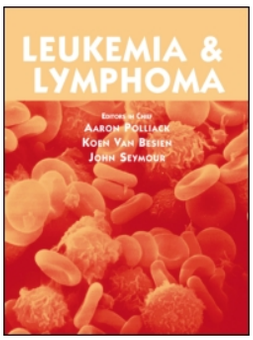

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Safety profile of lenalidomide in patients with lower-risk myelodysplastic syndromes without del(5q): results of a phase 3 trial

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ABSTRACT

The safety profile of lenalidomide use in lower-risk myelodysplastic syndromes (MDS) patients with del(5q) is well-established, but less is known in non-del(5q) patients. We provide safety data from a randomized, phase 3 trial evaluating lenalidomide in 239 patients with lower-risk non-del(5q) MDS ineligible/refractory to erythropoiesis-stimulating agents (ESAs). Compared with placebo, lenalidomide was associated with a higher incidence of grade 3–4 treatment-emergent adverse events (TEAEs; 86% vs. 44%), but not risk of infection ($p = .817$) or hemorrhagic events ($p = 1.000$). Grade 3–4 non-hematologic TEAEs were rare (the incidence of grade 3–4 pneumonia, e.g. was 5.6% in the lenalidomide group and 2.5% in the placebo group). Common grade 1–2 non-hematologic TEAEs did not require dose modifications or treatment discontinuation. Acute myeloid leukemia and second primary malignancies incidence was similar across treatment groups. Lenalidomide had a predictable and manageable safety profile in lower-risk non-del(5q) MDS patients ineligible/refractory to ESAs. Guidance on managing lenalidomide-related TEAEs is provided to help maintain patients on therapy to achieve maximum clinical benefit.
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Introduction

Myelodysplastic syndromes (MDS) represent a heterogeneous group of bone marrow failure disorders. The disease course in MDS varies widely, and outcomes of individual patients can be estimated using risk stratification scores such as the International Prognostic Scoring System (IPSS) [1] and the revised IPSS [2]. Patients with higher-risk disease have relatively short survival, whereas those with lower-risk disease have longer survival but face poor quality of life due to cytopenias [3,4]. Anemia remains the main therapeutic challenge in most patients with lower-risk MDS [3]. Lenalidomide is approved for the treatment of patients who have transfusion-dependent anemia due to IPSS lower-risk MDS associated with a deletion 5q cytogenetic abnormality (del[5q]). In this subgroup, lenalidomide yields red blood cell (RBC) transfusion independence (RBC-TI) in 56–67% of patients [5,6]. For patients without del(5q), the first line of therapy is erythropoiesis-stimulating agents (ESAs), with or without granulocyte colony-stimulating factor; however, ESA therapy is rarely effective if serum erythropoietin (EPO) levels exceed 500 mU/ml [7,8]. For patients who are ineligible for or become refractory to ESAs, treatment options are very limited [8] and outcomes are relatively poor [9].

Recently, the efficacy and safety of lenalidomide were evaluated in patients with RBC transfusion-dependent (RBC-TD), lower-risk, non-del(5q) MDS who were ineligible for or refractory to ESAs [10]. In this phase 3, randomized, placebo-controlled, double-blind, multicenter study (MDS-005), a statistically significant and clinically relevant proportion of lenalidomide-treated patients achieved RBC-TI lasting $\geq$8 weeks compared with placebo (26.9% vs. 2.5%, respectively; $p < .001$). Patients with serum EPO levels at screening $\leq$500 mU/ml were more likely to achieve RBC-TI $\geq$8 weeks than patients with EPO levels >500 mU/ml.

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Supplemental data for this article can be accessed here.

