BLOOD RESEARCH
VOLUME 56 · NUMBER 2
June 2021
ORIGINAL ARTICLE

Lenalidomide for anemia correction in lower-risk del(5q) myelodysplastic syndrome patients of Asian ethnicity

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on behalf of the AML/MDS Working Party of the Korean Society of Hematology

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p-ISSN 2287-979X / e-ISSN 2288-0011
https://doi.org/10.5045/br.2021.2021086
Blood Res 2021;56:102-108.

Received on April 23, 2021
Accepted on June 2, 2021

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Background
To estimate real-world outcomes in East Asian populations, we conducted a nationwide retrospective analysis of the efficacy and safety of lenalidomide for del(5q) myelodysplastic syndrome (MDS) patients with transfusion-dependent anemia in Korea.

Methods
Patients aged ≥19 years who had received lenalidomide for the treatment of lower-risk, red blood cell (RBC) transfusion-dependent del(5q) MDS were selected. A filled case report form (CRF) with information from electronic medical records was requested from members of the acute myeloid leukemia (AML)/MDS Working Party of the Korean Society of Hematology. All the CRFs were gathered and analyzed.

Results
A total of 31 patients were included in this study. Of 28 evaluable patients, 19 (67.9%) achieved RBC transfusion independence (RBC-TI). Female sex and the development of thrombocytopenia during treatment were associated with achieving RBC-TI. The most common non-hematologic toxicities were pruritus, fatigue, and rashes. All non-hematologic toxicities of grades ≥3 were limited to rash (12.9%) and pruritus (6.5%). Dose reduction was required in 15 of the 19 responders (78.9%). The most common final stable dosing schedule for the responders was 5 mg once every other day (31.6%).

Conclusion
Lenalidomide efficacy and tolerability were similar in the Asian del(5q) MDS patients and western patients. Dose reduction during treatment was common, but it was not associated with inferior outcomes.

Key Words 5q deletion syndrome, Myelodysplastic syndrome, Lenalidomide, Anemia

INTRODUCTION

Myelodysplastic syndrome (MDS) is a clonal hematologic stem cell disorder that presents with ineffective hematopoiesis and cytopenia of peripheral blood cells [1]. It is classified into lower- or higher-risk disease according to the degree of cytopenia, amount of bone marrow blasts, and cytogenetic abnormalities [2, 3]. Allogeneic hematopoietic stem cell transplantation is the only curative option for higher-risk MDS that, otherwise, has a dismal prognosis [4, 5]. For lower-risk MDS, the correction of cytopenia and delay of disease progression to secondary acute myeloid leukemia (AML) are the goals of treatment [1].

The deletion of the long arm of chromosome 5 [del(5q)] is the most common cytogenetic abnormality in patients with MDS at diagnosis [6]. Approximately 10% of MDS patients harboring del(5q) have the deletion as the sole cytogenetic abnormality [7], which is classified as 'MDS associated with isolated del(5q)' according to the 2018 World Health Organization (WHO) classification criteria [8]. Some of these patients, mostly with a deletion in the 5q315q33 chromosomal region, have distinctive features including transfusion-dependent macrocytic anemia, low to normal white blood cell count/absolute neutrophil count (ANC) ratio, and normal to increased platelet count; these characterize the del(5q) syndrome [9].

Lenalidomide is an analog of thalidomide, an immunomodulatory drug. It has been used as a standard treatment for patients with lower-risk MDS harboring del(5q) and red blood cell (RBC) transfusion dependency [1, 7]. Its effectiveness may be attributed to its unique mechanism of action, which suppresses clonal hematopoietic cells via synthetic lethality mediated by the cereblon-dependent degradation of haplodeficient proteins encoded within the deleted 5q region [10]. This karyotype-specific therapeutic approach can lead to a remarkable improvement in MDS treatment efficacy by achieving a high rate of erythroid response and RBC transfusion independence (RBC-TI) [11, 12] with a possible survival benefit [13].

Although lenalidomide has been approved for del(5q) MDS by the U.S. FDA and the European Medicines Agency in 2005 and 2013, respectively, data on East Asian del(5q) MDS patients are scarce. In East Asian populations, del(5q) MDS is rare, and its reported incidence is low [7, 14]. In the analysis from the International Working Group for Prognosis of MDS comparing 300 Japanese and 5838 Caucasian MDS patients, the prevalence of del(5q) was significantly lower in the Japanese population (1.9%) than in the Caucasians (8.6%) [15]. To the best of our knowledge, only one published study has reported the outcomes of 11 Japanese lower-risk MDS patients with del(5q) MDS and symptomatic anemia [16].

