Second primary malignancies in patients with haematological cancers treated with lenalidomide: a systematic review and meta-analysis

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TITLE PAGE

Lenalidomide's Effect on Second Primary Malignancies Varies Across Treatment Indications: A Systematic Review and Meta-analysis

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RESEARCH IN CONTEXT

Evidence before this study: Lenalidomide (LEN) has been shown to increase the incidence of second primary malignancies (SPM) when used as maintenance for multiple myeloma (MM) patients in the post-transplant setting. However, several new randomized studies utilizing LEN for other indications (such as follicular lymphoma) have not reported increased SPM in the LEN arm. We hypothesized that the effect of LEN on SPM is myeloma-specific. We searched Pubmed, Embase, CENTRAL, Europe Pubmed Central and Clinicaltrials.gov from 2004 to March 18th 2022 for published randomized controlled trials including at least one arm that was treated with LEN and one arm that was not. We used search terms representing the concepts of "lenalidomide" and "controlled clinical trial". Our search was restricted to studies published in English language. Our search yielded 38 eligible trials for meta-analysis with 14,058 patients, 18 of those trials in MM. We then conducted a meta-analysis to assess the relative risk (RR) of SPM with LEN use across various disease subtypes. The RR across all malignancies was 1.16 (95% CI, 0.96 – 1.39). However, there was heterogeneity across indications (P = 0.02). The RR when LEN was used for MM was 1.42 (95% CI, 1.09 – 1.84). There was no increase in SPM in lymphoma/chronic lymphocytic leukemia and myelodysplastic syndrome trials. In the setting of MM, LEN increased both solid and hematologic SPM, both in the no-transplant and post-transplant settings.

Added value of this study: To the best of our knowledge, this meta-analysis is the first to show that the effect of LEN on SPM is limited to MM patients. Furthermore, we note

that the effect of LEN on SPM is not specific to the post-transplant setting as we found that MM patients who do not receive transplant are still at higher risk of developing SPM with LEN use.

Implications of all available evidence: Our findings suggest that physicians should not hesitate to use LEN for indications other than MM because of apprehension about the risk of SPM. However, reports of B-ALL arising from CLL and MM treated with LEN should be taken into consideration. In the setting of MM, LEN continues to be a highly effective drug but there should be vigilance about increased incidence of hematologic and solid tumor SPM while on treatment.

SUMMARY

Background

Lenalidomide (LEN) has been standard therapy for multiple myeloma (MM) and other hematologic malignancies for over a decade. A meta-analysis published in 2014 identified an association between LEN and second primary malignancies (SPM) in the context of MM. However, newer randomized controlled studies using LEN for other indications have not reported increased SPM.

Methods

We performed a systematic review of randomized studies that reported SPM in patients treated with LEN. PubMed, Embase, CENTRAL, Europe PubMed Central and ClinicalTrials.gov were searched from 2004 through March 18th 2022. Randomized studies with at least one LEN arm and one non-LEN arm were selected. Summary data were extracted by two reviewers independently and verified by a third reviewer. We then conducted a meta-analysis to assess the relative risk (RR) of SPM with LEN use across various disease subtypes using a random-effects model. We chose random effects for the primary analysis because of anticipated heterogeneity between different diseases but then we used fixed effects for stratified meta-analysis of MM studies. Risk of bias was assessed with the PROTECT tool. The study was registered with PROSPERO (CRD42021257508).

Findings

Our search yielded 38 eligible trials for meta-analysis with 14,058 patients, 18 of those trials in MM. The RR across all malignancies was 1.16 (95% CI, 0.96 – 1.39). However, there was heterogeneity across indications (*P* = .02). The RR when LEN was used for MM was 1.42 (95% CI, 1.09 – 1.84). There was no increase in SPM in lymphoma/chronic lymphocytic leukemia and myelodysplastic syndrome trials. In the setting of MM, LEN increased both solid and hematologic SPM, both in the no-transplant and post-transplant settings. From the 38 studies, 21 studies have low risk for bias, 12 studies have unclear risk of bias, and 5 studies have high risk of bias.