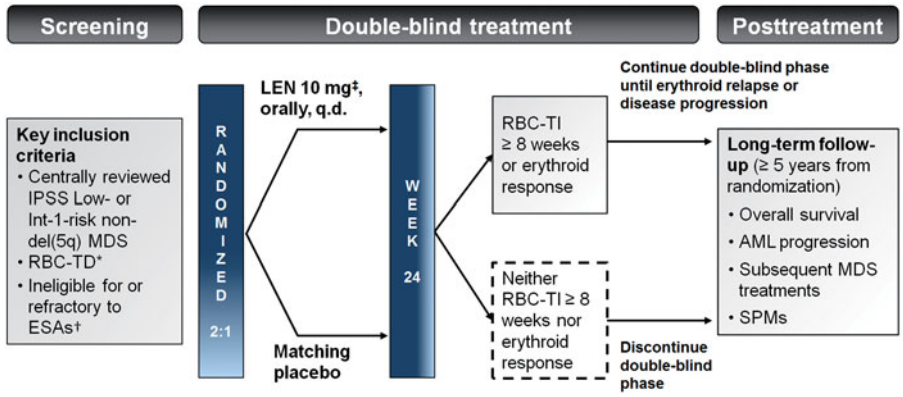

Figure 1. MDS-005 study design. AML: acute myeloid leukemia; ESA: erythropoiesis-stimulating agent; EPO: erythropoietin; Int: intermediate; IPSS: International Prognostic Scoring System; LEN: lenalidomide; MDS: myelodysplastic syndromes; q.d.: once daily; RBC-TD: red blood cell transfusion-dependent; RBC-TI: red blood cell transfusion-independence; rhEPO: recombinant human EPO; SPM: second primary malignancy. *Defined as an average transfusion requirement of ≥2 units packed RBCs/28 d and no 8 consecutive weeks without RBC transfusions within the 16 weeks immediately prior to randomization. †Defined as RBC-TD despite ESA treatment of ≥40,000 units/week rhEPO for 8 weeks or equivalent dose of darbepoetin, or serum EPO >500 mU/ml without prior ESA treatment. ‡LEN 5 mg for patients with creatinine clearance 40–60 ml/min.

The primary type of adverse event (AE) associated with lenalidomide is myelosuppression, including neutropenia and thrombocytopenia [5,10]. Among patients with del(5q) MDS, a reduction in neutrophil or platelet count has been associated with a higher likelihood of achieving RTC-TI, suggesting that lenalidomide-induced cytopenias may be a surrogate marker of clonal suppression [11].

Here, we characterize the safety profile of lenalidomide in patients with non-del(5q) MDS based on data from the phase 3 MDS-005 trial and provide recommendations for the effective management of treatment-emergent adverse events (TEAEs).

Methods

Trial design

Full details of patient eligibility criteria and study design have been described previously [10]. Briefly, RBC-TD patients with IPSS low- or intermediate-1-risk MDS without del(5q) who were ineligible for or refractory to ESAs were centrally randomized (2:1) to lenalidomide 10 mg once daily or matching placebo in 28-d cycles (Figure 1). Patients with creatinine clearance 40–60 ml/min received lenalidomide 5 mg once daily. Patients who achieved RBC-TI ≥8 weeks or erythroid response [12] by week 24 continued treatment until erythroid relapse, disease progression, unacceptable toxicity, or consent withdrawal. The study was approved by individual Institutional Review Boards of participating centers and conducted according to the Declaration of Helsinki. Written informed consent was obtained from all patients before enrollment.

Safety assessment and statistical methods

Safety was a prespecified endpoint of the MDS-005 study [10]. Data for all patients who received at least one dose of any study drug were included in the safety analysis. Additional methods are described in further detail in the online supplement.

Results

Baseline patient characteristics

A total of 239 patients were randomized; 160 received lenalidomide and 79 received placebo. Baseline characteristics for patients who received one or more study doses (safety population) are presented (Supplementary Table S1). Baseline characteristics were generally comparable across treatment groups. Overall, 67.8% were male, 61.5% had serum EPO levels ≤500 mU/ml, and 70.3% had ≥15% ring sideroblasts. The median age was 71 years in the lenalidomide group and 70 years in the placebo group. Approximately, 79% of patients had received prior ESA therapy.

Incidence of TEAEs

The median duration of treatment exposure was 164 d (range 7.0–1158.0) for patients in the lenalidomide group and 168 d (range 14.0–449.0) for patients in the placebo group. Grade 1–2 TEAEs were reported in 96.9% of patients in the lenalidomide group and 92.4% in the placebo group (Supplementary Table S2). The most common grade 1–2 TEAEs in the