In Korea, lenalidomide for del(5q) MDS was approved by the Korea Ministry of Food and Drug Safety (MFDS) in June 2018 and reimbursed by the National Health Insurance Review and Assessment Service (HIRA) in May 2019. To provide real-world evidence on lenalidomide for East Asian MDS patients, particularly focusing on the appropriateness of the recommended dose and dosing schedule of lenalidomide derived from previous studies involving western patients, we conducted a nationwide retrospective analysis of the efficacy and safety of lenalidomide treatment for MDS patients harboring del(5q) in Korea.

MATERIALS AND METHODS

Patients and ethics statement

Patients were included if they were 19 years or older and had ever received lenalidomide (Revlimid) for the treatment of lower-risk RBC transfusion-dependent del(5q) MDS between June 2018 and May 2020. Lower-risk MDS was defined as low- or intermediate-risk according to the International Prognosis Scoring System (IPSS), and RBC transfusion dependency as having received any RBC transfusion within the last 8 weeks and more than 8 units of RBC transfusion within the last 6 months. Patients who had both del(5q) and -7/del(7q), those who used lenalidomide for other reasons such as multiple myeloma treatment, and those who had an ANC of $<500/\mu L$ or a platelet count of $<25{,}000/\mu L$ were excluded from the analysis.

This study was approved by the Institutional Review Board (IRB) of each participating institution (approval number of the principal investigator's institution, University of Ulsan Asan Medical Center, Seoul, Republic of Korea: 2020-0930). The requirement for informed consent was waived by each IRB, considering the retrospective nature of the current study.

Treatment with lenalidomide

The recommended starting dose of lenalidomide was 10 mg once daily per os for 21 consecutive days, with rest for 7 days (1 cycle=28 days). Patients with other starting doses or schedules were included. Dose reduction or interruption was decided according to the discretion of the physicians based on recommendations for responding to hematologic and non-hematologic toxicities [11, 12]. If the RBC transfusion burden failed to improve with a reduction of $\geq$50% despite the lenalidomide administration over 4 months, it had to be discontinued according to the HIRA policy.

Data acquisition

The AML/MDS Working Party of the Korean Society of Hematology actively contacted the members and requested eligible patients. The responding hematologists were provided a protocol and auxiliary documents for the approval of the current study from the IRB of each institution. After approval, a filled case report form was requested, which consisted of items about the demographics of the patients (age, sex, height, and body weight), disease-related information (date of MDS diagnosis, WHO classification, IPSS risk, transfusion history, history of prior treatment, and base-

line laboratory data including G-banding karyotype), and treatment-related information (date of lenalidomide initiation, blood cell counts at 4, 8, 16, 24, and 48th weeks from treatment initiation, response to treatment, hematologic and non-hematologic toxicities according to the Common Terminology Criteria for Adverse Events v5.0, dose reduction or interruption during treatment, treatment discontinuation with the reason for discontinuation, and survival or last follow-up data). Considering the retrospective nature of this study, a window of ±4 days was allowed for the reports for the 4th and 8th weeks. Likewise, windows of ±7 days and ±14 days were allowed for the reports for the 12th to 16th week and thereafter, respectively. The efficacy of lenalidomide was estimated based on the rate of achieving RBC-TI, defined as maintaining RBC transfusion independence for ≥8 weeks during treatment with hematologic improvement-erythroid major (HI-E major) response according to the 2000 International Working Group criteria.

Statistical analysis

As the current study evaluated the efficacy and safety of a single agent (lenalidomide), most of the statistical analyses were descriptive. The frequency and ratio of the categorical variables are summarized in the tables. Fisher's exact test or Pearson's chi-squared test was performed to determine the non-random associations between the two categorical variables. The data for the continuous variables are expressed as median, range (minimum–maximal value), and mean±SEM. The values were two-sided, and statistical significance was set at $P<0.05$.

Table 1. Patient characteristics.

