Dose Escalation of Lenalidomide in Relapsed or Refractory Acute Leukemias

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ABSTRACT

Purpose

Lenalidomide is effective in myeloma and low-risk myelodysplastic syndromes with deletion 5q. We report results of a phase I dose-escalation trial of lenalidomide in relapsed or refractory acute leukemia.

Patients and Methods

Thirty-one adults with acute myeloid leukemia (AML) and four adults with acute lymphoblastic leukemia (ALL) were enrolled. Lenalidomide was given orally at escalating doses of 25 to 75 mg daily on days 1 through 21 of 28-day cycles to determine the dose-limiting toxicity (DLT) and maximum-tolerated dose (MTD), as well as to provide pharmacokinetic and preliminary efficacy data.

Results

Patients had a median age of 63 years (range, 22 to 79 years) and a median of two prior therapies (range, one to four therapies). The DLT was fatigue; 50 mg/d was the MTD. Infectious complications were frequent. Plasma lenalidomide concentration increased proportionally with dose. In AML, five (16%) of 31 patients achieved complete remission (CR); three of three patients with cytogenetic abnormalities achieved cytogenetic CR (none with deletion 5q). Response duration ranged from 5.6 to 14 months. All responses occurred in AML with low presenting WBC count. No patient with ALL responded. Two of four patients who received lenalidomide as initial therapy for AML relapse after allogeneic transplantation achieved durable CR after development of cutaneous graft-versus-host disease, without donor leukocyte infusion.

Conclusion

Lenalidomide was safely escalated to 50 mg daily for 21 days, every 4 weeks, and was active with relatively low toxicity in patients with relapsed/refractory AML. Remissions achieved after transplantation suggest a possible immunomodulatory effect of lenalidomide, and results provide enthusiasm for further studies in AML, either alone or in combination with conventional agents or other immunotherapies.

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INTRODUCTION

Adult patients with acute leukemia who do not respond to initial therapy or who experience relapse after initial complete remission (CR) are unlikely to experience long-term survival with currently available conventional therapies.¹ Via the immunologic graft-versus-leukemia effect, allogeneic transplantation has curative potential for these patients, but only a minority are eligible for transplantation because of the challenges of comorbidity, donor identification, and disease control.¹⁻⁵ Novel approaches and agents are needed to improve outcomes in patients with high-risk acute leukemia.

Lenalidomide is an immunomodulatory agent active in a number of hematologic malignancies; it is US Food and Drug Administration approved in patients with transfusion-dependent anemia as a result of lower risk myelodysplastic syndromes (MDS) with deletion of the long arm of chromosome 5 [del(5q)] and is also approved for second-line treatment of multiple myeloma.^{6,7} Its mechanisms of action remain incompletely understood, although numerous activities in different disease subsets include activation of cellular and innate immunity, enhancement of humoral antitumor immune response, inhibition of protein phosphatase 2A, induction of expression of the tumor suppressor

SPARC, antiangiogenesis, and cytokine inhibition.⁸⁻¹³ Lenalidomide has unique clinical activity for lower risk patients with MDS with del(5q), with a response rate of 76% and cytogenetic CR in 45% of patients.¹⁴ However, in higher risk patients with MDS with del(5q), the response rate decreases to 27% with only rare cytogenetic CRs.¹⁵ Similarly, the cytogenetic CR rate in patients with lower risk MDS without del(5q) is 9%.¹⁶ Logically, one would expect cytogenetic CR at the same dose to be even less common in patients with acute myeloid leukemia (AML) without del(5q).

The dose of lenalidomide in MDS is limited by myelosuppression; lenalidomide is initiated at 10 mg daily with frequent dose reductions and delays caused by myelotoxicity. Considering that conventional therapy for acute leukemia is typically associated with prolonged and severe myelosuppression, dose escalation of lenalidomide may be feasible with acceptable myelotoxicity in this population. We hypothesized that escalation of lenalidomide dose above 10 mg would have acceptable toxicity and might improve response in adult patients with acute leukemia with relapsed or refractory disease, and we performed a phase I dose-escalation trial to investigate this hypothesis.