Interpretation

LEN-induced SPM occur exclusively in MM patients. This risk is for both hematologic and solid tumor SPM regardless of the patients receiving a transplant before. To our knowledge, this is the first meta-analysis that details the risk of SPM with LEN across indications and the first to show a connection between LEN and SPM in MM patients that have not received a prior autologous transplant.

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INTRODUCTION

Lenalidomide (LEN) is an immunomodulatory, antineoplastic agent that has revolutionized the treatment of multiple hematological malignancies over the past two decades. Since its introduction nearly 15 years ago, LEN has remained one of the most commonly prescribed drugs for multiple myeloma (MM), and its use has led to a significant improvement in overall survival in this disease.[1] In addition to MM, the efficacy of LEN is established in myelodysplastic syndrome (MDS) and follicular lymphoma (FL), and it is now widely used as a first-line treatment option for these indications.[2,3] It is also used off-label for both relapsed diffuse large B-cell lymphoma (DLBCL) and systemic light-chain amyloidosis.[4,5] The efficacy of LEN is mediated by modulation of the activity of the ubiquitin E3 ligase, Cereblon, and subsequent induction of preferential degradation of key signaling proteins. In MM and B-cell malignancies, degradation of IKZF1 and IKFZ3 leads to cellular arrest.[6] In myelodysplastic syndrome (MDS) with heterozygous loss of chromosome 5q, LEN hinders proliferation via Cereblon-mediated degradation of CK1α.[7]

In the early 2010s, three clinical trials evaluating the use of LEN in MM reported an increased incidence of second primary malignancies (SPM).[8-10] A subsequent patient-level meta-analysis of seven MM trials confirmed these findings, noting the risk to be highest for second hematologic malignancies, especially in patients who had also received melphalan.[11] Another meta-analysis of maintenance studies post-autologous transplant also showed an increased risk for second hematologic and solid tumor malignancies.[12] However, subsequent studies of SPM in patients with MM, that did not receive melphalan, did not corroborate the findings of earlier studies.[13] Furthermore, the

evidence of association of LEN use with a higher risk of SPM in diseases other than MM is even weaker. For example, the RELEVANCE trial for follicular lymphoma showed a comparable risk of SPM among follicular lymphoma patients treated with LEN and rituximab compared to bendamustine and rituximab.[3] Given these contradictory findings across a spectrum of diseases and a significant amount of new data from clinical trials in various hematological malignancies and solid tumors, we performed a systematic review and meta-analysis across all malignancies that utilize LEN as a treatment modality. This systematic review was reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement.[14]

METHODS

Selection Criteria and Search Strategy

Any randomized trials with at least one LEN arm and at least one non-LEN arm qualified for further review. This strategy ensured that an appropriate control population was included in the analysis. Clinical trials in the pediatric population (< 18 years old) were excluded. For studies that SPM information was not available in the published literature or in ClinicalTrials.gov the authors contacted the investigators and/or the sponsors. Studies that did not collect SPM data were excluded from the analysis. Considering that long follow-up is needed to detect SPM, we further excluded trials with less than 12 months of follow-up. The initial protocol excluded studies with patients exposed to LEN before randomization. However, once data collection was initiated, the authors realized that this strategy would exclude a significant number of trials that had previously reported an increase in SPM, which would render the analysis biased. Thus,

LEN exposure before randomization was eventually allowed. The data were recorded in Microsoft Excel. A PROSPERO protocol (CRD42021257508) defining our *a priori* plan was submitted before the search for the studies was initiated.

