In a retrospective pooled analysis of 11 clinical trials of lenalidomide-based therapy for relapsed/refractory multiple myeloma (MM; \( N = 3846 \)), 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 relapsed or refractory MM (\( N = 703 \)), the overall IR of SPMs was 3.98 (95% confidence interval [CI], 2.51-6.31) with lenalidomide/dexamethasone and 1.38 (95% CI, 0.44-4.27) with placebo/dexamethasone; IRs of nonmelanoma 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 relapsed or refractory MM patients, the benefit/risk profile of lenalidomide/dexamethasone remains positive. (Blood. 2012;119(12): 2764-2767)

**Introduction**

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

Recently, an increased incidence of invasive secondary primary malignancies (SPMs) has been observed with lenalidomide (7.6%) compared with controls (2.9%) in patients with newly diagnosed MM receiving lenalidomide in combination with melphalan\(^4\) or as long-term maintenance therapy after high-dose melphalan with autologous stem cell transplantation\(^5,8\) (Celgene data on file, October 2011).

This analysis investigated the incidence of SPMs in patients with relapsed or refractory 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 relapsed or refractory MM (MM-007, MM-008, MM-009, MM-010, MM-012, MM-014, MM-016, MM-017, MM-018, MM-019, and MM-022).\(^1,2,10-13\) An additional analysis was conducted on patients randomized to lenalidomide/dexamethasone (\( n = 353 \)) or placebo plus dexamethasone (\( n = 351 \)) 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 after 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 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, nonmelanoma 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 nonmelanoma skin cancers and in situ malignancies.\(^14\) The data were analyzed by Celgene Corporation, and all authors had access to the primary data.
Table 1. Incidence of SPMs in patients treated with lenalidomide-based therapy

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>SPM IR</th>
<th>Patient-years</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 12 mo (n = 3149)</td>
<td>2.03</td>
<td>1281.20</td>
<td>1.38-2.96</td>
</tr>
<tr>
<td>⩾ 12 mo (n = 697)</td>
<td>2.12</td>
<td>1463.35</td>
<td>1.49-3.01</td>
</tr>
<tr>
<td>⩾ 18 mo (n = 450)</td>
<td>2.13</td>
<td>1175.78</td>
<td>1.44-3.15</td>
</tr>
<tr>
<td>⩾ 24 mo (n = 313)</td>
<td>2.35</td>
<td>937.28</td>
<td>1.55-3.56</td>
</tr>
<tr>
<td>⩾ 36 mo (n = 130)</td>
<td>2.45</td>
<td>490.52</td>
<td>1.39-4.31</td>
</tr>
<tr>
<td>All patients (N = 3846)</td>
<td>2.08</td>
<td>2744.55</td>
<td>1.60-2.60</td>
</tr>
</tbody>
</table>

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 75 years of age or older was 14%. Only 263 patients (7%) received lenalidomide monotherapy; the remaining patients received lenalidomide/dexamethasone. 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 myelodysplastic syndrome (MDS; n = 5), acute myeloid leukemia (AML; n = 1), B-cell lymphomas (n = 2), and solid tumors (n = 44). Notably, cases of Hodgkin lymphoma and B-cell acute lymphoblastic leukemia were not reported. The IR of invasive SPMs was 2.08 (Table 1). This IR is comparable with that expected for older adults, according to SEER data (2.1 per 100 patient-years for patients aged ⩾ 65 years).

In the pooled analysis, 313 patients received lenalidomide-based treatment for more than or equal to 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 with 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 lenalidomide/dexamethasone was 9.8 months (range, 0.0-58.3 months). Invasive SPMs in the lenalidomide/dexamethasone group included solid tumors (n = 6) and MDS (n = 2). French-American-British classification: refractory anemia with ringed sideroblasts, and refractory anemia with complex cytogenetics (del(5), del(7), t(11;17), del(20)). SPMs in the placebo plus dexamethasone group were solid tumors (n = 2). Noninvasive and nonmelanoma skin cancers, which included basal cell or squamous cell carcinomas, developed in 11 patients in the lenalidomide/dexamethasone group and 2 patients in the placebo plus dexamethasone 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 lenalidomide/dexamethasone arm (467 person-years) than those in the placebo plus dexamethasone arm (218.6 person-years).

The overall IR of SPMs with lenalidomide/dexamethasone was 3.98 (95% CI, 2.51-6.31) compared with 1.38 (95% CI, 0.44-4.27) with placebo plus dexamethasone. The observed difference in IR was attributed to the increased occurrence of nonmelanoma skin carcinomas in the lenalidomide/dexamethasone arm (2.40 [1.33-4.33] vs 0.91 [0.23-3.66] with placebo plus dexamethasone).

The IR of invasive SPMs was 1.71 (95% CI, 0.86-3.43) in the lenalidomide/dexamethasone group and 0.91 (95% CI, 0.23-3.66) in the placebo plus dexamethasone 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 60 to 64 years of age. Age-specific IRs of invasive cancers across all sites identified through the SEER program are 1.26 among persons 60 to 64 years of age, 1.74 among persons 65 to 69 years of age, 2.09 among persons 70 to 74 years of age, 2.39 among persons 75 to 79 years of age, 2.46 among persons 80 to 84 years of age, and 2.18 among persons 85 years of age or older.

There was no significant difference in time to invasive SPM between treatment groups: 1 to 45 months and 4 to 25 months in the lenalidomide/dexamethasone and placebo plus dexamethasone groups, respectively (hazard ratio = 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 lenalidomide/dexamethasone who achieved progression-free survival more than or equal to 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 nonmelanoma skin cancer was 2.3; there were no reports of second hematologic malignancies. Similarly, retrospective analysis of patients with newly diagnosed MM treated with lenalidomide and dexamethasone in combination with clarithromycin 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 lenalidomide/dexamethasone 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

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). HR indicates hazard ratio.
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 lymphoma, and an association with renal cell carcinoma has also been reported.

The risk of SPMs seems to be primarily confined to younger patients (<70 years of age 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.

In addition, immune suppression associated with SCT may increase the risk of SPMs. Noteworthy, most patients included in the analysis had received more than or equal to one therapy with known carcinogenic potential (prior alkylators, nonalkylator leukemogenic agents) or SCT. It is difficult to reconcile the currently known mechanisms of action of lenalidomide (tumorcidal 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 conclusion, an increase in the overall IR of SPMs was observed in clinical trials of patients with relapsed or refractory MM receiving lenalidomide/dexamethasone compared with controls. The observed difference in IR was attributed to the increased occurrence of nonmelanoma skin carcinomas in the lenalidomide/dexamethasone 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 preexisting MDS at baseline. Patients diagnosed with SPMs should receive appropriate treatment, as the risk of death is much higher than the risk of developing an SPM in MM. In the context of the observed survival benefit in relapsed or refractory MM patients, the benefit-risk profile of lenalidomide/dexamethasone remains positive.

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Authorship

Contributions: 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, performed the research, and edited the manuscript; Z.Y. performed statistical analysis and interpreted the data; and all authors reviewed and commented on the draft of the report and approved the final manuscript.

Conflict-of-interest disclosure: 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. R.N. declares no competing financial interests.

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References


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