Parameter	N (%)
Age at lenalidomide initiation (yr)	
Median (range)	66 (46–83)
Sex	
Male	8 (25.8)
Female	23 (74.2)
Time from initial MDS diagnosis to lenalidomide initiation (wk)	
Median	56
Range	0–424
Transfusion dependence	
At MDS diagnosis	23 (74.2)
At lenalidomide initiation	31 (100)
Karyotype	
Isolated del(5q) only	28 (90.3)
+1 additional abnormality	3 (9.7)
WHO classification	
MDS with isolate del(5q)	27 (87.1)
MDS, multilineage dysplasia	2 (6.5)
MDS, excess blast-1	1 (3.2)
MDS, unclassifiable	1 (3.2)
International Prognosis Scoring System (IPSS)	
Low	16 (51.6)
Intermediate-1	15 (48.4)
Intermediate-2 or high	0 (0%)
IPSS-revised (IPSS-R)	
Very low	2 (6.5)
Low	16 (51.6)
Intermediate	15 (41.9)
High/very high	0 (0)

Abbreviaion: MDS, myelodysplastic syndrome.

RESULTS

Patient characteristics

A total of 31 patients from 21 institutions were included in the study. Of them, 30 patients were native Koreans and 1 patient was a Chinese resident in Korea. There was a female predominance, and the median age of the patients at the time of the first exposure to lenalidomide was 67 years (range, 46–83 yr). The time interval from MDS diagnosis to the first exposure to lenalidomide varied as some patients had to wait for Korea MFDS approval and reimbursement for using lenalidomide to treat their disease. In addition, 12 of 31 patients (38.7%) were previously treated with erythropoiesis-stimulating agents (ESAs), and only 4 of them achieved RBC-TI (Supplementary Table 1), reflecting the poor response to ESAs for del(5q) MDS [17]. The patient characteristics are summarized in Table 1.

All 31 patients showed RBC transfusion dependence at the time of lenalidomide initiation. The baseline hemoglobin (Hb) level had a median value of 7.0 g/dL (range, 4.5–10.0) and a mean value of 7.2±0.2 g/dL. For RBC transfusion 8 weeks before lenalidomide initiation, the median number of units was 6 (range, 2–11), and the mean number of units was 5.3±0.4 units.

Efficacy of lenalidomide

The response of the three patients could not be evaluated. All of them discontinued lenalidomide after less than 28 days for the following reasons: toxicity (1 patient; in 18

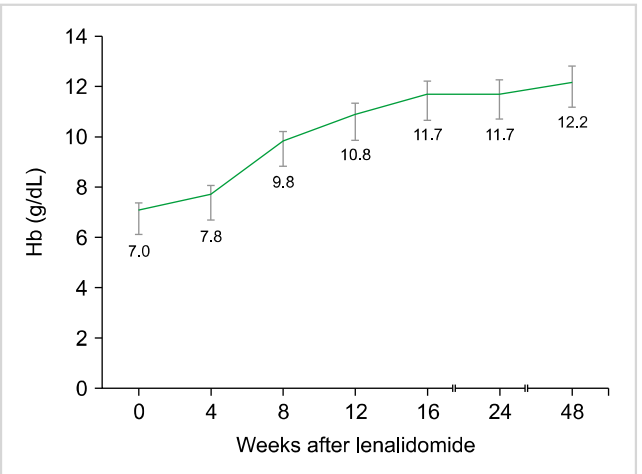

Fig. 1. Hemoglobin level changes in responders after lenalidomide treatment (mean±SEM).

days), rapid AML transformation (1 patient; in 20 days), and at will (1 patient, in 22 days). Of the remaining 28 patients, 19 (67.9%) achieved RBC-TI. The other 9 patients were non-responsive to lenalidomide, including one patient with a minor HI-E response (≥50% reduction in RBC transfusion but without independence). A follow-up bone marrow examination was performed for only 2 patients, both of whom achieved RBC-TI and showed partially decreased del(5q) cytogenetic abnormality with morphologic complete response.

The duration of lenalidomide use was significantly longer among responders (mean 24.7±2.5 mo) than among non-responders (mean 9.1±2.6 mo; $P<0.001$). At the time of data cutoff, all responders were still using lenalidomide. Among the responders, the mean Hb level began to increase during the 4th week after treatment initiation, showed a sharp increase from the 4th to 8th week, and maintained a gradually increasing trend thereafter (Fig. 1).

