

Patients with newly diagnosed myeloma who received lenalidomide had an increased risk of developing haematological second primary malignancies, driven mainly by treatment strategies that included a combination of lenalidomide and oral melphalan. These results suggest that alternatives, such as cyclophosphamide or alkylating-free combinations, should be considered instead of oral melphalan in combination with lenalidomide for myeloma.

Introduction

In patients with multiple myeloma, substantial improvements in survival have been obtained since the introduction of high-dose melphalan and autologous stem-cell transplantation (ASCT), as well as with bortezomib and the immunomodulatory agents thalidomide and lenalidomide (Celgene Corporation, Summit, NJ, USA).[1, 2 and 3] Increased survival, and therefore increased life expectancy, has led to renewed concern about the risk of second primary malignancies.[4 and 5]

Many factors contribute to the risk of second primary malignancies in myeloma, such as age. In the general population, the incidence of cancer per year of life is 0·3% in individuals aged 45–49 years, 1·7% in those aged 65–69 years, and 2·3% in those aged 85 years or older.[6] Myeloma also increases the risk of developing second primary malignancies. Registry data show that patients with myeloma are 1·26 times more at risk of having any second primary malignancies, and about twice as likely to develop haematological second primary malignancies than the general population, mainly as a result of myelodysplastic syndrome and acute myeloid leukaemia.[7]

A well known treatment-related risk factor for second primary malignancies is extended exposure to the cytotoxic agent melphalan. In the pretransplant era, 5-year cumulative incidence of myelodysplastic syndrome and acute myeloid leukaemia in patients who received alkylating agents was 3%.[8] The same analysis showed that melphalan was more oncogenic than cyclophosphamide, and reported a relation between length of treatment with melphalan and myelodysplastic syndrome and incidence of acute myeloid leukaemia.[8] In a recent report, 5-year cumulative incidence of myelodysplastic syndrome and acute myeloid leukaemia after ASCT was 1·0%.[9] Regarding immunomodulatory agents, there is a suggestion of an increased risk of developing second primary malignancies with exposure to thalidomide.[9] Furthermore, three phase 3 trials reported an increased incidence of second primary malignancies in patients with newly diagnosed myeloma given lenalidomide maintenance after melphalan-based induction, compared with patients who did not receive lenalidomide.[10, 11 and 12] In one trial, after 3 years, invasive second primary malignancies were noted in 7% of patients who received lenalidomide and 3% of those who did not.[10] No significantly increased risk of developing invasive second primary malignancies was reported in relapsed patients who received lenalidomide and dexamethasone.[13]

We did a meta-analysis of individual patient data from phase 3 trials in which at least one group received lenalidomide as part of first-line myeloma treatment. The primary purpose of this study was to compare the incidence of second primary malignancies in patients with and without lenalidomide exposure. Secondary aims were to assess the effects of treatment regimen (eg, coadministration with melphalan, cyclophosphamide, and dexamethasone) on risk of developing second primary malignancies, and compare the risk of death due to second primary malignancy versus the risks of death due to myeloma progression, or adverse events related to myeloma

treatment. We broadly divided our analysis by patients who received lenalidomide versus those who did not—and subsequently, into those who received lenalidomide in combination with melphalan, cyclophosphamide, or dexamethasone—based on clinical evidence that these agents have different oncogenic effects.

Methods

Search strategy and selection criteria

We searched PubMed, and abstracts from the annual meetings of the American Society of Clinical Oncology, the American Society of Hematology, and from the International Myeloma Workshop, which occurs every 2 years, with the search terms "lenalidomide" and "phase 3 trial/study" (or "randomised trial/study"), and "myeloma" and "up-front therapy" (or "diagnosis"). Searches were limited to reports published in English. The date of the last search was Dec 30, 2012. Randomised, controlled, phase 3 trials that recruited patients with newly diagnosed multiple myeloma between Jan 1, 2000, and Dec 15, 2012, and in which at least one group received lenalidomide were eligible for inclusion. AP, SB, AE, and GC undertook the review of the search data.

Individual patient data extraction and clinical endpoints

We asked the principal investigators of all eligible trials with available data to provide the following pertinent original data for each patient: age, sex, date of diagnosis, allocated treatment and received treatment, duration of treatment and cause of discontinuation (not available for all studies), maintenance treatment, date of first relapse, date of second primary malignancy diagnosis, type of second primary malignancy, date of death or last contact, and cause of death (not available for all patients).

We excluded patients who were randomly assigned to treatment but did not receive it; therefore patient numbers reported in the original study publications differ from those reported in our meta-analysis. Collaborating groups were asked to code data rendered anonymous in a standardised fashion for inclusion in a database. All site investigators provided written, signed confirmation of the number of reported second primary malignancies for the trials in which they participated.

Coordination of the meta-analysis and data management were done at one independent research organisation (Myeloma Unit, University of Turin, Turin, Italy).

