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A Phase II Study of Lenalidomide Alone in Relapsed/Refractory Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndromes With Chromosome 5 Abnormalities

Yiming Chen, **Hagop Kantarjian**, **Zeev Estrov**, **Stefan Faderl**, **Farhad Ravandi**, **Kristy Rey**, **Jorge Cortes**, and **Gautam Borthakur**
Department of Leukemia, University of Texas M.D. Anderson Cancer Center, Houston, TX

Abstract

This phase II study assessed the efficacy and safety of lenalidomide in patients with relapsed/refractory acute myeloid leukemia (N = 18) and high-risk myelodysplastic syndrome (N = 9) with chromosome 5 abnormalities. The overall complete remission rate with or without platelet recovery was 7% (2/27). Activity of lenalidomide was limited to patients with noncomplex cytogenetics.

Background—Lenalidomide is effective in low-risk myelodysplastic syndromes (MDS) with deletion 5q. We conducted a phase II study to evaluate the safety and efficacy of lenalidomide in patients with relapsed/refractory acute myeloid leukemia (AML) and high-risk MDS with any chromosome 5 abnormality.

Patients and Methods—Eighteen adults with AML and 9 with high-risk MDS were enrolled. Lenalidomide was given orally at doses 5 to 25 mg daily for 21 days of a 28-day cycle until disease progression or unacceptable adverse event.

Results—Median age for all 27 patients was 64 years (range, 39-88 years) with a median of 2 previous therapies (range, 1-6 lines). Two patients (7%) with AML and 5q deletion and +8 cytogenetic abnormality in 2 separate clones achieved complete remission (CR) or CR without platelet recovery (CRp). Response durations were 4 and 6 months, respectively. No responses were seen in patients with chromosome 5 abnormality in a complex cytogenetic background. Twenty patients (74%) developed neutropenic fever or infection requiring hospitalization.

Conclusions—Clinical activity of lenalidomide as single agent in AML and high-risk MDS with chromosome 5 abnormalities appears to be limited to patients with noncomplex cytogenetics.

Address for correspondence: Gautam Borthakur, MD, University of Texas M D, Anderson Cancer Center, Department of Leukemia, 1515 Holcombe Boulevard, Unit 428, Houston, TX 77030, Fax: 713-792-7885; gborthak@mdanderson.org.

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Keywords

Clinical trial; Deletion 5q; Response

Introduction

Lenalidomide is thought to act as an immunomodulatory agent by effect on the bone marrow microenvironment.[1] It has been shown to inhibit neoangiogenesis, induce apoptosis, and activate T cell and nature killer cells.[2-4] It also has direct antitumor effects. Lenalidomide has shown to be particularly effective in patients with low-risk myelodysplastic syndrome (MDS) and 5q deletion cytogenetic abnormality.[5,6] In the Myelodysplastic Syndrome 003 (MDS 003) study, transfusion independence was achieved in 67% of patients and complete cytogenetic responses in 45% of patients (including patients with complex karyotype). The median duration of response was 115.9 weeks.[6] In 2006, the Food and Drug Administration approved lenalidomide for transfusion-dependent anemia due to low-risk MDS with 5q- cytogenetic aberrations and for the treatment of relapsed/refractory multiple myeloma. However, the role of lenalidomide as single agent in high-risk MDS and acute myeloid leukemia (AML) associated with chromosome 5 abnormalities continues to evolve. The ability of lenalidomide in eliminating the del 5q clone in patients with low-risk MDS and occasional reports of remission in patients with high-risk MDS or AML with chromosome 5 abnormalities led us to hypothesize that lenalidomide will be active in patients with high-risk MDS or AML associated with chromosome 5 abnormalities. In the present study, we report the results of a phase 2 study of lenalidomide in the treatment of patients with relapsed/refractory AML or high risk of MDS with chromosome 5 abnormalities.