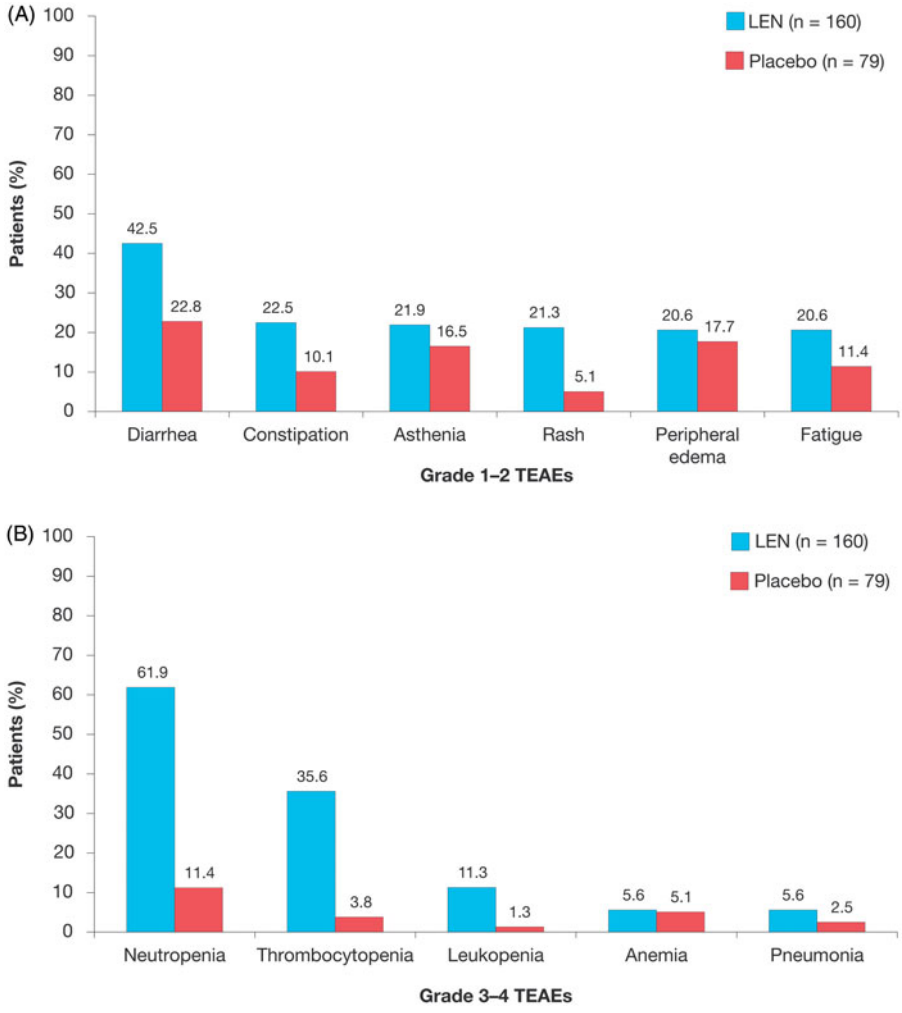

Figure 2. Most commonly occurring TEAEs according to randomized treatment group. (A) Grade 1–2 AEs in ≥20% of lenalidomide-treated patients. (B) Grade 3–4 TEAEs in ≥5% of lenalidomide-treated patients. LEN: lenalidomide; TEAE: treatment-emergent adverse event.

lenalidomide group were diarrhea (42.5% vs. 22.8% in the placebo group), constipation (22.5% vs. 10.1%), asthenia (21.9% vs. 16.5%), rash (21.3% vs. 5.1%), peripheral edema (20.6% vs. 17.7%), and fatigue (20.6% vs. 11.4%; Figure 2(A)).

Grade 3–4 TEAEs were reported in 86.3% of patients in the lenalidomide group and in 44.3% of patients in the placebo group (Supplementary Table S3). The most common grade 3–4 TEAEs in the lenalidomide group were neutropenia (61.9% vs. 11.4% in the placebo group) and thrombocytopenia (35.6% vs. 3.8%; Figure 2(B)). When these events were analyzed according to first onset during cycles 1–7, the per-cycle incidence in the lenalidomide group ranged from 13.3% to 32.9% for grade 3–4 neutropenia (Figure 3(A)), and from 4.9% to 15.7% for grade 3–4 thrombocytopenia (Figure 3(B)). The incidence of grade 3–4 neutropenia peaked during cycle 3 (32.9%) and decreased thereafter (Figure 3(A)), whereas the incidence of grade 3–4 thrombocytopenia peaked during cycle 2 (15.7%) and decreased thereafter (Figure 3(B)). The median time to first occurrence of neutropenia (any grade) was 57 d (range 1–541) and 29 d (range 1–169) for patients in the lenalidomide and placebo groups, respectively (data not shown). The median time to first occurrence of thrombocytopenia (any grade) was 49 d (range 1–543) and 69 d (range 26–182), respectively.

The incidence of grade 3–4 pneumonia was 5.6% in the lenalidomide group and 2.5% in the placebo group ($p = .35$; Supplementary Table S3). Overall rates of infection were similar between the lenalidomide and placebo arms: 83 of 160 patients (51.9%) and 34 of 79 patients (43.0%) experienced infections in the lenalidomide and placebo arms, respectively. In patients who developed neutropenia (any grade), no significant difference was seen in the incidence of infection between the lenalidomide and placebo groups (30.5% vs. 25.9%; $p = .817$; data not shown).