Our primary outcomes of interest were cumulative incidence at 3 years and 5 years of all second primary malignancies, haematological second primary malignancies, and solid second primary malignancies in patients who received lenalidomide and in those who received regimens that did not include lenalidomide. We also assessed the cumulative incidence of second primary malignancies according to treatment regimen (eg, co-administration with melphalan, cyclophosphamide, or dexamethasone), and of death due to all causes, myeloma, adverse events, and second primary malignancies. In all trials, haematological and solid second primary malignancies were diagnosed on the basis of occurrence of specific clinical signs or symptoms.

Statistical analysis

Patient data were pooled and analysed by an independent statistical organisation (Epidemiologia dei tumori, Turin, Italy). Methods used in the analysis were defined in advance and documented in a statistical plan that was then approved by the ethics committee (Turin, Italy).

This analysis was a one-step meta-analysis of individual participant data. Cumulative incidences of second primary malignancies were calculated considering death from any cause as a competing event using the method of Gooley and colleagues.[14] If a patient had more than one second primary malignancy, only the first was considered. The regression model of subdistribution hazards for clustered data was applied to assess the effect of lenalidomide (in terms of hazard ratios [HRs] and 95% CIs) on the cumulative incidence function of second primary malignancies, accounting for heterogeneity across studies.[15] The effect of lenalidomide was also adjusted for concomitant treatments (ie, with melphalan or cyclophosphamide), age, and sex. Cumulative incidence of mortality was estimated by the Kaplan-Meier method, and cause-specific mortality was calculated using the method of Gooley and colleagues.[14] Statistical analysis was done with STATA (version 11.1) and R (version 2.15.1). Clustering of patients within studies was accounted for by adjusting the standard errors of coefficients using an extension of the Fine and Gray model.[16] Formal assessment of heterogeneity using this approach and assessment of the risk of bias of individual studies were not done.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, or data interpretation. Medical writing support was funded by the sponsor. The authors directed development of the manuscript and were fully responsible for all content and editorial decisions. The corresponding author (AP) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Our initial search identified nine eligible trials: eight investigator-sponsored trials[11, 12, 16, 17, 18, 19, 20 and 21] and one manufacturer-sponsored trial.[10] At the time of analysis, after contacting the principal investigators of these studies, we excluded two studies because patient-level data were unobtainable;[11 and 21] four of the seven remaining trials were not published in peer-reviewed journals.[16, 17, 18 and 19] Descriptions of the seven trials included in the meta-analysis, including key inclusion and exclusion criteria for each individual trial, are presented in table 1.

Table 1. Trial characteristics

	GIMEMA RV-MM-PI-209[19]	RV-MM-EMN 441[17]	CALGB 100104[12]	ECOG E4A03[20]	RV-MM-PI-0521 (EMN01)[18]	MM-015[10]	HOVON 87 MM/NMSG18[16]
Recruitment							
Enrolment period	2007–09	2009–11	2005–09	2004–06	2009–11	2007–09	2009–12*
Total randomised	402	389	460	445	663	459	436
Eligibility criteria							
Age	≤65 years	≤65 years	≤70 years	None	≥65 years†	≥65 years	>65 years†
ECOG performance status	..	..	..	0–2	..	..	0–3‡
Karnofsky performance status	≥60%	≥60%	≥60%	..	≥60%	≥60%	..
Number assigned to treatment							
Lenalidomide before or after high-dose intravenous melphalan	200	195	231	156		-	-
Lenalidomide plus low-dose oral melphalan	202	-	..	..	218	305	220
High-dose intravenous melphalan	..	..	229	..	..	..	..
Low-dose oral melphalan	..	..	..	..	..	153	..
Lenalidomide plus dexamethasone	..	..	..	289	222	..	..
Lenalidomide plus cyclophosphamide	..	194	..	..	223	..	..
Low-dose oral melphalan plus thalidomide	..	..	..	..	..	..	216
Duration of treatment							
Induction, months	~9–12	~9–12	..	Until PD	9	9	9
Maintenance, months	Until PD	Until PD	Until PD	..	Until PD	Until PD	Until PD
Follow-up							
Patient-years	852·03	635·17	1356·43	1618·56	744·08	941·22	929·90
Median (IQR) months	26 (9–45)	24 (8–29)	36 (29–45)	55 (53–59)	12 (6–22)	17 (8–37)	25 (19–32)
Cumulative incidence of SPMs at 3 years							
All SPMs							
With lenalidomide	3·7%	2·6%	6·8%	2·5%	3·0%	6·7%	5·1%
Without lenalidomide	..	..	2·3%	..	..	4·0%	3·8%
Solid SPMs							
With lenalidomide	3·3%	2·6%	3·9%	2·3%	2·5%	1·8%	3·7%
Without lenalidomide	..	..	1·9%	..	..	2·9%	3·8%
Haematological SPMs							
With lenalidomide	0·4%	0	2·8%	0·2%	0·5%	5·0%	1·4%
Without lenalidomide	..	..	0·4%	..	..	1·0%	0
Cumulative incidence of SPMs at 5 years							
All SPMs							
With lenalidomide	5·0%	..	11·9%	3·8%	..	14·6%	..
Without lenalidomide	..	..	3·1%	..	..	..	..
Solid SPMs							
With lenalidomide	4·6%	..	4·7%	3·0%	..	5·1%	..
Without lenalidomide	..	..	2·7%	..	..	..	..
Haematological SPMs							
With lenalidomide	0·4%	..	7·2%	0·8%	..	9·5%	..
Without lenalidomide	..	..	0·4%	..	..	..	..

