A review of second primary malignancy in patients with relapsed or refractory multiple myeloma treated with lenalidomide

Short title: SPMs in patients with RRMM treated with lenalidomide

Meletios A. Dimopoulos,1 Paul G. Richardson,2 Nancy Brandenburg,3 Zhinuan Yu,3 Donna M. Weber,4 Ruben Niesvizky,5 and Gareth J. Morgan6

1Department of Clinical Therapeutics, University of Athens School of Medicine, Athens, Greece; 2Dana-Farber Cancer Institute, Boston, MA; 3Celgene Corporation, Summit, NJ; 4MD Anderson Cancer Center, Houston, TX; 5Weill Medical College, Cornell University, New York, NY; and 6Institute of Cancer Research, Royal Marsden Hospital, London, UK

Correspondence: Professor Meletios A. Dimopoulos, Department of Clinical Therapeutics, University of Athens School of Medicine, Alexandra Hospital, 80 Vas. Sofias, Athens 11528, Greece; e-mail: mdimop@med.uoa.gr.
Tel.: +30 210 3381541; Fax: +30 210 3381511

This work was first presented at the 13th International Myeloma Workshop, Paris, France, May 3-6, 2011; the 47th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 4-8, 2011; and the 16th Congress of the European Hematology Association, London, UK, June 9-12, 2011.
Abstract

In a retrospective pooled analysis of 11 clinical trials of lenalidomide-based therapy for relapsed/refractory multiple myeloma (RRMM; N=3846), the overall incidence rate (IR, events per 100 patient-years) of second primary malignancies (SPMs) was 3.62. IR of invasive (hematologic and solid tumor) SPMs was 2.08, consistent with the background incidence of developing cancer. In a separate analysis of pooled data from pivotal phase 3 trials of RRMM (N=703), the overall IR of SPMs was 3.98 (95% CI, 2.51-6.31) with lenalidomide/dexamethasone and 1.38 (95% CI, 0.44-4.27) with placebo/dexamethasone; IRs of non-melanoma skin cancers were 2.40 (95% CI, 1.33-4.33) and 0.91 (95% CI, 0.23-3.66), respectively; IRs of invasive SPMs were 1.71 (95% CI, 0.86-3.43) and 0.91 (95% CI, 0.23-3.66), respectively. The risk of SPMs must be taken into account before initiating lenalidomide treatment. In the context of the observed survival benefit in RRMM patients, the benefit/risk profile of lenalidomide/dexamethasone remains positive.
Introduction

Lenalidomide in combination with dexamethasone (Len/Dex) is a standard treatment option for patients with multiple myeloma (MM) who have received ≥ 1 prior therapy. Pooled data from the phase 3 registration trials (MM-009 and MM-010)\(^1,2\) showed that Len/Dex significantly prolonged overall survival (OS; 38 vs 31.6 months; \(P = .045\)) compared with placebo plus dexamethasone (Placebo/Dex) after a median follow-up of 48 months.\(^3\) The survival benefit was observed despite the fact that 48% of patients assigned to Placebo/Dex crossed over to receive Len/Dex at progression or study unblinding.\(^3\) Lenalidomide-based therapy is associated with significant progression-free survival (PFS) benefits in patients with newly diagnosed (ND) MM\(^4-9\) and maintenance lenalidomide is associated with an emerging OS benefit.\(^9\)

Recently, an increased incidence of invasive second primary malignancies (SPMs) has been observed with lenalidomide (7.6%) compared with controls (2.9%) in patients with NDMM receiving lenalidomide in combination with melphalan\(^5\) or as long-term maintenance therapy following high-dose melphalan with autologous stem cell transplantation (ASCT)\(^8,9\) (Celgene data on file, October 2011).

This analysis investigated the incidence of SPMs in patients with relapsed or refractory (RR) MM treated with lenalidomide-based therapy in clinical trials.

Methods

The pooled analysis (N=3846) was based on 11 manufacturer-sponsored studies of lenalidomide-based therapy for RRMM (MM-007, -008, -009, -010, -012, -014, -016, -017, -018, -019, and -022).\(^1,2,10-13\) An additional analysis was conducted on patients randomized to Len/Dex (n=353) or Placebo/Dex (n=351) in the MM-009 and MM-010 trials.\(^1,2\) Treatment continued until disease progression or unacceptable toxicity. For study MM-009, enrollment began in February 2003; patients were on study or were followed up for survival after study
discontinuation (extended follow-up phase) until July 2008, when the number of deaths was reached for the final analysis of OS per protocol. For study MM-010, enrollment began in September 2003; the follow-up (either on-study or post-study) was until March 2008. Serious adverse events were thoroughly collected in the safety database during the treatment phase of both trials. Safety information was not collected during the extended follow-up phase.