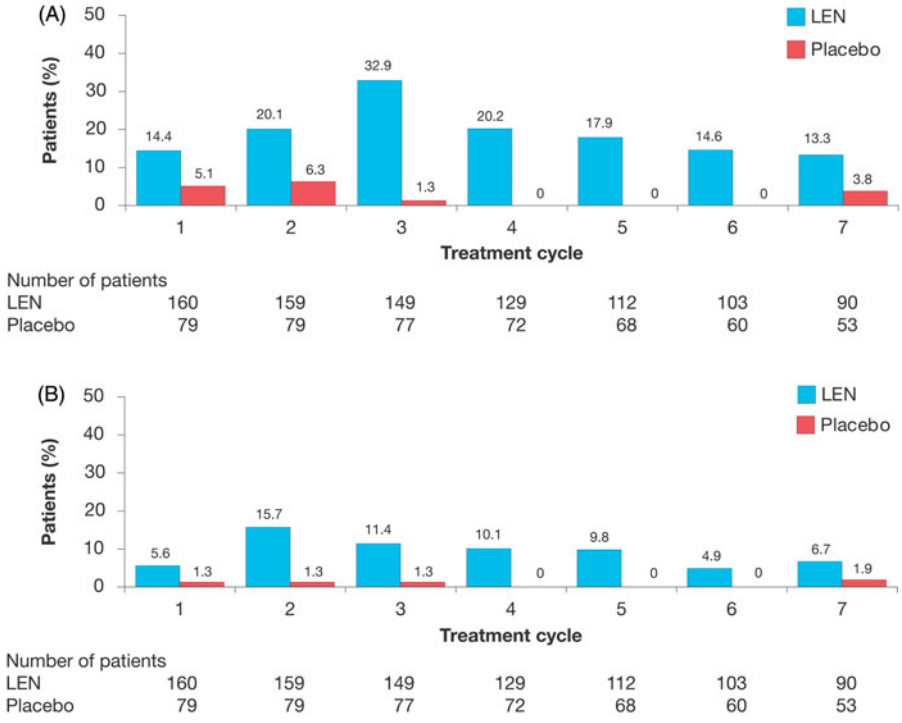

Figure 3. Incidence of new-onset grade 3–4 hematologic TEAEs by treatment cycle. (A) Neutropenia. (B) Thrombocytopenia. LEN: lenalidomide; TEAE: treatment-emergent adverse event.

Similarly, rates of infection in patients without neutropenia did not differ significantly between treatment groups (56.3% vs. 40.4%; $p = .182$). Overall, 33 of 160 patients (20.6%) and 8 of 79 patients (10.1%) experienced hemorrhage in the lenalidomide and placebo arms, respectively. In patients with thrombocytopenia (any grade), the frequency of hemorrhagic events did not significantly differ between the lenalidomide and placebo groups (22.4% vs. 14.3%, respectively; $p = 1.000$); similar results were seen in patients without thrombocytopenia (12.9% vs. 9.7%, respectively; $p = .627$).

Grade 3–4 deep-vein thrombosis (DVT) was reported in three patients (1.9%) in the lenalidomide group; no DVT was reported in the placebo group (Supplementary Table S3). Four patients in the lenalidomide group had an increase in serum creatinine, and there was one case each of acute renal failure, chronic renal failure, and renal impairment; no renal-related TEAEs were reported in the placebo group.

There was no difference in the incidence of AML or second primary malignancies (SPMs) between treatment groups, although assessing the number of events was limited by the relatively short follow-up time for this analysis. With a follow-up of 261.5 person-years in the lenalidomide group and 121.8 person-years in the placebo group, the incidence of AML progression was 1.91 per 100 person-years (95% confidence interval [CI], 0.80–4.59) and 2.46 per 100 person-years (95% CI, 0.79–7.64), respectively (data not shown). With a median follow-up duration for SPM assessment of 2.0 years (range 0.2–3.6) in the lenalidomide group and 1.9 years (range 0.1–4.0) in the placebo group, the incidence of SPM was 3.8% for both groups. In the lenalidomide group, reported SPMs included T-cell chronic lymphocytic leukemia, adenocarcinoma of the colon, invasive ductal breast carcinoma, lung squamous cell carcinoma stage IV, squamous cell carcinoma of the tongue, and basal cell carcinoma ($n = 1$ for each event). In the placebo group, reported SPMs included prostate cancer, squamous cell carcinoma of the lung, and transitional cell carcinoma ($n = 1$ for each event).

Grade 5 TEAEs occurred in four patients (2.5%) in the lenalidomide group and in two patients (2.5%) in the placebo group. Treatment-emergent deaths in the lenalidomide group were due to neutropenic sepsis ($n = 1$), myocardial infarction ($n = 1$), staphylococcal infection and MDS progression ($n = 1$), and multi-organ failure and bronchopulmonary aspergillosis ($n = 1$). Treatment-emergent deaths in the placebo group were due to pneumonia ($n = 1$) and pulmonary edema and acute myocardial infarction ($n = 1$).