ECOG=Eastern Cooperative Oncology Group. PD=progressive disease. SPM=second primary malignancy. *The study was closed October, 2012, with 668 patients included; this SPM analysis used data from the first 436 patients. †Or younger and transplant ineligible. ‡WHO performance status 0–3 for patients <75 years and WHO performance status 0–2 for patients ≥75 years.

The seven trials randomly assigned 3254 newly diagnosed patients to treatment. Of these patients, 3218 (99%) received treatment and were included in this analysis (2620 had received lenalidomide and 598 had not). Patient characteristics are summarised in table 2.

Table 2. Patient characteristics

	Lenalidomide (n=2620)	No lenalidomide (n=598)	p value
Age, years	67 (58–73)	69 (61–75)	<0·0001
Age group			<0·0001
<55 years	448 (17%)	89 (15%)	..
55–64 years	718 (27%)	103 (17%)	..
65–74 years	985 (38%)	268 (45%)	..
75–84 years	438 (17%)	135 (23%)	..
≥85 years	31 (1%)	3 (1%)	..
Sex			0·779
Men	1381 (53%)	319 (53%)	..
Women	1239 (47%)	279 (46%)	..
Follow-up			
Patient-years	5663·0	1414·4	..
Median (IQR), months	25 (11–39)	28 (20–37)	0·023
Treatment			
High-dose intravenous melphalan	780 (30%)	229 (38%)	..
Low-dose oral melphalan	929 (35%)	153 (26%)	..
Lenalidomide plus dexamethasone	498 (19%)	0	..
Lenalidomide plus cyclophosphamide	413 (16%)	0	..
Low-dose oral melphalan plus thalidomide	0	216 (36%)	..

Data are median (IQR), or number (%), unless otherwise specified.

Solid and haematological second primary malignancies were documented in 105 (3%) of 3218 patients overall, in 87 (3%) of 2620 patients who had received lenalidomide, and 18 (3%) of 598 who had not. Cumulative incidence is shown in table 3; incidence of all second primary malignancies was significantly higher in patients who received lenalidomide than in those that did not (HR 1·55 [95% CI 1·03–2·34]; p=0·037). The cumulative incidences of second primary malignancies at 3 years and 5 years within each included trial are shown in table 1, and the main features of the documented second primary malignancies are shown in the appendix.

Table 3. Cumulative incidence of second primary malignancies, and death at 3 years and 5 years

	3-year cumulative incidence		5-year cumulative incidence	
	Lenalidomide	No lenalidomide	Lenalidomide	No lenalidomide
SPMs				
Overall	3·9% (3·0–4·9)	3·3% (1·7–4·9)	6·9% (5·3–8·5)	4·8% (2·0–7·6)
Solid	2·6% (1·8–3·3)	2·9% (1·4–4·4)	3·8% (2·7–4·9)	3·4% (1·6–5·2)
Haematological	1·4% (0·8–2·0)	0·4% (0·0–0·9)	3·1% (1·9–4·3)	1·4% (0·0–3·6)
Death				
All causes	23·5% (21·4–25·7)	24·8% (20·6–29·6)	47·0% (43·1–51·1)	68·2% (56·9–78·9)
Myeloma	13·3% (11·6–15·1)	14·6% (11·0–18·3)	25·6% (22·4–28·8)	36·3% (25·9–46·6)
Adverse events	6·7% (5·5–7·9)	6·4% (3·8–8·9)	9·8% (8·0–11·6)	19·2% (12·1–26·3)
SPMs	1·0% (0·5–1·5)	0·7% (0·0–1·5)	2·4% (1·3–3·5)	0·7% (0·0–1·5)

Data are % (95% CI). SPM=second primary malignancy.