PATIENTS AND METHODS

Eligibility Criteria and Study Design

This study enrolled adult patients (≥ 18 years old) with relapsed/refractory non-M3 AML or acute lymphoblastic leukemia (ALL). Patients were required to have total bilirubin $\leq 2 \times$ upper limit of normal, creatinine ≤ 2.0 mg/dL, ALT/AST $\leq 5 \times$ upper limit of normal, left ventricular ejection fraction at least 40%, and Eastern Cooperative Oncology Group performance status ≤ 2 . Active infection was permitted if controlled. Informed written consent approved by The Ohio State University Human Studies Committee was obtained for all patients before study entry.

Lenalidomide dose was escalated in separate cohorts using a classic 3+3 phase I design schema to determine the maximum-tolerated dose (MTD). The cohort doses of lenalidomide were 25, 35, 50, and 75 mg with no intrapatient dose escalation. After establishment of the MTD, a planned 12-patient expansion group was included to better estimate the tolerability of this dose and to provide a preliminary efficacy assessment. Lenalidomide was administered daily on days 1 through 21 of 28-day cycles. The initial response assessment occurred after cycle 1 of treatment. Patients were eligible to receive additional cycles of treatment beyond cycle 1 in the absence of disease progression, which was defined as a 25% increase in blood or bone marrow (BM) blasts. During the dose escalation, patients who were removed from study before completion of cycle 1 were replaced if the patient did not experience significant drug toxicity (and was not evaluable for dose-limiting toxicity [DLT] assessment). Responses were defined according to International Working Group criteria for AML.¹⁷ Hydroxyurea was permitted before treatment and during the first week of treatment, if necessary, to maintain a WBC count less than 40,000/ μ L, but no other antileukemic therapies were permitted.

Definition of DLT

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). DLT was defined with cycle 1 of therapy. Nonhematologic grade 3 to 4 or uncontrolled or intolerable grade 2 toxicities attributable to lenalidomide were defined as DLTs. If the toxicity occurred in two or more patients at a single dose level, then that dose was deemed intolerable and the next lower dose level was expanded to increase confidence in toxicity assessment at the MTD. Given the high frequency of infectious complications with conventional chemotherapy in this population and prevalence of disease-related cytopenias, infectious complications were not considered DLT unless severity or duration was longer than that expected with conventional treatment. Hematologic DLT was de-

fined as failure to achieve an absolute neutrophil count greater than 1,000/ μ L and a platelet count greater than 25,000/ μ L (without platelet transfusion for the 7 preceding days) within 5 weeks from the last dose of lenalidomide in patients whose BM biopsy at end of cycle 1 (days 25 to 28) showed less than 5% blasts.

Pharmacokinetic Analysis

Lenalidomide plasma concentrations were measured by ABC Laboratories (Columbia, MO) with a validated liquid chromatography–tandem mass spectrometry assay for the determination of lenalidomide in human plasma containing K₂ EDTA as the anticoagulant in the linear range of 5 to 1,000 ng/mL. The extraction used 0.200 mL of human plasma, and carbon-13–lenalidomide was used as the internal standard. Plasma samples were collected before dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 24 hours after dose on day 1, as well as before morning dosing on days 8, 15, and 21 during the first cycle of therapy. Resulting concentration–time data for each patient were used to generate noncompartmental pharmacokinetic (PK) parameter estimates in WINNonlin (version 5.2; Pharsight Corp, Mountain View, CA).

RESULTS

Patient characteristics are listed in Table 1.

Table 1. Patient Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	No. of Patients
AML	31
ALL	4
Age, years	
Median	63
Range	22-80
Presenting WBC, $\times 103/\mu$ L	
Median	2.1
Range	0.2-45
No. of prior therapies	
Median	2
Range	1-4
Previous transplantation	
Autologous	1
Allogeneic	7
Untreated relapse after allogeneic transplantation	4
Refractory to last therapy	23
Primary refractory AML	8
Untreated relapse	12
Last CR duration < 1 year	8
Prior anthracycline/high-dose cytarabine*	30
Adverse risk cytogenetics†	17
del(5q) present	
Sole abnormality	1
Complex karyotype	1
Molecular characterization studies‡	32
NPM1 mutation	3
CEPBA mutation	3
FLT3 ITD	5

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CR, complete remission; ITD, internal tandem duplication.