Materials and Methods

Study Group

Adults (≥18 years old) with relapsed/refractory AML or high-risk MDS[7] (International Prognostic Scoring System [IPSS] intermediate risk 2 and higher) who had any abnormality in chromosome 5 with/without additional abnormalities were eligible after informed consent was signed according to the institutional guidelines. Untreated patients with high-risk MDS were allowed. Patients with MDS who had marrow blast percentage of ≥10% were considered high-risk. Limited use of hydroxyurea to control proliferative disease was allowed. Additional eligibility criteria included: no treatment for AML or MDS within 2 weeks of starting lenalidomide, Eastern Cooperative Oncology Group (ECOG) performance status ≤2 at study entry, absence of the chromosome translocation t(15;17), all nonhematological adverse event of previous cancer therapy ≤ grade 1, adequate organ function (total bilirubin ≤1.5 mg/dL, aspartate aminotransferase or alanine aminotransferase ≤2 times the upper limit of normal or 5 times the upper limit of normal if related to disease, serum creatinine ≤1.5 mg per day), disease free of previous malignancies for ≥2 years, no known allergy to thalidomide, nursing, pregnant women, and patients seropositive for HIV or hepatitis B or C were excluded. Participants were required to follow contraception methods according to established guidelines for lenalidomide. The study was conducted in

accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the University of Texas M.D. Anderson Cancer Center.

Treatment Plan

This was an open-label, prospective, single-arm phase II study of oral lenalidomide (15-25 mg daily based on treating physician preference) for 21 days of a 28-day cycle with 7 days off therapy. Further reductions were allowed in the best interest of the patient. Patients who continued to benefit or any patient without progressive disease after 3 cycles of therapy continued with lenalidomide treatment until disease progression or unacceptable adverse event. Treatment could be discontinued before completion of 3 cycles for clear lack of response by the patient. Dose interruptions and reductions for nonhematologic adverse events were according to standard guidelines for lenalidomide. For patients who started therapy with platelet count $\geq 50 \times 10^9$/L, the next cycle could start only after platelet count has recovered to $>10{,}000 \times 10^9$/L. The National Cancer Institution Common Terminology Criteria for Adverse Events version 3.0 was used to determine severity of adverse events.

Response Criteria

Response for AML was defined according to the 2003 criteria reported by the International Working Group (IWG).[8] Complete remission (CR) required an absolute neutrophil count (ANC) $>1 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and <5% of blast cells in bone marrow. CRp was defined as above except platelet count $<100 \times 10^9$/L. Partial remission (PR) was defined as CR except for the presence of 5% to 25% marrow blasts and with a decrease of marrow blast at least 50%. Response for MDS was defined based on the 2006 International Working Group criteria.[9] All patients with MDS who achieved hematological CR, PR, marrow CR, and hematological improvement were considered responders.

Statistical Design

This was an activity trial with the targeted overall response rate (ORR) at 12 weeks being 20%, which included CR, PR, or hematological improvement and adverse event cutoff of 20% of any grade 3 or greater nonhematological adverse events within 12 weeks post treatment. Stopping boundaries corresponding to these probability criteria were to terminate the trial if overall response rate was ≤0/10 or 1/20 or numbers of patients with adverse events were ≥3/5, 5/10, 7/15, 8/20, or 10/25.

Results

Patient Characteristics

Eighteen adults with AML and 9 with high-risk MDS were enrolled and median age was 64 years (range, 39-88 years; Table 1). Thirteen patients (52%) were female. Twenty-four patients (89%) had complex cytogenetic abnormalities (≥3 chromosome aberrations). Of 18 AML cases, 5 had AML secondary to MDS (n = 4) or essential thrombocytosis (n = 1), 2 had therapy-related AML, and 11 had de novo AML. Of 9 MDS cases, 5 had intermediate-2 risk (IPSS score, 1.5-2), and 4 had high risk (IPSS score, 3-3.5). The median lines of previous therapies were 2 for patients with AML (range, 1-6 lines) and 1 for patients with MDS (range, 0-2 lines). Twelve out of 18 (67%) patients with AML had previous therapy

with high dose cytarabine based regimens and 5 (23%) were treated with hypomethylating agents. Four (44%) patients with MDS were treated with hypomethylating agents, 4 were previously untreated and 1 received clofarabine. The median time from diagnosis of AML/MDS to enrollment on study was 7 months (range, 1-29 months).