Solid second primary malignancies were documented in 70 (2%) of 3218 patients overall (55 [2%] of 2620 patients who received lenalidomide vs 15 [3%] of 598 patients who did not). The median time to occurrence of solid second primary malignancies was 25 months (IQR 11–37) in the lenalidomide group, and 20 months (13–35) in the no lenalidomide group (appendix). Cumulative incidence is shown in table 3; incidence of solid second primary malignancies increased linearly over time, without significant differences between groups (HR 1·1 [95% CI 0·62–2·00]; p=0·72; figure 1) or between regimens (figure 1 and table 4). In a post-hoc analysis of the 2386 patients for whom lenalidomide treatment duration data were available, 51 (3%) of 1884 patients who received lenalidomide for less than 24 months had a solid second primary malignancy compared with 21 (4%) of 502 who received it for more than 24 months.

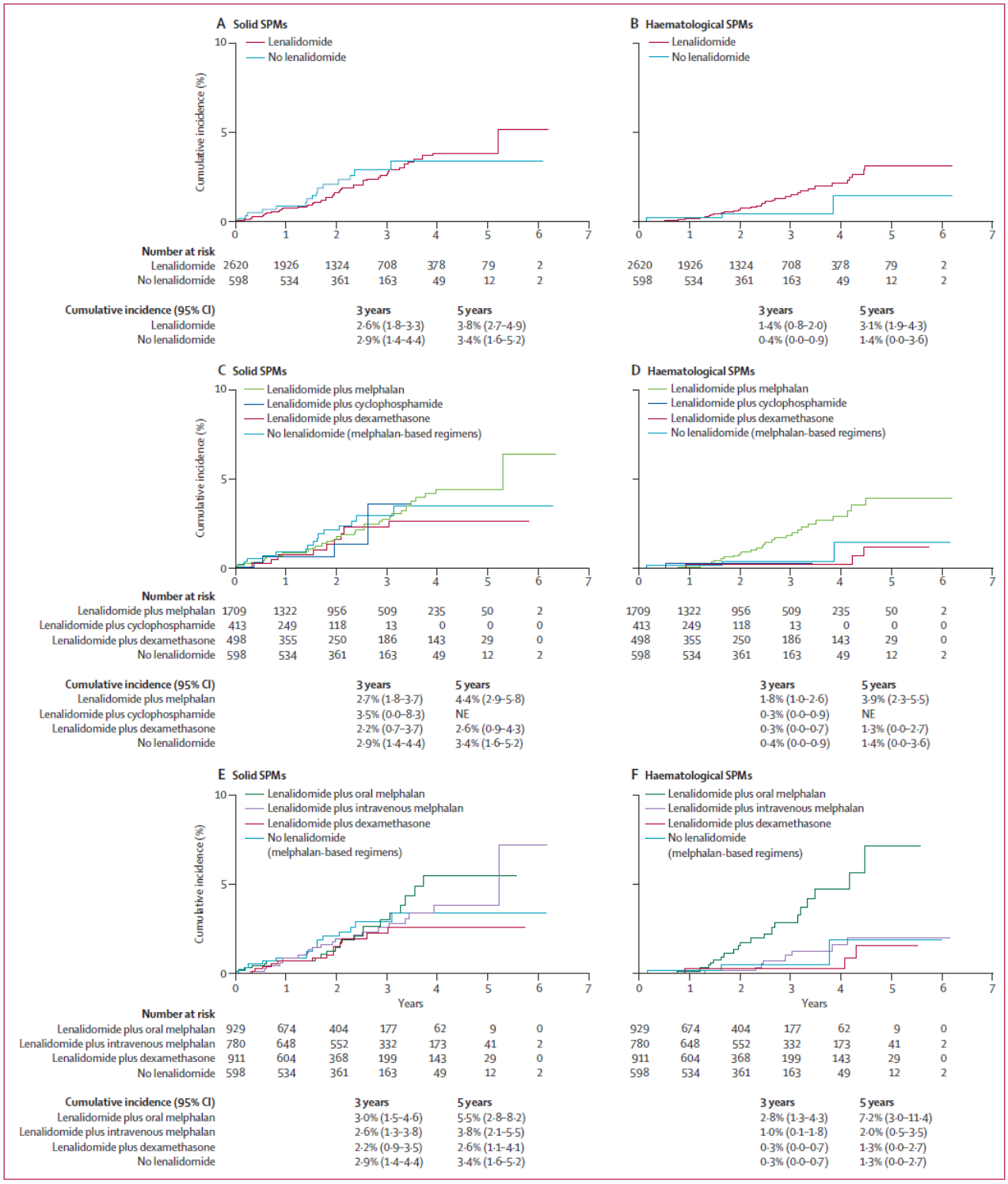

Figure 1. Cumulative incidence of solid and haematological second primary malignancies

Solid SPMs (A) and haematological SPMs (B) in patients who received lenalidomide and those who did not. Solid SPMs (C) and haematological SPMs (D) according to lenalidomide combination. Solid SPMs (E) and haematological SPMs (F) according to use of lenalidomide in combination with oral or intravenous melphalan. NE=not estimable. SPMs=second primary malignancies.