Female sex and the development of thrombocytopenia during treatment were associated with achieving RBC-TI. Younger age, lower pre-treatment RBC transfusion burden, and higher ANC and platelet count showed a tendency toward achieving RBC-TI; however, the results were not statistically significant (Table 2).

Tolerability of lenalidomide

All 31 patients were evaluated for toxicity (Table 3). Overall, 22 (71.0%) and 8 (25.8%) patients had grade 3 or 4 neutropenia and thrombocytopenia, respectively. The most common non-hematologic toxicities were pruritus, fatigue, and rashes. Grade 3 or 4 non-hematologic toxicities were limited to rash (4 patients; 12.9%) and pruritus (2 patients; 6.5%).

A dose reduction in lenalidomide was required for 15 of 19 responders (78.9%) and 3 of 9 non-responders (33.3%). A dose interruption in lenalidomide was required for 7 of 19 responders (36.8%). A total of 12 patients eventually discontinued lenalidomide for the following reasons: no response (6 patients), intolerable toxicity under a non-responsive state (4 patients), rapid AML progression (1 patient), and at will (1 patient).

The most common final stable dosing schedule of lenalidomide for the 19 responders was 5 mg per os once every other day (N=6, 31.6%; Table 4). There was no significant association between the final dose intensity of lenalidomide and the body mass index (r=0.133, P=0.588) or bodyweight (r=0.325, P=1.000) of the patients.

DISCUSSION

In this study, we demonstrated acceptable lenalidomide efficacy and tolerability in del(5q) MDS patients of East Asian ethnicity. The RBC-TI rate of 67.9% is comparable to that reported in western studies, which is encouraging considering that it is based on real-world data.

Our main objective was to determine whether Asian patients, who have lower body mass indexes than westerners [18], have a higher incidence and severity of toxicity with the current standard dose of lenalidomide. Even among Westerners, frequent dose reduction and interruption have been reported for lenalidomide [11, 12, 19]. The toxicities were generally mild and manageable, with adequate supportive care. The incidence of hematologic toxicities was similar to that reported in previous studies. Febrile neutropenia was observed in 9.7% of patients, and all patients recovered without sequelae, suggesting that the risk of infectious complication was not high. Nevertheless, care should be taken in older adults or comorbid patients. The profiles of non-hematologic toxicities were in agreement with the western data,

Table 2. Evaluation of potential predictors for RBC-TI.

	Response no	Response yes	*P*
Male	5	2	0.020
Female	4	17	
Age < median	7	8	0.086
Age ≥ median	2	11	
MDS diagnosis to lenalidomide initiation < 2 yr	4	11	0.410
MDS diagnosis to lenalidomide initiation ≥ 2 yr	5	8	
IPSS low	5	10	0.604
IPSS intermediate-1	4	9	
Pre-treatment red blood cell transfusion ≤ 4 U/8 wk	3	11	0.210
Pre-treatment red blood cell transfusion > 4U/8 wk	6	8	
Pre-treatment neutrophil ≥ 1,000/μL	5	16	0.123
Pre-treatment neutrophil < 1,000/μL	4	3	
Pre-treatment platelet ≥ 150K/μL	5	17	0.064
Pre-treatment platelet < 150K/μL	4	2	
Development of thrombocytopenia during treatment	1	7	0.038
No development of thrombocytopenia during treatment	8	12	

Abbreviation: IPSS, International prognostic scoring system.

Table 3. Hematologic and non-hematologic toxicities (worst during treatment).

Toxicity	None	Grade 1	Grade 2	Grade 3	Grade 4	Any (%)	Grade 3/4 (%)
Hematologic							
Neutropenia	7	1	1	13	9	24 (77.4)	22 (71.0)
Lymphopenia	20	5	3	3	0	8 (25.8)	3 (9.7)
Thrombocytopenia	11	9	3	3	5	20 (64.5)	8 (25.8)
Febrile neutropenia	28	-[a]	-[a]	3	0	3 (9.7)	3 (9.7)
Non-hematologic							
Pruritus	16	8	5	2	0	15 (48.4)	2 (6.5)
Fatigue	17	12	2	0	0	14 (45.2)	0
Rash	22	5	0	4	0	9 (29.0)	4 (12.9)
Diarrhea	26	3	2	0	0	5 (16.2)	0
Dyspepsia	28	1	2	0	0	3 (9.7)	0
Constipation	29	2	0	0	0	2 (6.5)	0
Headache	30	0	1	0	0	1 (3.2)	0
Insomnia	30	0	1	0	0	1 (3.2)	0
Deep vein thrombosis	30	0	1	0	0	1 (3.2)	0
Dyspnea	30	1	0	0	0	1 (3.2)	0
Tongue discoloration	30	1	0	0	0	1 (3.2)	0
Loss of appetite	30	1	0	0	0	1 (3.2)	0
Increased creatinine	30	0	1	0	0	1 (3.2)	0

[a]Grade 1 or 2 febrile neutropenia is not defined in the Common Toxicity Criteria for Adverse Events v5.0.