*The other five patients were 68, 70, 70, 74, and 78 years of age; each had previously received decitabine for a median of 5 months (range, 3 to 8 months) without response (all listed as primary refractory).

†Cytogenetic risk was assessed by Cancer and Leukemia Group B criteria.^{18,19}

‡Molecular studies used previously published methods.²⁰⁻²²

Dose Escalation and Treatment

Patients were treated orally once daily with lenalidomide on days 1 through 21 of 28-day cycles at the following dose levels: 25 mg (n = 4), 35 mg (n = 9), 50 mg (n = 19, including the expansion at the MTD), and 75 mg (n = 3). The median number of cycles received was one (range, one to seven cycles). The DLT was fatigue, occurring in two patients at 75 mg; thus, 50 mg was declared the recommended phase II dose. The 35-mg dose level was expanded as a result of sudden death in an 80-year-old man with AML in first relapse (presumed to be a result of sepsis; autopsy ruled out pulmonary embolism). The 50-mg dose level was expanded initially because of line-associated thrombosis and then further expanded for preliminary efficacy assessment at the MTD.

No patient was replaced as a result of toxicity. Six patients were replaced as a result of disease progression before completion of cycle 1, including one patient at 25 mg, three patients at 35 mg, and one patient at 50 mg daily. One patient at 35 mg was replaced because of withdrawal of consent after one dose; the patient had no toxicity but elected alternative therapy. Replaced patients were included in the denominator for clinical response. Over the course of the entire trial, discontinuation of therapy occurred for the following reasons: no response (n = 27), toxicity without response (n = 3), toxicity in patients achieving CR (n = 2), relapse after achieving CR (n = 2), and patient decision to withdraw consent (n = 1). One patient in whom therapy was discontinued after no response subsequently achieved CR 2 months later with no intervening therapy.

Toxicities

No patient experienced hematologic DLT. Although typically administered in the outpatient setting, the treatment approach was associated with infectious complications frequently requiring inpatient hospitalization. Febrile neutropenia or grade 3 or higher infectious complications occurred in 17 patients (48%). Death from any cause within 30 days of trial entry occurred in five (14%) of 35 patients. Death was a result of progressive disease in three patients and sepsis in the setting of active leukemia in the other two patients. Grade 3 or higher nonhematologic toxicities regardless of attribution are listed in Table 2. Toxicities meeting DLT criteria, including patients in the MTD expansion at 50 mg, were sudden death (35 mg, n = 1; patient previously described), rash (50 mg, n = 1), line-associated thrombosis (50 mg, n = 1), and fatigue (50 mg, n = 1; 75 mg, n = 2). The rash occurred in a patient with AML who

received lenalidomide for relapse after allogeneic transplantation and is described in more detail in the following section. Despite concerns that higher dose lenalidomide would be associated with increased risk of thromboembolism, this toxicity was infrequent, even during multiple cycles of therapy. One thrombosis event occurred as noted; it was line associated and not life threatening. It was managed successfully with line removal and supportive care without anticoagulation because of severe thrombocytopenia.

Fatigue was significant and dose limiting. Recognizing that fatigue is a commonly encountered disease-related problem in this population, the fatigue attributed to lenalidomide was beyond that typically seen in patients with acute leukemia. Two patients treated at 75 mg experienced profound fatigue (one with grade 3 and one with grade 4). In the patient with grade 4 fatigue, the patient took lenalidomide for less than 1 week. Fatigue was improving 48 hours after discontinuation when the patient developed new symptoms ultimately caused by *Candida* sepsis, which was fatal. In the patient with grade 3 fatigue, the symptoms worsened to this grade in the third week of lenalidomide treatment and then improved with discontinuation of the drug.

Clinical Responses

Of 31 patients with AML, five patients achieved response, all of which were CRs. None of the four patients with ALL responded. Presenting characteristics and laboratory parameters during treatment for responding patients are listed in Table 3. Responses occurred only in patients with lower baseline WBC count; the highest presenting WBC count in a responder was 3,500/ μ L (except one patient with solely extramedullary disease and normal blood counts; Fig 1). None of the responding patients had del(5q). Of the five responders, three had pretreatment cytogenetic abnormalities (patients had complex karyotype, monosomy 7, or trisomy 13).²³ All three patients achieved cytogenetic CR. The response duration ranged from 5.6 to 14 months. We previously reported CR in the patient with trisomy 13.²³ There was no correlation of mutational status for *FLT3*, *NPM1*, or *CEBPA* with response.