Table 4. Univariate and multivariate analyses of factors potentially affecting solid and haematological second primary malignancy development

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Solid				
No lenalidomide (melphalan-based regimens)	1	NA	1	NA
Lenalidomide plus dexamethasone	0·69 (0·41–1·17)	0·171	0·63 (0·43–0·92)	0·016
Lenalidomide plus intravenous melphalan	0·99 (0·57–1·73)	0·986	1·28 (0·68–2·40)	0·440
Lenalidomide plus oral melphalan	1·26 (0·85–1·88)	0·250	0·98 (0·70–1·38)	0·906
Lenalidomide plus cyclophosphamide	0·69 (0·17–2·28)	0·608	0·75 (0·13–4·30)	0·747
Age	1·03 (1·00–1·05)	0·022	1·04 (1·01–1·07)	0·018
Sex (male *vs* female)	1·34 (0·97–1·85)	0·079	1·38 (1·01–1·88)	0·043
Haematological				
No lenalidomide (melphalan-based regimens)	1	NA	1	NA
Lenalidomide plus dexamethasone	0·96 (0·34–2·68)	0·936	0·86 (0·33–2·24)	0·760
Lenalidomide plus intravenous melphalan	0·66 (0·10–4·28)	0·667	2·21 (0·49–10·02)	0·304
Lenalidomide plus oral melphalan	4·29 (1·66–11·11)	0·0027	4·86 (2·79–8·46)	<0·0001
Lenalidomide plus cyclophosphamide	1·15 (0·19–6·96)	0·876	1·26 (0·30–5·38)	0·754
Age	1·04 (0·98–1·11)	0·217	1·03 (0·98–1·09)	0·184
Sex (male *vs* female)	1·43 (1·01–2·01)	0·044	1·47 (1·02–2·12)	0·037

HR=hazard ratio. NA=not applicable.

The distribution of solid tumour types in the two groups was similar, with the exception of urinary tract tumours, which were diagnosed more frequently in patients who received lenalidomide than in those who did not (appendix). Non-invasive and non-melanoma skin cancer, including basal-cell or squamous-cell carcinomas, developed in 27 (1%) of 2620 patients who received lenalidomide, and nine (2%) of 598 who did not, and were excluded from the malignancy count because they are not invasive.

Haematological second primary malignancies were documented in 35 (1%) of 3218 patients overall (32 [1%] of 2620 who received lenalidomide vs three [1%] of 598 patients who did not). The median time to occurrence was 29 months (IQR 19–39) in the lenalidomide group and 20 months (2–46) in the no lenalidomide group (appendix). Cumulative incidence of haematological second primary malignancies is shown in table 3; in patients who received lenalidomide, incidence increased linearly over time, and was significantly higher than in those who did not receive lenalidomide (HR 3·8 [95% CI 1·15–12·62]; p=0·029; figure 1).

The difference in the proportion of haematological second primary malignancies reported between the lenalidomide and no lenalidomide groups might be mainly attributable to an increased incidence

in patients exposed to both lenalidomide and melphalan (rather than lenalidomide plus cyclophosphamide, or lenalidomide plus dexamethasone; figure 1). The incidence of haematological second primary malignancies was significantly higher in patients who received lenalidomide plus oral melphalan compared with those who received lenalidomide and high-dose intravenous melphalan (HR 3·3 [95% CI 1·46–7·46]; p=0·0041; figure 1).

In a multivariate analysis, patients who received lenalidomide and oral melphalan were more at risk of developing a haematological second primary malignancy than were those who received melphalan alone (table 4). Although not statistically significant, the risk was numerically higher in patients who received lenalidomide plus intravenous melphalan than in those who received melphalan alone; however, the risk did not increase when patients were given lenalidomide plus cyclophosphamide, or lenalidomide plus dexamethasone (table 4). Patients who received melphalan plus lenalidomide regimens were significantly more at risk of developing a second primary malignancy than were those who did not receive lenalidomide (HR 4·41 [95% CI 2·4–8·1]; p<0·0001). Lenalidomide used as induction therapy also increased risk compared with melphalan alone, although not significantly so (HR 2·76 [0·98–7·79]; p=0·055; appendix). In a post-hoc analysis of the 2386 patients for whom lenalidomide treatment duration data were available, the proportion of patients with haematological second primary malignancies was 16 (1%) of 1884 patients who received lenalidomide for less than 24 months, and eight (2%) of 502 patients who received it for more than 24 months.