Response and Outcome

The median duration of therapy was 60 days (range, 5-238 days). Of 18 AML patients, 2 (11%) responded with 1 CR and 1 CRp. Both of the 2 responders had +8 cytogenetic abnormality in a clone separate from the 1 with chromosome 5 abnormality. Both patients failed or relapsed after previous hypomethylating agent therapies. Of 9 high-risk MDS patients, 2 had stable disease without progression for >8 weeks.

The first patient with response was 74 years old whose previous treatment with decitabine had failed. The patient started lenalidomide at 25 mg dose and achieved CR after 3 cycles. She needed dose reductions due to grade 2 diarrhea and recurrent infections and eventually lenalidomide was held after cycle 5 for these complications. Two months after lenalidomide being held she sustained a cerebrovascular accident and died. CR duration was 4 months. The second patient was 79 years old who achieved CRp while receiving therapy with decitabine and gemtuzumab ozogamicin before progressing. This patient achieved CRp after 2 months of therapy with lenalidomide. She started at 15 mg dose level but needed dose reductions to 10 mg every alternate day due to atrial fibrillation and thrombocytopenia. Response lasted for 6 months. Seven other patients with +8 cytogenetic abnormality in a complex karyotype did not respond.

Adverse Events

Grade 3 or higher hematological adverse events observed attributable to lenalidomide were thrombocytopenia (n = 14; 52%) and neutropenia (n = 8; 30%; Table 2). Nonhematological adverse events regardless of attribution seen in more than 1 patient are listed in Table 2. Twenty patients (74%) required hospitalization for fevers, including neutropenic fever (n = 4), neutropenic fever with pneumonia (n = 3), nonneutropenic infection (n = 13; 9 pneumonia, 1 each of enterocolitis, cellulitis, urinary tract infection, and E. Coli infection). Other severe adverse events requiring hospitalization were 1 each of gastrointestinal (GI) bleeding, pericardial effusion, myocardial infarction (MI), acute renal failure, and stroke. Sixteen patients (59%) required at least 1 treatment interruption and/or dose reduction due to neutropenic fever/infection (n = 13), fatigue (n = 3), and 1 each of thrombocytopenia, GI bleeding, elevated bilirubin, pancytopenia, myocardial infarction, rash, and neutropenia.

Dosing and Dose Reductions

Starting dose of lenalidomide was 25 mg for 6 patients, 15 mg for 10, 10 mg for 6, and 5 mg for 5 patients. Three patients each in the 25 and 15 mg cohort went beyond cycle 1 and 5 out of these 6 needed dose reduction. Only 1 patient in the 10-mg cohort and 3 in the 5-mg cohort went beyond cycle 1 and all could continue at the starting dose. Eight patients completed 1 cycle but did not proceed to cycle 2 due to disease progression. Seven patients discontinued therapy before completing 1 cycle; 2 due to early death, 1 due to enteritis and GI bleed, 3 due to disease progression, and 1 proceeded to stem cell transplantation (SCT).

Discussion

Lenalidomide has been demonstrated to alleviate transfusion dependence and eliminate the cytogenetically abnormal clone in patients with low-risk MDS and 5q deletion.[5,6] In the pivotal study that included a population of transfusion-dependent patients largely treated with growth factor or iron chelation, there were no significant differences in the frequency of transfusions or cytogenetic responses among patient who had 5q deletion with or without additional cytogenetic abnormalities.[6] In studies of lenalidomide in higher risk MDS or AML, most responses are seen in patients with minimal previous exposure to chemotherapy and in patients with 5q abnormality in a noncomplex background.[10-14] Data are limited on the role of lenalidomide in the patients with relapsed/refractory high-risk MDS or AML and who have chromosome 5q aberrations as part of a complex karyotype.