CR occurred at each tolerable dose level of 25 mg (n = 1), 35 mg (n = 1), and 50 mg (n = 3). Achievement of CR was delayed beyond 2 months from initiation of therapy in each patient, although four of five responding patients showed evidence of activity during the first cycle. In one patient without early improvement, the patient achieved CR 2 months after therapy had been discontinued because of persistent disease after two cycles. No further therapy had been administered in the interim.

Seven patients were enrolled after AML relapse after allogeneic transplantation. Of four patients who received lenalidomide as initial therapy for relapse in this setting, two patients achieved CR, with response durations of 8.9 and 14 months. In each patient, withdrawal of immunosuppression was ineffective and associated with no graft-versus-host disease (GVHD). Lenalidomide was initiated more than 1 month after the withdrawal. Both patients experienced a pruritic rash within 2 weeks of starting lenalidomide requiring temporary discontinuation of drug. Skin biopsies were inconclusive for etiology but consistent with GVHD. No donor leukocyte infusion was given to any of these patients.

Both responders were treated with an initial lenalidomide dose of 50 mg daily but required dose reductions as a result of rash. One patient received a total of only 19 days of lenalidomide therapy over 2

Table 2. Grade 3 or Higher Nonhematologic Toxicities Regardless of Attribution by Dose Level

Dose Level (mg)	No. of Patients at Dose Level	Toxicity
25	4	Febrile neutropenia (n = 1)
35	9	Pneumonia (n = 2), febrile neutropenia (n = 2), sepsis/hypotension (n = 1)*
50	19	Catheter-associated DVT (n = 1), pneumonia (n = 4), rash (n = 3), febrile neutropenia (n = 7), fatigue (n = 1)
75	3	Fatigue (n = 2), sepsis (n = 1)

Abbreviation: DVT, deep vein thrombosis.

*Death from sepsis.

Table 3. Characteristics and Treatment Course for Responding Patients With AML

Dose	Age (years)	History	Cytogenetics	Laboratory Parameters					Time to CR (weeks)
				WBC (μL)	ANC (μL)	Platelets (μL)	Marrow Blasts (%)	Cytogenetics	
35 mg	68	Untreated first relapse; first CR duration, 3.5 years	94(4n),XXYY,+13,+13						
Pretreatment				1,700	530	45,000	40	Trisomy 13	
4 weeks				1,200	10	16,000	16	Trisomy 13	
8 weeks				900	40	27,000	Not done	Not done	
At CR				7,500	4,275	210,000	< 5	Normal	11
50 mg	70	Experienced failure with first-line decitabine	Normal						
Pretreatment				3,500	110	17,000	33		
4 weeks				2,400	50	12,000	29		
8 weeks				2,200	0	9,000	34		
At CR				3,500	1,500	142,000	3		16
50 mg	63	Allogeneic transplantation performed in second CR; relapse day +258	-7						
Pretreatment				1,300	665	15,000	18	-7	
4 weeks				1,300	90	21,000	5	-7	
8 weeks				2,300	1,000	163,000	Not done	Not done	
At CR				3,200	1,700	144,000	0	Normal	12
50 mg	66	Allogeneic transplantation performed in second CR; relapse day +130	45,XY,-7,-17,der(21)add(21)(p11.2)add(21)(q22),+mar1						
Pretreatment				1,300	640	61,000	40	Abnormal	
4 weeks				500	20	4,000	40	Abnormal	
8 weeks				900	40	23,000	0	Normal	
At CR				6,500	5,100	156,000	0	Normal	12
25 mg	74	Untreated second relapse with extramedullary only disease*							

Abbreviations: AML, acute myeloid leukemia; ANC, absolute neutrophil count; CR, complete remission.