After a median follow-up of 26 months (IQR 13–38), 688 (21%) of 3218 patients had died (545 [21%] of 2620 patients who received lenalidomide vs 143 [24%] of 598 in those who did not). In the 2620 patients in the lenalidomide group, 23 (1%) patients died due to development of second primary malignancies, 145 (6%) died due to adverse events, and 377 (14%) died due to disease progression. In the 598 patients who did not receive lenalidomide, three (1%) patients died due to development of second primary malignancies, 41 (7%) died due to adverse events, and 99 (17%) died due to myeloma progression. The second primary malignancies that led to death were 11 solid cancers (three lung, four intestine, three genital-urinary, one melanoma) and 12 haematological cancers (ten acute myelodysplastic syndrome and acute myeloid leukaemia, two lymphoblastic leukaemia) in the lenalidomide group, and three solid cancers (one adenocarcinoma, one intestine, one kidney) in the no lenalidomide group. The most common adverse events that led to death were similar in both groups: infections (54 [2%] of 2620 patients in the lenalidomide group vs 19 [3%] of 598 patients in the no lenalidomide group), cardiovascular events (46 [2%] vs five [1%]), venous thromboembolism (13 [0·5%] vs five [1%]), and bleeding (six [0·2%] vs five [1%]).

At 5 years, cumulative incidence of death due to second primary malignancies was higher in the lenalidomide group than in the no lenalidomide group, but not significantly so (HR 2·93 [95% CI 0·39–21·92]; p=0·30). In both groups, however, deaths due to myeloma and adverse events were higher than deaths due to second primary malignancies (table 3 and figure 2).

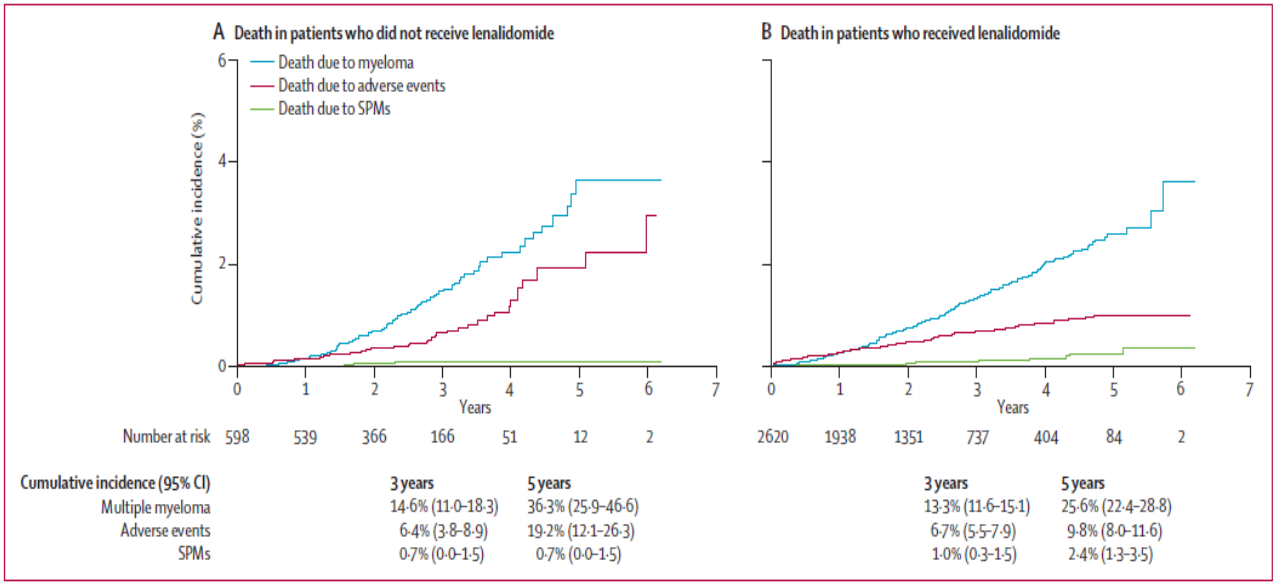

Figure 2. Cumulative incidence of death due to myeloma, adverse events, or second primary malignancies

In patients who did not receive lenalidomide (A) and in those who did (B). SPMs=second primary malignancies.

Discussion

This meta-analysis of pooled individual participant data from 3254 patients with newly diagnosed multiple myeloma shows that lenalidomide is associated with an increased rate of haematological second primary malignancies. We noted no difference in the incidence of solid tumours. The increased risk of developing haematological second primary malignancies was mainly driven by coexposure to lenalidomide and melphalan; we found no difference in the risk of developing haematological second primary malignancies between lenalidomide plus cyclophosphamide, or lenalidomide plus dexamethasone, compared with treatment with melphalan alone. Incidences of death due to myeloma or treatment-associated adverse events were substantially higher than those due to second primary malignancies, irrespective of treatment type.