Impact of TEAEs on patient management

The proportion of patients who experienced TEAEs that led to dose interruption, dose reduction, or

treatment discontinuation is presented (Table 1). Compared with patients in the placebo group, those in the lenalidomide group were more likely to experience TEAEs requiring dose interruption (54.4% vs. 13.9%), dose reduction (6.3% vs. 1.3%), and treatment discontinuation (31.9% vs. 11.4%). The incidence of TEAEs that required dose interruption and subsequent dose reduction was also higher in the lenalidomide group (42.5%) versus 6.3% in the placebo group. The median time to first dose interruption or reduction due to TEAEs was 57 d (range 6–504) in the lenalidomide group ($n = 73$) and 22 d (range 16–44) in the placebo group ($n = 5$; data not shown). The median duration of first dose interruption due to TEAEs was 14.5 d (range 1–80) in lenalidomide-treated patients ($n = 68$) and 6 d (range 5–7) in patients receiving placebo ($n = 4$). The median time to treatment discontinuation due to grade 3–4 TEAEs was 60 d (range 8–618) in the lenalidomide group ($n = 41$) and 85 d (range 37–148) in the placebo group ($n = 6$).

The proportion of patients experiencing TEAEs that led to hospitalization was 35.6% in the lenalidomide group and 17.7% in the placebo group (data not shown). The median duration of hospitalization due to a TEAE was 11 d (range 1–76) and 9 d (range 1–66) in the lenalidomide and placebo groups, respectively. The most common reasons for hospitalization due to TEAEs in the lenalidomide group were pneumonia (5.6% vs. 2.5% in the placebo group), anemia (2.5% vs. 0%), neutropenic sepsis (1.9% vs. 1.3%), pleural effusion (1.9% vs. 0%), and cardiac failure (1.9% vs. 1.3%).

The most common TEAEs requiring treatment modifications in the lenalidomide group were neutropenia and thrombocytopenia (Table 1). Neutropenia led to dose interruption in 28.8% of patients, interruption with subsequent dose reduction in 25.0% of patients, and lenalidomide discontinuation in 4.4% of patients. Thrombocytopenia led to dose interruption in 19.4% of patients, interruption with subsequent dose reduction in 16.3% of patients, and lenalidomide discontinuation in 8.8% of patients. In addition, one patient in the lenalidomide group discontinued treatment because of leukopenia and another discontinued treatment because of anemia (data not shown).

Among patients treated with lenalidomide, the incidence of grade 3–4 thrombocytopenia was similar in responders ($n = 43$) and non-responders ($n = 117$; 35% vs. 36%, respectively), as was the incidence of grade 3–4 anemia (5% vs. 6%, respectively; data not shown). However, compared with non-responders, more responders developed grade 3–4 neutropenia (81% vs. 55%) and grade 3–4 leukopenia (23% vs. 7%, respectively).

Table 1. Most common TEAEs requiring dose interruption, dose reduction, or treatment discontinuation.

TEAE	Lenalidomide ($n = 160$)	Placebo ($n = 79$)
TEAEs requiring dose interruption in ≥10% of patients, *n* (%)		
Any TEAE	87 (54.4)	11 (13.9)
Neutropenia	46 (28.8)	2 (2.5)
Thrombocytopenia	31 (19.4)	2 (2.5)
TEAEs requiring dose reduction in ≥1.5% of patients, *n* (%)		
Any TEAE	10 (6.3)	1 (1.3)
Neutropenia	5 (3.1)	1 (1.3)
TEAEs requiring dose interruption with subsequent reduction in ≥1.5% of patients, *n* (%)		
Any TEAE	68 (42.5)	5 (6.3)
Neutropenia	40 (25.0)	2 (2.5)
Thrombocytopenia	26 (16.3)	0
Pruritus	1 (0.6)	2 (2.5)
Constipation	0	2 (2.5)
Rash	3 (1.9)	0
TEAEs requiring treatment discontinuation in ≥1.5% of patients, *n* (%)		
Any TEAE	51 (31.9)	9 (11.4)
Thrombocytopenia	14 (8.8)	0
Neutropenia	7 (4.4)	2 (2.5)
AML[a]	0	2 (2.5)
Deep-vein thrombosis	3 (1.9)	0

AML: acute myeloid leukemia; TEAE: treatment-emergent adverse event.
[a]In the short follow-up period, no increased incidence of AML or second primary malignancies was observed.

