Original Study

# Risk of Rash Associated With Lenalidomide in Cancer Patients: A Systematic Review of the Literature and Meta-analysis

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## Abstract

**Lenalidomide (Len) is indicated for treatment of multiple myeloma (MM) in combination with dexamethasone (Dex) and as single agent in myelodysplastic syndromes (MDS). We conducted a systematic review and meta-analysis of the literature to determine the incidence and risk of developing rash. Our findings have demonstrated that lenalidomide is associated with a significant risk of rash in cancer patients, that is independent of dose, tumor type, or combination with dexamethasone.**

**Background:** Lenalidomide is indicated for treatment of multiple myeloma in combination with dexamethasone and as a single agent in myelodysplastic syndromes. The incidence and risk of rash has been inconsistently reported. **Materials and Methods:** We conducted a systematic review and metaanalysis of the literature to determine the incidence and risk of developing rash. Relevant studies were identified from PubMed and abstracts presented at American Society of Clinical Oncology annual meetings. Incidence, relative risk, and 95% confidence intervals were calculated. **Results:** Ten trials were available for analysis, and the overall incidence of all-grade and high-grade rash was 27.2% and 3.6%, respectively. Lenalidomide was associated with increased risk of all-grade rash ($P < .001$). **Conclusion:** Further studies for prevention and treatment of this toxicity are needed to minimize effect on quality of life and dose intensity.

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## Introduction

The introduction of thalidomide and lenalidomide into standard therapy has had a positive effect on survival in patients with multiple myeloma (MM) and myelodysplastic syndromes (MDS). Although ongoing studies continue to refine the optimal use of these agents with regard to combination, sequence, and duration of therapy, they now have established roles in the management of patients with MM.[1] Lenalidomide is an oral bioavailable analogue of thalidomide belonging to a class of immunomodulatory drugs. Compared with thalidomide, it has been reported to have more potent immunomodulatory, antiangiogenic, and antitumor activities and a better safety profile.[2-4] Lenalidomide (Revlimid) has been approved for use in MM, in patients who have received at least 1 previous therapy, at 25 mg orally once a day in combination with dexamethasone 40 mg and for MDS associated with a 5q deletion, with or without additional cytogenetic abnormalities, as a single agent at 10 mg orally daily. It was originally developed to overcome some of the adverse events (AEs) associated with thalidomide, and provide more potent inhibition of tumor necrosis factor (TNF)-$\alpha$[5]; lenalidomide has direct tumoricidal and immunomodulatory effects in MM.[6]

Lenalidomide can inhibit malignant cell growth via antiangiogenesis, apoptosis, and direct effects on the immune system and tumor microenvironment. In chronic leukemia it has been shown that lenalidomide down-regulates prosurvival cytokines, such as interleukin (IL)-6 and TNF-$\alpha$, stimulates natural killer and T-cell proliferation, leading to elevated inhibitory cytokines, such as IL-2 and interferon-$\gamma$. Additionally, it seems to upregulate B-cell activation

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markers, such as CD40 and CD86, inhibit stromal cell protection of leukemia cell survival, and modify the Akt phosphorylation signaling pathway, which plays a key survival role in cancer.[2,6]

The use of this agent resulted in a decreased AEs, especially dermatologic toxicities, compared to thalidomide,[7,8] however, distinct AEs have been reported during lenalidomide therapy. The primary AEs are hematologic, including neutropenia and thromboembolic events.

Additionally, dermatologic AEs, such as rash have also been reported, although the exact mechanism by which lenalidomide causes skin rash is not clearly understood.[7,9] The incidence of rash has not been systematically investigated and varies between studies. The recognition and subsequent management of skin toxicities are critical issues, because they can lead to morbidity and compromise the efficacy of treatment because of dose reductions or discontinuation. We conducted a systematic review of the literature to identify published clinical trials of lenalidomide, and performed a meta-analysis to determine the overall incidence and risk of developing rash in patients receiving lenalidomide in monotherapy or in combination with dexamethasone.