Several mechanisms underlie development of second primary malignancies in myeloma survivors. The disease itself increases the risk of developing new malignancies: individuals with monoclonal gammopathy of undetermined significance not receiving any treatment are eight times more at risk, according to the standardised incidence ratio, of myelodysplastic syndrome and acute myeloid leukaemia than are the general population.[7] Host-related factors and ageing also increase the risk of developing second primary malignancies.[6 and 7] Genetic factors contribute to an individual's susceptibility to development of haematological second primary malignancies,[22] and myeloma treatment induces complex cytogenetic abnormalities, or deletions in chromosomes 5 and 7, suggesting a possible mutagenic contribution to second primary malignancy pathogenesis.[23 and 24] To the best of our knowledge, no genetic data are available on lymphoid second primary malignancies. Taking all this information together, data from cytogenetic analyses before and after development of second primary malignancies could have been useful to further investigate whether genomic instability exists in patients who develop haematological second primary malignancies. Unfortunately, this type of analysis was not prospectively planned in our protocol, and thus these data were not available. Since we found no difference in the incidence of solid tumours, the risk

factors for the development of these malignancies are likely to be similar to those in the general population.

In the current analysis, upfront coexposure to lenalidomide and oral melphalan was the main driver of increased risk of developing haematological second primary malignancies. These findings support previous findings that myelodysplastic syndrome and acute myeloid leukaemia might be associated with duration and cumulative dose of oral melphalan.[8] However, regarding intravenous administration, results of several studies suggest that conventional chemotherapy before ASCT might be a more probable contributing factor to the development of second primary malignancies than intravenous melphalan.[7, 9 and 23] In patients who received lenalidomide and melphalan, continuous lenalidomide slightly increased the risk of developing haematological second primary malignancies compared with melphalan alone, and prolonged duration of lenalidomide treatment slightly increased the risk of developing haematological second primary malignancies. This association between increased risk of developing second primary malignancies and duration of lenalidomide treatment needs to be confirmed with longer follow-up. Future trials should try to establish the optimal duration of maintenance therapy.

In our analysis, the risk of developing second primary malignancies did not increase when patients were treated with lenalidomide plus cyclophosphamide, nor with lenalidomide plus dexamethasone. This finding confirms previous reports showing that dexamethasone does not increase second primary malignancy risk, and that cyclophosphamide is less leukaemogenic than melphalan.[8 and 25] The absence of an increased risk of second primary malignancies with cyclophosphamide in our analysis contrasts with findings from studies in patients with non-Hodgkin lymphoma.[26 and 27] However, some important differences exist between studies that assessed the incidence of second primary malignancies in non-Hodgkin lymphoma and our analysis: patients with non-Hodgkin lymphoma received a higher dose of cyclophosphamide (1–1·5 g/m^2 for 4 days); different combinations of chemotherapeutic agents were used (eg, carmustine, etoposide, and cytarabine); cyclophosphamide is associated with total body irradiation (12–14 Gy); not all patients with non-Hodgkin lymphoma included in the analyses had newly diagnosed disease (some were at relapse); and some patients with non-Hodgkin lymphoma had received previous chemotherapy or radiotherapy. Therefore, trials in different disease areas and with different treatment strategies are difficult to compare. As such, conclusions and comparisons cannot be drawn.

Three recent trials showed that in transplant-ineligible patients aged 65 years or older, oral melphalan in combination with lenalidomide or bortezomib did not improve progression-free survival compared with lenalidomide or bortezomib in combination with cyclophosphamide, dexamethasone, or thalidomide, especially when lenalidomide or bortezomib was given as part of the treatment strategy.[18, 28 and 29] Although longer follow-up is needed, these data suggest that oral melphalan might not offer a substantial additional clinical benefit. The increased risk of developing second primary malignancies and long-term haematological toxicities with oral melphalan might be another limitation, especially in frail elderly patients.

Solid tumour types were equally distributed in the two groups with the exception of urinary tract tumours, which were diagnosed more frequently in the lenalidomide group, possibly as a result of the renal excretion of lenalidomide.

Cumulative incidences of death due to myeloma or to treatment-related adverse events were far higher than were those due to development of second primary malignancies. The adverse events that most frequently led to death were infection and cardiovascular events. A more proactive approach before treatment is started, such as a better assessment and definition of the frail

population, with the intention to reduce adverse events related to currently used therapies, might improve outcomes.

We should also consider the possible limitations of meta-analyses. Firstly, non-publication of studies can affect interpretation if they are not included in the analysis. In this respect, two ongoing, phase 3 studies (CC-5013-MM-020 [NCT00689936] and Myeloma XI [ISRCTN49407852]) are investigating patients with previously untreated myeloma receiving lenalidomide in various combinations. In the first of these unpublished trials, an increased risk of myelodysplastic syndrome and acute myeloid leukaemia was noted in patients receiving melphalan, prednisone, and thalidomide,[30 and 31] further supporting the more leukaemogenic role of melphalan compared with lenalidomide. No data are available for the second trial.