Non-hematologic TEAEs that led to treatment interruption and subsequent dose reduction were uncommon in the lenalidomide group (Table 1); these TEAEs included pruritus (0.6%) and rash (1.9%). Although diarrhea was common (42.5% of patients had grade 1–2 diarrhea; Supplementary Table S2), it did not require lenalidomide discontinuation in any patient; some cases were managed by dose interruption ($n = 1$) or interruption followed by dose reduction ($n = 2$). Few patients discontinued lenalidomide because of non-hematologic TEAEs; TEAEs of interest requiring discontinuation included DVT (1.9%), pneumonia (1.3%), and rash (0.6%).

Discussion

The results of this analysis confirm that AEs associated with lenalidomide treatment are predictable and manageable in patients with lower-risk non-del(5q) MDS. These results were comparable to the safety data of lenalidomide, with no new safety concerns raised [5,6,13]. The most common grade 3–4 TEAEs were neutropenia and thrombocytopenia, which is consistent with the known safety profile of lenalidomide in lower-risk MDS [5,6,13]. These events tended to occur early in the treatment course (i.e. within the first two to three cycles) and, in most cases, were successfully managed with dose interruptions and/or reductions, avoiding the need for treatment discontinuation. Diarrhea was the most common grade 1–2 TEAE, and

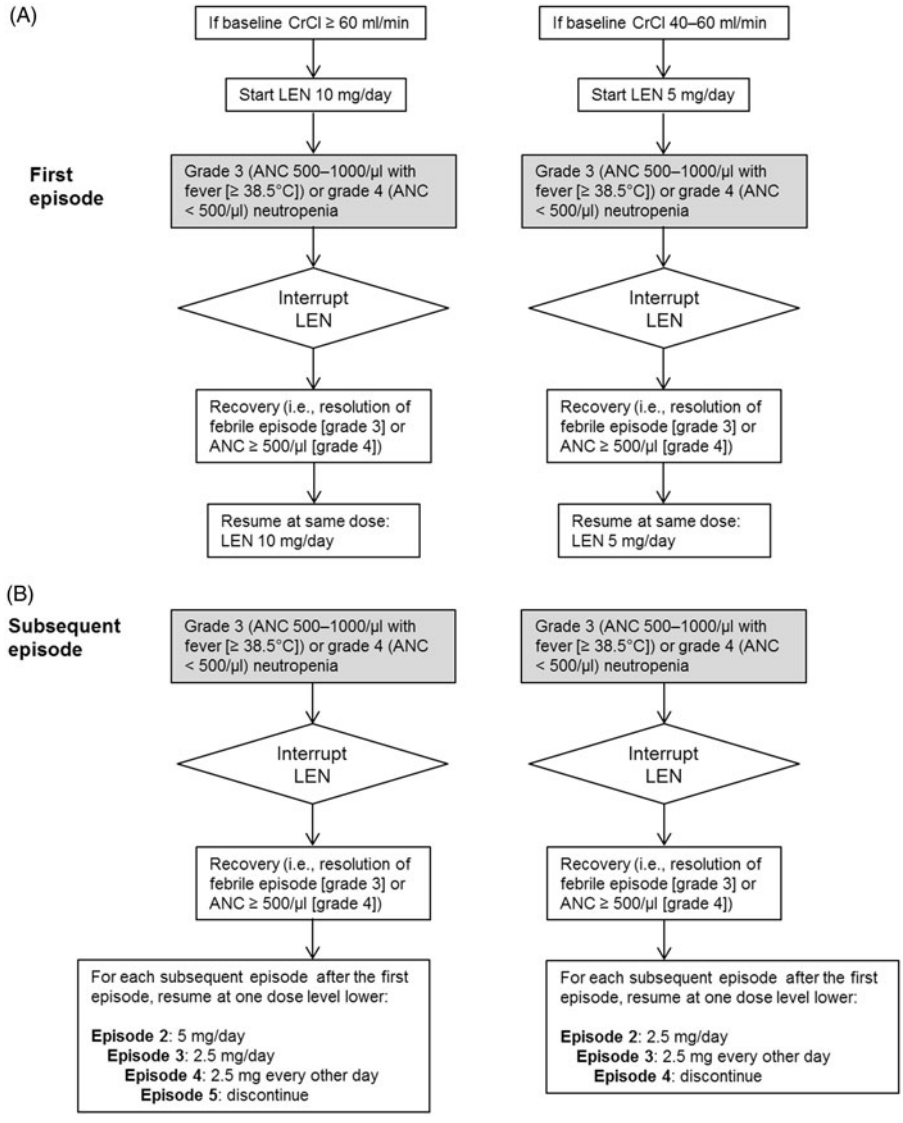

Figure 4. Recommended dose modifications for grade 3–4 neutropenia. (A) First episode. (B) Subsequent episode. ANC: absolute neutrophil count; CrCl: creatinine clearance; LEN: lenalidomide.

grade 1–2 TEAEs generally did not require dose reduction or discontinuation.