Studies were identified by searching the bibliographic databases PubMed, Embase.com, the Cochrane Central Register of Controlled Trials (CENTRAL; Wiley), Europe PubMed Central and Clinicaltrials.gov. A health sciences librarian (MLK) designed the PubMed search string and then translated it for use in Embase and CENTRAL (**Appendix A**). For all three databases, a search string was created consisting of natural language terms and controlled vocabulary, e.g., Medical Subject Headings (MeSH), representing the search concept of "lenalidomide". In PubMed and Embase.com, the search string was combined (using the Boolean operator AND) with filters for identifying randomized controlled trials developed by the Cochrane Collaboration.[15] The searches were run on March 18th 2022, and available limits to English language studies were applied. The new drug approval application for LEN was accepted by the FDA in 2004; therefore, a publication date limit of January 1, 2004, to present was applied to all search results. In addition to bibliographic databases, a search was run in Europe Pubmed Central on March 22nd 2022 and was limited to preprint manuscripts only. A search on ClinicalTrials.gov for completed trials containing the terms “lenalidomide” and “randomized” was completed on the same day. The results of the database searches were downloaded to an EndNote (version X9.3.3) library. Duplicate records were removed using the Amsterdam Efficient Deduplication Method and a process developed by Bremer and colleagues.[16,17]

Data Analysis

The initial broad screening (title and abstract) was conducted by three reviewers using DistillerSR. Each study was initially screened by only one reviewer for relevance to the topic. Any questions regarding study eligibility were raised to the other two reviewers, and the final decision was made by majority rule (two out of three). The studies that qualified from the first screen underwent a second full-text screen from at least two reviewers independently. After the final studies were selected, the data were extracted by two reviewers independently. A third reviewer confirmed the extracted data with source studies.

The following data were extracted: regimens used, duration of LEN treatment, number of patients in the LEN and non-LEN arms, SPM in LEN and non-LEN arms (including solid and hematologic subcategories), type of disease treated, post-transplant or no-transplant status, median age, overall survival difference and median follow-up. Our primary outcome of interest was any SPM occurrence per study arm. SPM were defined as any malignancies that developed after randomization. However, any malignancies reported as likely to have been present but not discovered before randomization were not excluded from the analysis. Some studies reported SPM at the subject level; for subjects who developed more than one SPM event, only one event per subject was considered for the analysis. For multi-arm trials, the LEN arms or the non-LEN arms were combined in one group and the continuous data were averaged based on the number of patients in each arm. There were no cluster or crossover trials, but some trials had patients that received LEN after progression as LEN is a very active MM medication. An adjustment for these patients was not possible so all data was analyzed

as intention-to-treat. One study, MDS-004, was functionally a crossover trial (80% of patients crossed-over at 16 weeks) and was excluded from the analysis.

We performed a meta-analysis using the risk ratio (RR) of developing SPM in the arm treated with LEN compared to the non-LEN arm as the primary outcome. As the populations treated were expected to be highly heterogeneous (several different malignancies), we decided *a priori* to use the random-effects model. Furthermore, we chose the restricted maximum likelihood method over the DerSimonian and Laird method, given the risk of bias associated with the latter.[18] For the stratified meta-analysis of MM studies we used the fixed-effects model (the Mantel-Haenszel method) as this population was relatively homogeneous.

We also planned *a priori* to perform a subgroup analysis, via stratification or meta-regression, to assess the effect of the following variables on the outcomes: i) type of primary malignancy (solid tumor versus hematologic) ii) the median age of patients, iii) median follow-up duration, iv) the no-transplant versus post-transplant status of the patients, v) median cumulative LEN dose, vi) duration of LEN treatment, and vii) treatment with single-agent LEN (steroids allowed) vs. combination with other agents. As not all studies reported these variables, the subgroup analysis was performed only in studies that included the specific variable. Unfortunately, once data extraction was underway, it was found that median cumulative LEN dose was not available for most studies. Thus, the exploratory analysis for this variable was not performed. Meta-regression on all studies was used to assess the impact of continuous variables (age, follow-up, duration of treatment). Stratification was used to delineate the LEN effect in MM patients and a χ^2 test was used for sub-group comparison.