## Materials and Methods

### *Data Source*

An independent search of citations was conducted using the PubMed database (1998-July 2011). The key word "lenalidomide" was used in all database searches. Additionally, we searched abstracts containing the term "lenalidomide" that were presented at the American Society of Clinical Oncology (ASCO) Annual Meetings from 2004 through 2011 to further identify relevant clinical trials. An independent search using the Web of Science database (Institute for Scientific Information) was also conducted to identify additional relevant studies. We reviewed each citation and only the complete or most recent report of a clinical trial was included when duplicate publications of the trial were identified. The current package insert of lenalidomide (Food and Drug Administration [FDA] label v.03-12-12) was also reviewed for related information. When data were not available, efforts were made to contact the investigators and the manufacturer of lenalidomide. We extracted details on study characteristics, treatment information, results, and safety profiles from all cited trials.

### *Study Selection*

To ensure practical significance, we determined the risk of rash in cancer patients receiving lenalidomide at FDA-approved dose levels. Thus, phase I clinical trials have been excluded from analyses because of variable dose levels. Trials that met the following criteria were selected for final analysis: (1) prospective phase II and III clinical trials in cancer patients; (2) assignment of participants to treatment with lenalidomide as a single agent at a dose of 10 or 25 mg orally once daily and in combination with dexamethasone at a dose of 25 mg orally daily (dexamethasone at a dose of 40 mg); (3) data available regarding the incidence of rash. Clinical trials investigating solid tumors were excluded.

### *Clinical End Points*

Clinical end points were extracted from a safety profile for each trial. This included studies that reported the incidence of rash grade 1 to 4 (all-grade) or grade 3 and above (high-grade). They were recorded according to versions 2.0 or 3.0 of the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute.[10] Both versions are very similar regarding the grading of rash as described: grade 1, macular or papular eruption or erythema without associated symptoms; grade 2, macular or papular eruption or erythema with pruritus or other associated symptoms or localized desquamation or other lesions covering $< 50\%$ of the body surface area (BSA); grade 3, severe generalized erythroderma or macular, papular, or vesicular eruption or desquamation covering $> 50\%$ BSA; grade 4, generalized exfoliative, ulcerative, or bullous dermatitis; and grade 5, death. We included the incidence of all patients with rash grade $\geq 1$.

### *Statistical Analysis*

All statistical analyses were done using version 2 of the Comprehensive MetaAnalysis program (Biostat). The number of patients with all-grade and high-grade rash were extracted from cited trials as already described. For each trial, the incidence of rash was calculated and the 95% confidence interval (CI) was derived. The relative risk (RR) of rash among patients assigned to lenalidomide was calculated and compared only with patients assigned to control treatment in the same trial. For metaanalysis, the fixed-effects model (weighted with inverse variance) and the random-effects model were considered. For each metaanalysis, the Cochran Q statistic was first calculated to assess the heterogeneity of the included trials. For $P$ values $< .1$, the assumption of homogeneity was deemed invalid, and the random-effects model was used. Otherwise, results from the fixed-effects model and the random-effects model were evaluated. If the results of the fixed-effects and the random-effects model were similar, only fixed-effects model results were reported. A 2-tailed $P$ value of $< .05$ was considered statistically significant.

## Results

### *Search Results*

Both database searches yielded a total of 147 potentially relevant clinical studies on lenalidomide (Figure 1). The PubMed search identified 105 articles, of which 96 were excluded per stated criteria after reviewing the publication. Nine original studies, including randomized controlled and single-arm phase II and III trials, satisfied the search criteria and were included in final analysis.[11-19] The search of ASCO abstracts yielded 42 potentially relevant citations, of which only 1 met inclusion criteria after reviewing each abstract.[20] Overall, 10 prospective clinical trials were included in the final analysis (Table 1).[11-18,20]

### *Patients*

Data from a total of 737 patients in 10 clinical trials qualified for analysis, of which 350 patients received lenalidomide monotherapy (10 mg: n = 189; 25 mg: n = 161) and 387 lenalidomide in combination with dexamethasone (25 mg/40 mg). There were 2 randomized controlled trials (RCTs) that used placebo.[12,17] Rash was not listed as a preexisting condition in any of the analyzed trials. Underlying malignancies included MM,[12,14,17] myelodisplastic syndrome,[15] chronic lymphocytic leukemia,[11,20] myelofibrosis with