In the present study of 27 patients with AML or high-risk MDS, 24 patients had complex cytogenetic abnormalities and 22 patients (82%) had previous therapy. The majority of the patients with AML enrolled onto this study were refractory to their immediate previous treatments. Our result demonstrated that lenalidomide monotherapy has limited clinical antileukemic efficacy in relapsed/refractory AML and MDS patients who had chromosome 5 abnormalities, with responses being limited to patients with 1 additional chromosomal abnormality. Our data are consistent with a study of 47 patients (36 previously untreated) with high-risk MDS and 5q deletion by a French study group (lenalidomide 10 mg daily for 21 days of a 28-day cycle), in which only 1 of 38 patients with 1 additional cytogenetic abnormalities and none of the ones with complex karyotype obtained remission, but 6 of 9 patients with isolated 5q deletion achieved CR.[10]

A recent study using lenalidomide alone at high dose (50 mg/day) in 37 patients with previously untreated AML and deletion 5q by SWOG reported CR or PR in 5 patients (14%), 2 with isolated 5q deletion, and 3 with complex cytogenetics.[14] The authors hypothesized that lenalidomide at higher doses, has nonspecific cytotoxic effects through non-5q deletion-mediated mechanisms. A similar report of responses in patients with AML without chromosome 5 abnormality supports this hypothesis.[11]

There are reports of patients with trisomy 13 or trisomy 8/micro-duplication on chromosome 8 (in non-5q AML/MDS) responding to treatment with high dose lenalidomide or lenalidomide plus azacitidine.[15,16] While in the report with high dose lenalidomide, the trisomy 13 clone was eliminated from the marrow at response, in 1 of our 2 patients who had available data after treatment, the abnormal trisomy 8 clone was not eliminated. Whether this difference at the level of cytogenetic response is a function of lenalidomide dose is unclear.

Conclusion

Our study confirms limited activity of lenalidomide at standard dose in patients with relapsed/refractory AML or MDS associated with chromosome 5 abnormality in a complex karyotype background. On the other hand, responses in patients with nonintensive previous therapy and noncomplex karyotype shows that even with standard dose, lenalidomide may

be a treatment option for patients with AML/MDS who have chromosome 5 abnormality and noncomplex karyotype, particularly for the ones not considered fit for intensive chemotherapy.

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Clinical Practice Points

- Lenalidomide provides transfusion independence in 67% of patients and complete cytogenetic responses in 45% of patients with low-risk MDS and 5q deletion cytogenetic abnormality.
- Our study indicates that responses in patients with high-risk MDS or AML with any chromosome 5 abnormality is limited to patients with noncomplex cytogenetics.
- Lenalidomide may be a therapeutic option for such patients.

Table 1
Patient Characteristic at Presentation (N = 27)

Characteristic	Median (Range or %)
Age, Years	64 (39-88)
Hemoglobin g/dL	9.3 (7.8-11.6)
Leukocyte Count, 10^9/L	2.1 (1.8-6.4)
Platelet Count, 10^9/L	26 (2-378)
BM Blast %	20 (2-72)
Female	13 (52%)
ECOG Status	
0	5 (18.5%)
1	17 (63.0%)
2	5 (18.5%)
Diagnosis	
AML	18 (67%)
MDS	9 (33%)
Cytogenetic Category	
Complex	24 (89%)
5q and 1 Additional Abnormality	3 (11%)
Number of Previous Therapies	2 (0-6)
Previous Therapy	
High Dose Cytarabine	12 (44%)
Hypomethylating Agent	9 (33%)
Clofarabine	1 (4%)
Untreated	5 (19%)

Abbreviations: AML = acute myeloid leukemia; BM = bone marrow; ECOG = Eastern Cooperative Oncology Group; MDS, myelodysplastic syndromes.

Table 2
Most Frequent Grade 3 or Higher Adverse Events

Adverse Events	Number of Patients (%)
Neutropenia	8 (30)
Thrombocytopenia	14 (52)
Neutropenia Fever	4 (15)
Neutropenic Fever With Pneumonia	3 (11)
Nonneutropenic Infection	13 (48)
Fatigue	3 (11)