To investigate any possible bias in our results we performed several sensitivity analyses. First, we performed the primary analysis using a fixed-effects model. Furthermore, as death is a competing event with SPM, we run our primary analysis only with studies that did not have a survival benefit. Finally, we conducted our primary analysis including only low-risk bias studies.

The risk of bias was assessed by two independent reviewers using the PROTECT checklist, a risk-of-bias tool designed for meta-analysis of adverse events.[19] The funnel plot and the Egger test were used to assess publication bias. We assessed the overall quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. Heterogeneity was assessed with the I^2 statistic and 50% or more was defined as substantial heterogeneity based on the Cochrane Handbook for Systematic Reviews of Interventions.[20] All analyses were performed using STATA/SE 17.0, College Station, Texas.

Role of funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report.

RESULTS

The study selection is shown in **Fig. 1**. After the screening, a total of 38 studies were included comprising 14,058 patients.[3,11,21-58] Studies that were excluded due to short follow-up, SPM not being collected, and other reasons are detailed in **Sup. Table 1** and **Sup. Table 2**.[59-87] The study characteristics are shown in **Table 1**. We would like

to note here that for several studies some missing data were provided directly by the investigators or were obtained by clinical study reports.[21,27,29,32,39,43,51,53,55,57,71,72]. The average risk ratio across all diseases treated with LEN was 1.16 (95% CI, 0.96 – 1.39, **Fig. 2**). The analysis of RR based on malignancy type was significant (χ^2 P = .02). The RR of developing SPM was higher in MM (RR 1.42, 95% CI, 1.09 – 1.84) compared to Lymphoma/CLL (RR 0.90, 95% CI, 0.76 – 1.08) and MDS (RR 0.96, 95% CI, 0.23 – 3.97), as can be seen in **Fig. 2**. The overall I^2 statistic was 42.2%. Based on the meta-regression analysis, age (P = 0.329), median duration of treatment (P = 0.126) and duration of follow-up (P = 0.733) was not associated with a higher likelihood of SPM.

Based on prior knowledge of LEN use in MM being associated mainly with an increased incidence of hematological malignancies, we sought to further explore the effect of LEN on subtypes of SPM. This analysis excluded two studies because of missing data on subcategories of SPM. LEN was found to be associated with an increased risk of solid tumor SPM in MM patients (RR 1.30, 95% CI, 1.06 – 1.60, **Fig.3A**). Regarding second hematologic malignancies, LEN use did not reach statistical significance (RR 1.23, 95% CI, 0.91 – 1.66, **Fig.3B**). The RR of second hematologic malignancies was likely heavily influenced by the FIRST trial due to its large size (n= 1,613) and the fact that the non-LEN arm of this trial used melphalan, a drug with known association with increased hematologic SPM. Importantly, the LEN arm did not include melphalan. Indeed, after the FIRST was excluded from the analysis, the RR for hematological SPM became statistically significant (RR 1.56, 95% CI, 1.11 – 2.19). Furthermore, based on prior reports that showed an increase in SPM mainly in the post-transplant MM setting, we performed a stratified analysis based on transplant status

(which omitted three studies due to the mixed population in terms of prior transplant). We found that both the RR for SPM in the post-transplant MM setting (RR 1.90, 95% CI, 1.44 – 2.52, **Fig.4**) and the RR for SPM in the no-transplant setting (RR 1.25, 95% CI, 1.04-1.51, **Fig.4**) were significant. Similar to before, the no-transplant setting was heavily influenced by the FIRST trial which compared LEN to a known carcinogenic drug (melphalan). When the FIRST trial was excluded, the RR for the no-transplant setting was higher (RR 1.48, 95% CI, 1.18 – 1.85). A subgroup of the no-transplant setting is smoldering MM. When we analyzed only the two studies of smoldering MM, we found similar results (RR 3.96, 95% CI, 1.36 – 11.53). Finally, subgroup analysis on studies that utilized LEN as monotherapy (including LEN in combination with dexamethasone) vs. LEN as part of combination show a difference in RR between the groups ($P = 0.04$) likely because of the absence of active treatment control group in most trials with monotherapy LEN (**Sup.Fig.1**).