SPMs were defined using the Medical Dictionary for Regulatory Activities (MedDRA) terms found under the System Organ Class “Neoplasms”. Incidence rates (IRs; events per 100 patient-years) and their confidence intervals (CIs) were calculated. Patient-year was defined as the time in years from the first dose to SPM onset for patients with an SPM, and the time from the first dose to the last dose for patients without an SPM. Overall IRs include noninvasive, non-melanoma skin carcinomas and invasive SPMs. Invasive SPMs are defined as hematologic or solid tumor malignancies. Background rates of SPMs were determined using the Surveillance, Epidemiology, and End Results (SEER) database. Per the SEER definition, background rates of SPM did not include non-melanoma skin cancers and in situ malignancies. The data were analyzed by Celgene Corporation and all authors had access to the primary data.
Results and Discussion

Pooled analysis

For the 3846 patients included in the pooled analysis, the median age was 64 years (range, 29-92 years). The proportion of patients aged ≥ 75 years was 14%. Only 263 patients (7%) received lenalidomide monotherapy; the remaining patients received Len/Dex. The median duration of lenalidomide-based therapy was 5 months (range, 0.03-58 months).

The overall IR of SPMs, including noninvasive skin cancers, was 3.62. A total of 52 invasive SPMs were reported, including MDS (n=5), AML (n=1), B-cell lymphomas (n=2), and solid tumors (n=44). Notably, cases of Hodgkin’s lymphoma and B-cell ALL were not reported. The IR of invasive SPMs was 2.08 (Table 1). This IR is comparable to that expected for older adults, according to SEER data (2.1 per 100 patient-years for patients aged ≥ 65 years).14

In the pooled analysis, 313 patients received lenalidomide-based treatment for ≥ 24 months. Based on the available follow-up data, median OS has not been reached for these patients; survival was 94% at 36 months and 86% at 48 months. The IR of SPMs in this patient group was 2.35 (95% CI, 1.6-3.6) and was comparable to the IR in patients with shorter duration of treatment (Table 1). No B-cell malignancies were reported in these patients.

MM-009 and MM-010 analysis

A second analysis was conducted on 703 patients who constituted the safety population of MM-009 and MM-010. The median age was 63 years (range, 33-86 years). The median duration of treatment with Len/Dex was 9.8 months (range, 0.0-58.3 months). Invasive SPMs in the Len/Dex group included solid tumors (n=6) and MDS (n=2, FAB refractory anemia with ringed sideroblasts, and refractory anemia with complex cytogenetics [del(5); del(7), t(11;17), del(20)]). SPMs in the Placebo/Dex group were solid tumors (n=2). Noninvasive
and non-melanoma skin cancers, which included basal cell or squamous cell carcinomas, developed in 11 patients in the Len/Dex group and 2 patients in the Placebo/Dex group.

The median follow-up for SPMs was significantly longer for lenalidomide-treated patients (10.4 months) versus placebo-treated patients (5.3 months) because of the extended time to disease progression associated with lenalidomide treatment. The total on-study observation time was correspondingly longer for patients in the Len/Dex arm (467 person-years) than those in the Placebo/Dex arm (218.6 person-years). The overall IR of SPMs with Len/Dex was 3.98 (95% CI, 2.51-6.31) compared with 1.38 (95% CI, 0.44-4.27) with Placebo/Dex. The observed difference in IR was attributed to the increased occurrence of non-melanoma skin carcinomas in the Len/Dex arm (2.40 [1.33-4.33] vs 0.91 [0.23-3.66] with Placebo/Dex).

The IR of invasive SPMs was 1.71 (95% CI, 0.86-3.43) in the Len/Dex group and 0.91 (95% CI, 0.23-3.66) in the Placebo/Dex group. These IRs were not significantly different between the treatment groups, and were consistent with the expected incidence of invasive cancer in the general population aged 60-64 years. Age-specific IRs of invasive cancers across all sites identified through the SEER program are 1.26 among persons aged 60-64 years; 1.74 among persons aged 65-69 years; 2.09 among persons aged 70-74 years; 2.39 among persons aged 75-79 years; 2.46 among persons aged 80-84 years; and 2.18 among persons aged ≥ 85 years.14

There was no significant difference in time to invasive SPM between treatment groups (1-45 months and 4-25 months in the Len/Dex and Placebo/Dex groups, respectively; HR = 1.45 (95% CI, 0.29-7.09, log-rank test \( P = .649 \)) (Figure 1).

Long-term safety analysis identified 64 patients (18%) treated with Len/Dex who achieved PFS ≥ 2 years after median treatment duration of 46 months (range, 11–58 months). The 3-year OS was 94%. The IR of second solid tumors was 1.8 and that of non-melanoma skin cancer was 2.3; there were no reports of second hematologic malignancies. Similarly, retrospective analysis of patients with NDMM treated with lenalidomide and dexamethasone in combination with clarithromycin (BiRD regimen) until disease progression
did not show an increased rate of SPMs and there were no reports of MDS/AML after 6 years of follow-up. These data indicate that long-term treatment with Len/Dex is not associated with an increased risk of SPMs.