Table 4. Final stable dose of lenalidomide for responders (N=19).

Lenalidomide dosing	Patient No.	Dose intensity (mg/day)
10 mg once daily	1	10
10 mg once daily for 3 wk, 1-wk rest	3	7.5
10 mg once every other day	1	5
5 mg once daily	4	5
5 mg once daily for 3 wk, 1-wk rest	4	3.75
5 mg once every other day	6	2.5

except for the lower incidence and severity of venous thromboembolism (VTE). In a randomized phase 3 trial, the most common non-hematologic grade 3 or 4 adverse events were venous thrombosis (4 of 69 patients in the 10 mg group) and one death due to pulmonary embolism [12]. In addition, the French GFM group reported that 8 of 95 patients (9.5%) developed VTE after a median of 16 weeks (range, 8–90 wk) of treatment [19]. In contrast, our study included only one patient (3.2%) with VTE, who was a 60-year-old woman with deep vein thrombosis of the left upper proximal extremities after 12 weeks of treatment. In general, patients with del(5q) MDS have thrombophilic risk factors, including older age, female predominance, higher baseline platelet count, increased hemoglobin level after lenalidomide use, and previous exposure to ESAs. Although a careful interpretation of the results should be made due to the limited sample size, the difference may be attributed to the lower incidence of VTE in Asian populations [20].

In the MDS-003 trial [11], there were no differences between the efficacy and safety profiles of the two dosing schedules of lenalidomide (10 mg/day on days 1 to 28 vs. 10 mg/day on days 1 to 21 followed by 7 days of rest). In the phase 3 MDS-004 trial [12], a smaller dose (5 mg/day on days 1 to 28) was compared to 10 mg/day for 21 days. Although there was no significant difference between 10 mg/day for 21 days and 5 mg/day for 28 days, the 10 mg/day for 21 days dose was recommended because it had some advantages. However, after this starting dose, subsequent dose reductions were common, ranging from 48% to 84% [11, 12, 19]. In our study, 18 of 28 evaluable patients (64.3%) required dose reduction, and the most common stable dose was 5 mg once every other day. Interestingly, the rate of dose adjustment was higher among responders than among non-responders (78.9% vs. 33.3%, P=0.03), suggesting that dose reduction did not result in a suboptimal response. A dose reduction in lenalidomide due to toxicity was predictable and common among responders; thus, there was no need to hesitate when it was necessary during treatment.

We found no association between the body mass indexes or bodyweights of patients and the stable dose of lenalidomide. Moreover, the overall incidence and severity of adverse events in our study were not significantly greater than those reported by western studies. This suggests that patients with a lean body mass are not more vulnerable to lenalidomide-related toxicities than those without a lean body mass. Based on the results, an identical initial dosing schedule should be applied to Asian populations with the readiness to provide timely and appropriate dose adjustment and supportive care in response to the development of adverse events.

A drop in the platelet count during treatment, particularly

after lenalidomide use, is known to be associated with the erythroid response, indicating the successful reduction of MDS clones due to the synthetic lethal activity of lenalidomide. This effect was also observed in the present study. Female sex was associated with the achievement of RBC-TI. However, the result was not conclusive because the patients, especially the male patients, were few.

Although there were no deaths and one patient had rapid AML progression, a robust evaluation of the long-term disease course and survival was not feasible due to the short follow-up period. This may be considered a limitation of the current study. Nevertheless, we successfully demonstrated that RBC-TI could be effectively achieved with lenalidomide monotherapy in Asian del(5q) MDS patients.

In conclusion, lenalidomide efficacy and tolerability were similar in Asian del(5q) MDS patients and western patients. A dose reduction in lenalidomide during treatment was common and was not associated with inferior outcomes.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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