*Patient had extensive leukemia cutis with no blood or marrow involvement at enrollment. Disease resolved completely after 3 months of treatment.

months before achieving morphologic and cytogenetic CR durable for more than 14 months. Pretreatment chimerism studies showed 30% donor CD3 cells and 82% donor CD33 cells. Chimerism studies at CR showed 100% donor cells in all compartments. The second patient developed rash after only 2 days of drug and ultimately completed two cycles of lenalidomide before CR was documented. Pretreatment chimerism studies from peripheral blood showed 6% donor CD3 cells and 100% donor CD33 cells (patient did not have circulating blasts, and disease was in marrow including cytogenetic relapse). In contrast to the first patient, chimerism studies at CR showed 0% donor CD3 cells and 100% donor CD33 cells. These responses after allogeneic transplantation are described in greater detail in the Appendix (online only).

Fig 1. Clinical response by presenting WBC count for each patient with acute myeloid leukemia (AML; n = 31).

PK Analysis

Data from 26 patients were available for analysis; additional patients accrued at the MTD were not assessed for PK end points. Mean concentration-time data are presented for each dose level in Figure 2A, and a summary of PK parameter estimates is presented in Table 4. Lenalidomide maximum plasma concentrations ($C_{\max}$) and PK parameter estimates were similar to those previously reported.^{24,25} $C_{\max}$ ($R^2 = 0.54$, $P < .001$) and area under the concentration-time curve ($R^2 = 0.28$, $P = .005$) increased proportionally with dose. Drug clearance was independent of dose and correlated with calculated creatinine clearance ($R^2 = 0.43$, $P < .001$), as indicated in Figure 2B. Trough plasma concentrations measured on days 8, 15, and 21 were variable among patients. Mean trough concentrations for each dose level on day 21 ranged from 13 to 91 ng/mL and indicated little or no accumulation during the 3 weeks of treatment. At the MTD, the mean $C_{\max}$, area under the concentration-time curve from 0 to 24 hours, and half-life were 946 ± 382 ng/mL, 5509 ± 2086 h $\times$ ng/mL, and 4.11 ± 1.23 hours, respectively. No significant associations were observed between PK parameters and clinical outcomes.

DISCUSSION

Lenalidomide can be safely dose escalated in acute leukemia above the MDS starting dose of 10 mg daily. High-dose, single-agent lenalidomide was administered in the outpatient setting with acceptable tolerability at doses up to 50 mg daily in patients with poor risk, relapsed, or refractory adult acute leukemia. Doses of lenalidomide greater than 50

Fig 2. (A) Lenalidomide pharmacokinetics. Mean plasma lenalidomide concentration-time profiles for each dose level. Error bars are standard deviations. (B) Creatinine and lenalidomide clearance. Data points represent estimated noncompartmental lenalidomide clearance (CL/F) and calculated creatinine clearance (CL; Cockcroft-Gault formula).

mg produced significant fatigue that was dose limiting in this population. Although all patients experienced myelosuppression and many had infectious complications, the regimen had reduced toxicity relative to typical reinduction approaches with combination chemotherapy. Plasma levels reached or exceeded lenalidomide concentrations previously shown to enhance ligand-dependent activation of natural killer cells,²⁶ reverse impaired immunologic synapse formation in T cells,¹³ and reverse humoral tolerance to chronic lymphocytic leukemia cells.⁸

Clinical activity in AML was observed with a 16% CR rate; responses were durable, lasting 5.6 to 14 months. The majority of the patients with AML (27 of 31 patients) enrolled onto this study were refractory to the last treatment administered or had experienced relapse within 1 year of prior CR. Historical experience in relapsed/refractory AML highlights the importance of first CR duration in estimating likelihood of achieving subsequent remission with conventional therapy, with an expected CR rate of only 14% with combination cytotoxic chemotherapy for patients with first relapse of AML with CR duration of less than 1 year.²⁷ Recent reports in this setting with conventional chemotherapy alone or in combination with novel therapeutics had similar CR rates.^{28,29} The limitations of our phase I study include small patient numbers with somewhat varied natural history that prevent us from making more than inferences about future directions for development of lenalidomide in AML. Although a preliminary CR rate of 16% remains far from acceptable, the response rate in relapsed and refractory AML with new therapeutics is generally low and often is much higher when applied to de novo patients, as was seen with both clofarabine and decitabine, for example.³⁰⁻³³ Our observations provide encouragement for further clinical development of lenalidomide in AML irrespective of cytogenetic subtype.