A second limitation is that a latency period typically occurs between exposure to a mutagenic agent and the development of a second primary malignancy. In our analysis, the occurrence of second primary malignancies first started to increase at about 18–20 months, and then increased linearly over time. However, two of the studies included in our meta-analysis had a median follow-up of less than 2 years, which might be too short a timeframe to appreciate the real incidence of second primary malignancies. However, we were able to detect a significantly increased risk of haematological second primary malignancies when lenalidomide and oral melphalan were combined. Furthermore, Chakraborty and colleagues[32] previously showed that the risk of haematological second primary malignancies was highest in the first year after diagnosis of multiple myeloma (HR 3·26 for the first 6 months and 4·37 for the next 6 months; $p<0·001$), and decreased in the subsequent 4 years (HR 1·49 for 1–5 years; $p=0·04$). A possible explanation for this finding is that exposure to cytotoxic agents could interact with a genetic predisposition to haematological cancers causing second primary malignancies to develop earlier than they would have done without exposure. As for solid second primary malignancies, two publications have previously shown a non-significant increase in the incidence of solid second primary malignancies (from 2% to 4%) with lenalidomide.[11 and 12] In our meta-analysis, we noted only a slight increase in solid second primary malignancies in patients who received lenalidomide plus intravenous melphalan. However, we clearly cannot draw any conclusions about the possible incidence of malignancies over longer-term follow-up—eg, at 10 years.

A third limitation of our analysis is that two studies identified by our searches were not analysed.[11 and 21] No data for second primary malignancies were available from one of these studies.[21] The other study showed that lenalidomide maintenance after ASCT was associated with an increased incidence of second primary malignancies compared with placebo (HR 2·24 [95% CI 1·10–4·55]; $p=0·03$).[11] Finally, recording of second primary malignancy incidence was not a prospectively defined endpoint in any of the included studies, and higher incidences of asymptomatic second primary malignancies have been reported when appropriate screening was used to prospectively detect early second primary malignancies.[33]

In conclusion, we report an increased incidence of haematological second primary malignancies in patients with newly diagnosed myeloma who received lenalidomide. The difference between study groups was driven mainly by treatment strategies that included both lenalidomide and oral melphalan. These data suggest that the future role of oral melphalan in combination with lenalidomide could be readdressed using alternatives, such as cyclophosphamide or alkylating-free combinations. The risk of dying from myeloma or treatment-related adverse events remains higher than the risk of death due to second primary malignancies.

Contributors

AP, SB, SKK, MB, KA, BB, PS, and PLM designed the study, and supervised its conduct and the data analysis. SKK, SU, AW, BvdH, PM, MO, MTP, SZ, AKN, AS, MAD, RH, MC, PR, SL, KA, BB, PS, and PLM recruited patients in the source studies and provided relevant data. SB, GL, and AL obtained and assembled the data. AE and GC did the statistical analysis. AP, SB, and GL analysed and interpreted the data. AP drafted the initial manuscript. All authors were given unrestricted access to the data, critically reviewed the manuscript drafts, approved the final version, and made the decision to submit for publication.

Declaration of interests

AP has received honoraria and consultancy fees from Amgen, Bristol-Myers Squibb, Celgene, Janssen, Millennium, and Onyx. SB has received honoraria from Celgene, Janssen, and Novartis, consultancy fees from Onyx, and has served on the advisory committee for Merck Sharp & Dohme. SKK received institutional clinical trial funding from Celgene, Novartis, Onyx, Millennium, Cephalon, Merck, and Abbott. AW has served on advisory boards for Celgene and Janssen-Cilag. AL has received honoraria from Celgene and Janssen-Cilag. PM has received honoraria and research funds from Celgene. MO received honoraria from Celgene, Janssen, Mundipharma, Novartis, and Amgen. MTP has received honoraria from Celgene and Janssen-Cilag, and served on an advisory committee for Bristol-Myers Squibb. SZ has served on advisory boards for Celgene, Millennium and Janssen, and has received research grants from Celgene and Janssen. MAD has received honoraria from Celgene, Ortho-Biotech, and Onyx. RH has received funding from Celgene. MC has received honoraria and served on speakers' bureaux for Janssen-Cilag and Celgene, and has received consultancy fees from Millennium, Bristol-Myers Squibb, Amgen and Onyx. PR is an advisory board member for Celgene. SL is a consultant for Millennium, Celgene, Novartis, Bristol-Myers Squibb, Onyx, Sanofi, and Janssen. MB has received research support, consultancy fees, and has served on an advisory board for Celgene and Janssen-Cilag. KA has consulted for Celgene, Onyx, Gilead, and Sanofi-Aventis, and is scientific founder of Acetylon, Oncopep. BB has received research funding from, and is a consultant to, Celgene and Millennium, and is co-inventor on patents and patent applications related to use of gene expression profiling in cancer medicine that have been licensed to Myeloma Health. PS has received research support from Celgene, Janssen, Onyx, and Millennium. PLM has served on advisory boards and received honoraria from Celgene, Millennium, and Janssen. All other authors declare that they have no competing interests.

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