Adverse events were thoroughly collected in the treatment phase of the studies; however, once patients discontinued the active treatment, collection of adverse-event data was not mandated. As patients who discontinued the study were followed for survival only, this retrospective review detected no cases of SPM in either treatment group during the extended follow-up period of the MM-009/MM-010 trials. Thus, a major limitation of our analysis is that the reliable period for detecting SPMs occurred only while patients were receiving lenalidomide.

MM is associated with an increased risk of certain SPMs such as AML and non-Hodgkin's lymphoma, and an association with renal cell carcinoma has also been reported. The risk of SPMs seems to be primarily confined to younger patients (aged < 70 years at diagnosis), but the low number of SPM cases did not allow for a meaningful analysis in the present study. Exposure to melphalan has been associated with the development of AML, although disease-related factors also appear to play a role. Additionally, immune suppression associated with SCT may increase the risk of SPMs. Noteworthy, most patients included in the analysis had received ≥ 1 therapies with known carcinogenic potential (prior alkylators, non-alkylator leukemogenic agents) or SCT. It is difficult to reconcile the currently known mechanisms of action of lenalidomide (tumoricidal and immunomodulatory) with the generation of SPMs. Further studies are required to evaluate whether lenalidomide can potentiate the carcinogenic properties of certain agents when used in sequence.

In summary, an increase of the overall IR of SPMs was observed in clinical trials of patients with RRMM receiving Len/Dex compared to controls. The observed difference in IR was attributed to the increased occurrence of non-melanoma skin carcinomas in the Len/Dex arm. Patients, especially those with prior history of cancer, should be carefully
evaluated for SPMs before and during lenalidomide treatment using standard cancer screening. Bone marrow samples should be evaluated for pre-existing MDS at baseline. Patients diagnosed with SPMs should receive appropriate treatment, as the risk of death is much higher than the risk of developing a SPM in MM. In the context of the observed survival benefit in RRMM patients, the benefit/risk profile of lenalidomide/dexamethasone remains positive.

Acknowledgments

The authors received editorial support in the preparation of this manuscript provided by Anna Georgieva, MD, PhD, of Excerpta Medica, funded by Celgene Corporation. The authors were fully responsible for content and editorial decisions for this paper.

Authorship

Contribution: M.A.D. designed the research and wrote the paper. M.A.D., P.G.R., N.B., D.M.W., R.N. and G.J.M. collected data, edited the paper, and performed the research. Z.Y. performed statistical analysis and interpreted the data. All authors reviewed and commented on the draft of the report and approved the final manuscript.

Conflict-of-interest disclosure: All studies included in these analyses were sponsored by Celgene Corporation. Databases were provided by and analyzed by Celgene Corporation. M.A.D. has been a consultant for and received honoraria from Celgene Corporation. P.G.R. has been a member of advisory committees for Millennium Pharmaceuticals, Celgene Corporation, Novartis Pharmaceuticals, Johnson & Johnson, and Bristol-Myers Squibb. N.B. and Z.Y. are employees of Celgene. D.M.W. has received grant support and honoraria from Celgene Corporation. G.J.M. received payment for lectures including service on speakers’ bureaus from Novartis, Celgene Corporation, and Ortho Biotech, as well as payment for the
development of educational presentations and reimbursement of costs to attend scientific meetings from Celgene Corporation.
References


National Cancer Institute, Bethesda, MD. NIH Publ. No. 05-5302, 2006. Available at:


25. European Medicines Agency concludes that benefit-risk balance of Revlimid remains positive. Press release September 23, 2011. Available at:
Table 1. Incidence of SPMs in patients treated with lenalidomide-based therapy

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>&lt; 12 months (n = 3149)</th>
<th>≥ 12 months (n = 697)</th>
<th>≥ 18 months (n = 450)</th>
<th>≥ 24 months (n = 313)</th>
<th>≥ 36 months (n = 130)</th>
<th>All patients (N = 3846)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPM IR</td>
<td>2.03</td>
<td>2.12</td>
<td>2.13</td>
<td>2.35</td>
<td>2.45</td>
<td>2.08</td>
</tr>
<tr>
<td>Patient-years</td>
<td>1281.20</td>
<td>1463.35</td>
<td>1175.78</td>
<td>937.28</td>
<td>490.52</td>
<td>2744.55</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.38-2.98</td>
<td>1.49-3.01</td>
<td>1.44-3.15</td>
<td>1.55-3.56</td>
<td>1.39-4.31</td>
<td>1.60-2.60</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; IR, incidence rate per 100 patient-years; SPM, second primary malignancy.
**Figure 1.** Kaplan-Meier analysis of time to invasive SPM in studies MM-009 and MM-010.

Analyses are based on the safety population (n = 703).

CI indicates confidence interval; HR, hazard ratio; SPM, second primary malignancy.
A review of second primary malignancy in patients with relapsed or refractory multiple myeloma treated with lenalidomide