To verify the results of our primary analysis, we proceeded with several sensitivity analyses. First, an analysis using the fixed-effects model was conducted for all 38 studies, which yielded results similar to those obtained with the random-effects model; however, this methodology pushed the average RR of SPM with LEN use across all malignancies to significance (RR 1.19, 95% CI, 1.06 – 1.33, subgroup $P < .01$, **Sup.Fig. 2**). Because death is a competing event to the development of SPM and could bias the analysis, a sensitivity analysis was performed using only those studies that did not show an overall survival benefit. This analysis yielded similar results to our primary analysis (average RR 1.10, 95% CI, 0.90 – 1.33, subgroup $P = .01$, **Sup.Fig. 3**). Finally,

an analysis of only low-risk studies yielded the same results (average RR 1.15, 95% CI, 0.93 – 1.42, subgroup *P* = 0.02, **Sup. Fig. 4**)

In terms of publications bias, the funnel plot (**Sup.Fig. 5**) did not indicate possible bias which was confirmed by Egger's test (*P* = 0.6247). Finally, the risk of bias for the studies analyzed is presented in **Sup.Table 3**. The assessments for the individual studies are all available in **Appendix B**. Most of the studies were low risk, but there were 12 studies of unclear risk and 5 studies of high risk, mostly because of different attrition rates between the randomized groups. Although the difference in attrition could have biased the studies, the absolute difference in attrition was small and thus it is unlikely that the overall result was influenced significantly. In terms of the GRADE scale, certainty of evidence was high for the Lymphoma/CLL category, high for the Multiple Myeloma category and low for the MDS category (due to imprecision) (**Sup. Table 4**).

DISCUSSION

Over the past decade, there has been an increasing concern among the oncological community about SPM second to LEN use, and reporting on SPM has become standard in all LEN trials over time. However, despite the considerable data available from LEN trials and over a decade of real-world experience, the association between LEN use and the development of SPM in different clinical settings remains unclear. Our meta-analysis, which included 38 studies with over 14,000 patients, aimed to address this question. We showed that the risk of developing SPM with LEN use occurred exclusively in MM and not in other malignancies. Furthermore, this risk encompasses both solid tumor and hematologic malignancies regardless of prior

transplant status. However, solids tumor SPM in this study including non-melanoma skin cancers and hematologic SPM included myeloproliferative disorders, thus some of these SPM are not life-threatening.

The factors that can link LEN use and carcinogenesis are likely diverse. These include age, follow-up, duration of treatment and type of underlying disease. Our meta-regression analysis suggested that older age and increased follow-up did not increase the RR within the range of the studies included. The follow-up result is not surprising as we included only studies with at least 12 months of follow-up. The duration of treatment was close to achieving significance (P = 0.126). We examined possible non-linear effect of duration of treatment with quartile regression, which also did not meet statistical significance. This result should be taken with caution as meta-regression uses summary and not individual patient data and thus is much less powerful to detect this effect. On the other side, the type of underlying disease appears to be significant (P = .02), as shown by the increase in the risk of SPM in patients with MM but not MDS or lymphoma/CLL.

This phenomenon is difficult to explain. A recent publication describes that LEN treatment leads to expansion of TP53-mutant hematopoietic stem and progenitor cells likely due to degradation of Ck1α.[88] MM itself is a known risk factor for hematologic SPM[89] and the alkylating agents such as melphalan administered during autologous stem cell transplant is another known risk for the development of hematological SPM.[90] It is possible that the tumor microenvironment of MM and the mutational burden induced by melphalan create a field effect that is exacerbated by LEN. However, the above arguments do not fully explain why there is not such an effect in other diseases, why

solid tumor SPM are increased as well and why this phenomenon is also seen in the no-transplant setting. A possible theory is that the genetic polymorphisms that increase the probability of developing MM also potentiate the LEN effect on SPM.[91] Another explanation would be that due to initial reports of SPMs in MM there was increased surveillance and reporting in MM studies but not in other diseases.