Other studies have also indicated that neutropenia and thrombocytopenia are the two most common grade 3–4 TEAEs in patients with lower-risk non-del(5q) MDS treated with lenalidomide [14–16]. Rates of grade 3–4 neutropenia were higher among lenalidomide-treated patients in this study when compared with lenalidomide-treated patients in the earlier study by Raza et al. [14]. Studies evaluating the administration of lenalidomide on days 1–21 of each 28-d cycle generally report lower rates of severe myelosuppression, although Raza et al. [14] found little difference between a 21-d dosing schedule and continuous dosing (days 1–28) with regard to the incidence of grade 3–4 neutropenia (23% vs. 27%, respectively) or thrombocytopenia (18% vs. 22%, respectively). Rates of grade 3–4 non-hematologic TEAEs are consistently low across studies. Concomitant use of lenalidomide and ESAs does not appear to increase the incidence or severity of lenalidomide-related TEAEs [15,16], and this approach has been added to the updated National Comprehensive Cancer Network guidelines as a treatment option for patients with lower-risk non-del(5q) MDS who fail to respond or stop responding to ESAs [8].

The AE profile of lenalidomide in patients with non-del(5q) MDS is also consistent with data in patients with del(5q) MDS [5,6]. In a retrospective analysis of pooled data from seven clinical studies of lenalidomide in non-del(5q) ($n = 416$) and del(5q) ($n = 243$) MDS, neutropenia and thrombocytopenia were the most commonly reported TEAEs. The frequency of these events was lower in patients with non-del(5q)

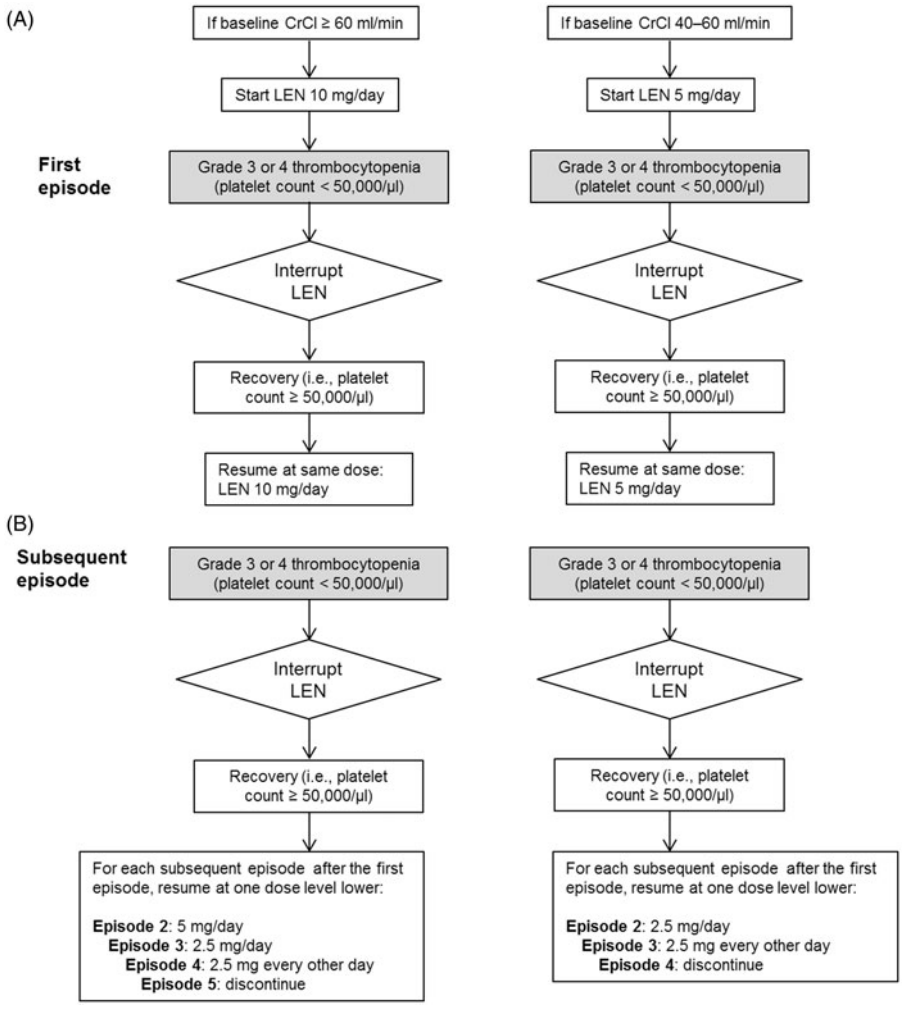

Figure 5. Recommended dose modifications for grade 3–4 thrombocytopenia. (A) First episode. (B) Subsequent episode. CrCl: creatinine clearance; LEN: lenalidomide.

than patients with del(5q) (45% vs. 72%, respectively, for grade 3–4 neutropenia and 31% vs. 53%, respectively, for grade 3–4 thrombocytopenia) [17].