Examination of the pretreatment features of the patients with AML who responded to lenalidomide and exploration of its known mechanisms of action can provide prospective hypotheses on which to build subsequent studies with this agent. Patients in this trial who responded to lenalidomide did not have a high WBC count (a marker of proliferation) and had a higher frequency of response in the setting of relapse after allogeneic stem-cell transplantation. All of the patients who responded after transplantation had received immunosuppression withdrawal and continued to have evidence of active leukemia with no GVHD at initiation of treatment. Given that lenalidomide has been shown by several groups, including our own, to enhance innate, cellular, and humoral activation,^{8,10,34-37} an immunologic mechanism of action contributing to the antileukemic effect in this setting is likely. Indeed, since closure of this study, we have treated with lenalidomide (50 mg/day) an additional patient with MDS who experienced relapse after allogeneic stem-cell transplantation. The patient developed clinical evidence of skin GVHD after 2 weeks of treatment, which was then discontinued; the patient subsequently achieved CR with full donor chimerism (duration > 1 year at last follow-up). Moving forward with this hypothesis, an attractive time to administer lenalidomide is as maintenance therapy after allogeneic stem-cell transplantation for patients with high-risk AML without serious GVHD. Given the observations in this study, we have embarked on a phase I study of lenalidomide beginning 60 days after allogeneic transplantation for patients

Table 4. Plasma Lenalidomide Pharmacokinetic Parameters After a 25- to 75-mg Dose of Lenalidomide on Day 1 of Treatment

Dose (mg)	No. of Patients	C _{max} (ng/mL)		T _{max} (hours)		AUC ₀₋₂₄ (h×ng/mL)		K _{el} (h ⁻¹)		t _{1/2} (hours)		CL/F (mL/min)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
25	4	423	83	1.19	0.55	2,415	1,368	0.203	0.081	3.89	1.66	201	106
35	9	770	216	1.42	0.78	5,085	2,778	0.166	0.045	4.66	2.13	134	57
50	10	946	382	1.91	1.66	5,509	2,086	0.186	0.067	4.11	1.23	168	73
75	3	1,690	495	1.52	0.48	12,888	11,013	0.188	0.133	5.11	3.24	143	101

Abbreviations: C_{max}, maximum plasma concentration; T_{max}, time to maximum serum concentration; AUC₀₋₂₄, area under the concentration-time curve from 0 to 24 hours; K_{el}, elimination rate constant; t_{1/2}, terminal half-life; CL/F, drug clearance; SD, standard deviation.

with high-risk AML. Further studies should follow-up on the surprising observation that one of the two patients who achieved response after allogeneic transplantation in this study had 0% donor CD3 cells at the time of CR. Additional patient experience with this therapy will be important to discern whether a lenalidomide-induced graft-versus-leukemia effect reproducibly exists and whether this effect is a result of donor effector cells that are not T lymphocytes.

In chronic lymphocytic leukemia, we have demonstrated that lenalidomide can reverse tolerance, and we observed promotion of antitumor antibodies in at least one patient who had a durable remission with this treatment.⁸ An elegant report recently showed formation of antibodies specifically targeting the AML antigen nucleolar and spindle-associated protein 1 (NuSAP1) after allogeneic BM transplantation.³⁸ Although this work was unrelated to lenalidomide, the potential for lenalidomide to enhance humoral response to AML in the post-allogeneic transplantation setting should be explored. Investigations of modulation of innate, cellular, and humoral response to the AML clone are ongoing. Although our clinical data support an immunologic mechanism of action of lenalidomide in this setting, alternative direct antitumor effects such as induction of SPARC expression¹¹ or protein phosphatase 2A activity⁹ represent other potential mechanisms of action of this drug in AML, which are currently under active investigation by our group.

These data justify further trials of lenalidomide as a single agent in de novo AML and in AML after allogeneic transplantation. Studies in combination with cytotoxic agents or alternative immune-based therapies should also be pursued. Given the small number of patients treated in this trial and limited experience of this treatment, use of lenalidomide in AML should only be applied in the context of a clinical trial. The novel mechanisms of lenalidomide activity, which remain incompletely understood, provide hope for productive new avenues of research in this area.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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