It is important to note, that although the most common hematologic SPM reported in clinical trials were MDS and AML, there are several reports of B-ALL developing while on LEN maintenance both in the MM and the CLL settings.[92-99] This type of B-ALL seems to not be clonally related to the underlying MM and to have a high incidence of TP53 mutations.[94,97] Intriguingly, there is a report of remission after stopping LEN without any B-ALL-directed treatment .[99]

Our study had several strengths. Firstly, the high number of studies and patients in our analysis allowed us to calculate the relative risk with high precision. Furthermore, all the studies included in the analysis were controlled, allowing comparison between patients who received LEN and those who did not receive LEN in the context of the same study. This comparison gives great insight to the clinicians, who can use this information to weigh LEN against non-LEN-based treatments, an opportunity that is lacking in treatment versus observation models. This study is also the first meta-analysis of LEN-induced SPM that includes LEN trials for indications other than MM, namely, lymphoma and MDS. Inclusion of the trials for these non-myeloma LEN indications has highlighted the myeloma-specific SPM-inducing effect of LEN, which will be reassuring to clinicians treating non-myeloma hematologic malignancies. Finally, we

also made the novel discovery that LEN increases the risk of SPM in MM patients in the no-transplant setting as well.

Our meta-analysis also has several limitations. The reporting of second primary malignancies was inconsistent throughout the studies analyzed. Certain studies reported only aggregate SPM and did not report subcategories i.e., solid and hematologic malignancies. This deficiency in reporting could have introduced bias in the subgroup analysis as the trials that lacked this reporting had to be omitted. We also relied on the published manuscripts for reporting accuracy and did not obtain any patient-level data from the trials analyzed. In addition, the control arms of the studies were quite different from each other. Some studies had control arm treatment protocols with a high tendency to cause SPM (such as melphalan) whereas others had just observation or placebo. Thus, the interpretation of the RR is very different for each study. The majority however, twenty-three out of thirty-eight studies, had comparator arms that did not include agents responsible for second malignancies. Finally, because death is a competing event with the development of SPM, the overall survival benefit seen in multiple studies in the LEN treatment arm could have confounded the risk of developing SPM. We addressed this concern with a sensitivity analysis, which included only the trials without any overall survival benefit, which yielded results similar to the primary analysis.

In conclusion, this is the first meta-analysis showing that LEN does not increase the risk of SPM when used for indications other than MM. However, there are case reports of B-ALL arising from CLL and MM in the context of LEN treatment which need to be taken into consideration. In the case of MM, LEN use is associated with an

increased risk of both solid tumor and hematologic SPM, both in the no-transplant and post-transplant setting. However, continuous LEN treatment has shown significant improvement in overall survival in MM patients, and the therapeutic benefit of LEN remains greater than the impact of SPM. Nevertheless, clinicians should acknowledge the risk of LEN-induced solid tumor and hematologic SPM and apply it on an individual patient basis when making therapeutic decisions.

CONTRIBUTORS

K.S. screened studies, extracted data, and wrote the manuscript. J.F. screened studies and verified extracted data. ML.K. performed the literature search. J.Y. oversaw the statistical analysis of the study. M.B., J.R.J. and N.S. provided critical insight on the methodology of the study and the manuscript. K.L. conceptualized the question, screened studies, extracted data, analyzed data, and wrote the manuscript. All authors had full access to the all the data in the study and had final responsibility for the decision to submit for publication. K.S, J.F. and K.L. accessed and verified the data before the final analysis.

DECLARATION OF INTERESTS

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DATA SHARING

All data included in this manuscript are already public.

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