Our findings also highlight the importance of frequent monitoring, particularly during the first cycles of therapy. Grade 3–4 neutropenia and thrombocytopenia tended to occur early in the course of treatment, which is consistent with previous experience of lenalidomide in patients with del(5q) MDS [5,6]. Weekly monitoring, including complete blood counts, has been recommended for at least the first 2 months of lenalidomide therapy; thereafter, biweekly or monthly monitoring may be considered, depending on hematologic status [18].

In the MDS-005 study, lenalidomide resulted in RBC-TI ≥8 weeks in 27% of patients who were ineligible for or refractory to ESAs, and achievement of RBC-TI ≥8 weeks was associated with significant improvements in health-related quality of life in this population [10]. These potential benefits underscore the importance of effective management of TEAEs so that patients may continue to receive therapy. Recommended strategies for managing neutropenia and thrombocytopenia have been formulated, with an emphasis on using dose interruptions and reductions to avoid discontinuing treatment whenever possible (Figures 4 and 5). The ability to continue therapy in responding patients is particularly important in this population, given the limited treatment alternatives that are available [8].

Median time to onset of RBC-TI ≥8 weeks with lenalidomide was 10.1 weeks in the MDS-005 study, with 90% of responses achieved within four cycles of treatment [10], which is potentially longer than the time to response reported for patients with del(5q) MDS [5,6]. Based on this observation, the duration of lenalidomide treatment in non-responding patients can be limited to four to six treatment cycles. Discontinuation within this timeframe should be

avoided to ensure that patients are given the maximum opportunity to respond.

Optimal drug exposure by maintaining the highest possible dose and minimizing the time off therapy may also be important to patient outcomes. In a *post hoc* analysis of the MDS-005 study, patients undergoing lenalidomide dose reductions had a longer duration of treatment, received a higher overall lenalidomide dose, and were more likely to achieve RBC-TI and clinical benefit [19]. These data are consistent with previous findings in patients with del(5q) MDS, showing that lenalidomide dose reductions are significantly associated with improved AML-free survival and overall survival [20].

Rates of hematologic TEAEs were generally similar in responding and non-responding patients treated with lenalidomide, aside from grade 3–4 neutropenia, which was higher in responders (81% vs. 55%). In a previous analysis of data from two phase 2 trials of lenalidomide in patients with lower-risk MDS, a reduction in platelet or neutrophil count was associated with achievement of RBC-TI in patients with del(5q) MDS, but not in those with non-del(5q) MDS [11]. Similarly, myelosuppression in MDS-005 did not predict response to lenalidomide (data not shown). These findings suggest that in patients with del(5q) MDS, lenalidomide directly suppresses the del(5q) clone, and lenalidomide-related cytopenias may act as a surrogate marker of clonal suppression. In patients with non-del(5q) MDS, however, cytopenias may not be a reliable predictor of response, as the activity of lenalidomide may be due to its other effects on MDS clones and the tumor microenvironment [11,14].

One limitation of this analysis is the relatively short follow-up time. Although there were no major differences in incidence rates for AML between treatment groups, only a small number of AML events were reported. Similarly, the incidence of SPMs was the same in both the lenalidomide and placebo groups (3.8%). Additional analyses with longer follow-up may be needed to better characterize the long-term safety profile of lenalidomide in patients with non-del(5q) MDS. A second limitation is that patients who could not tolerate lenalidomide 2.5 mg every other day on a 28-d schedule were discontinued from the study, as the trial protocol did not include lower dosages. Further research is needed to determine whether lower doses are better tolerated and effective in this setting.

Conclusions

The MDS-005 study demonstrated that lenalidomide is active in patients with lower-risk non-del(5q) MDS who are ineligible for or refractory to ESAs [10]. For clinicians considering lenalidomide as a treatment option for these patients (or for the subgroup of patients with endogenous EPO levels $\leq$500 mU/ml who are more likely to respond), it is important to be aware of the safety profile of lenalidomide in this setting. The data reported here suggest that lenalidomide has a predictable and manageable safety profile in patients with lower-risk non-del(5q) MDS who are ineligible for or refractory to ESAs. TEAEs were common but infrequently necessitated treatment discontinuation. Effective management of TEAEs, particularly neutropenia and thrombocytopenia using dose interruptions or reductions, can help patients continue to receive lenalidomide therapy in order to derive maximum clinical benefit.

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