A phase 2 study of lenalidomide monotherapy in patients with deletion 5q acute myeloid leukemia: Southwest Oncology Group Study S0605

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Older acute myeloid leukemia (AML) patients with a chromosome 5q deletion have poor outcomes with conventional chemotherapy. This phase 2 study explored the safety and efficacy of single-agent lenalidomide in previously untreated older AML patients with del(5q) who declined standard chemotherapy. Patients were treated with lenalidomide 50 mg daily for 28 days as induction therapy and 10 mg daily for 21 days of a 28-day cycle as maintenance until disease progression or unacceptable toxicity. Among 37 evaluable patients, the median age was 74 years (range, 60-94), 21 (57%) were female, 19 (51%) had prior myelodysplastic syndrome, and 30 (81%) had pretreatment cytogenetic studies evaluated centrally. Six had isolated del(5q), 1 had del(5q) and +8, 23 had complex cytogenetics, and 7 others had del(5q) identified locally. Fourteen patients (38%) completed induction therapy: 7 patients died during induction therapy, 8 had disease progression, 7 had nonfatal adverse events, and 1 entered hospice. Eight patients started maintenance therapy. Five patients (14%) achieved a partial or complete response, 2 with isolated del(5q) and 3 with complex cytogenetics. Relapse-free survival was 5 months (range, 0-19). Median overall survival was 2 months for the entire population. In conclusion, lenalidomide as a single agent has modest activity in older del(5q) AML patients. Southwest Oncology Group Study S0605 is registered at www.clinicaltrials.gov as NCT00352365. (*Blood*. 2011;118(3):523-528)

Introduction

Acute myeloid leukemia (AML) is a disease of older adults, with a median age at onset of 67 years in the United States.[1] Older AML patients (> 60 years) have a dismal prognosis: complete response (CR) rates with cytarabine-based cytotoxic induction therapy are 15%-45% lower than those in their younger counterparts (40%-55% compared with 70%-85%, respectively); 5-year disease-free survival rates may be as low as one-fifth that of younger adults (5%-15% compared with 30%-40%, respectively); and there are even greater differences when the very old are compared with the very young.[2-6] This is caused in large part by differences in the pathobiology of the disease for older adults, including: chemotherapy resistance due to drug efflux pumps such as the multidrug resistance protein (MDR1), evolution of AML from antecedent hematologic disorders such as myelodysplastic syndrome (MDS), and higher rates of nonfavorable cytogenetic abnormalities compared with younger AML patients.[7-10] Specifically, up to 20%-30% of older patients harbor abnormalities of chromosome 5, alone or in combination with other cytogenetic abnormalities. In these patients, CR rates decrease by an additional 20%-30% to approximately 20%-25%.[8]

Most AML patients, particularly the very old, are not offered chemotherapy. One study of Medicare recipients reported that only 30% of AML patients over the age of 65 years received any type of therapy, which could have included low- or high-dose regimens.[11] It also is not clear that induction therapy benefits older adults, with some prospective and retrospective analyses supporting the use of cytarabine-based ablative therapies, particularly in select subgroups of older adults, and others finding no clear benefit to dose intensification.[12-15] Further, potential improvements in outcome are often offset by treatment-related mortality associated with induction chemotherapy that may approach 25%, thus negating any survival benefit.

Efforts have been made to expand the use of less-toxic chemotherapy regimens to older AML patients. Low-dose cytarabine yields CR in 18% of patients, although the benefit is limited to patients without adverse cytogenetics. Hypomethylating agents (azacitidine in particular) have been shown to improve survival compared with standard chemotherapy in patients with unfavorable karyotype and in AML patients with < 30% blasts.[15-17] Another MDS therapy, lenalidomide, has particular efficacy in lower-risk MDS patients with del(5q), selectively suppressing the clone through inhibition of haplodeficient cell cycle–regulatory targets coded within the 5q31 commonly deleted region[18,19] complemented by effects on the bone marrow microenvironment. In these patients, transfusion independence was achieved in 67% and cytogenetic CRs in 44%.[20] In a phase 2 study of lenalidomide in higher-risk MDS patients who harbored the del(5q) abnormality (alone or in combination with other cytogenetic abnormalities), 20% of patients—all of whom had isolated del(5q) lesions—responded to lenalidomide.[21] Isolated reports of CRs to lenalidomide treatment

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of AML patients with del(5q) suggest that activity may extend to cytogenetically related myeloid malignancies such as AML.[22-24] Whether AML patients with the del(5q) cytogenetic abnormality retain similar enough disease biology to MDS patients with the same abnormality to routinely respond similarly to lenalidomide has not yet been determined. This phase 2 study explored the safety and efficacy of high-dose, single-agent lenalidomide in previously untreated older patients with AML and the del(5q) cytogenetic abnormality.

Methods

Patients

Older patients (> 60 years) with untreated AML defined by 2001 World Health Organization (WHO) criteria without t(15;17) who harbored a del(5q) cytogenetic abnormality (alone or in combination with other abnormalities) and who declined or were felt to be poor candidates for intensive induction chemotherapy were eligible. This included patients with both de novo and secondary AML (after an antecedent hematologic disorder or after chemotherapy or radiation therapy for a non-AML malignancy). Patients must not have received prior systemic chemotherapy for acute leukemia with the exception of hydroxyurea, but could have previously received disease-modifying therapy for MDS, with the exception of lenalidomide, cytarabine > 100 mg/m^2 daily, or stem cell transplantation. The protocol and informed consent document were approved by the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute and the institutional review boards of participating Southwest Oncology Group (SWOG) member sites. Written informed consent was obtained from all patients before enrollment in accordance with the Declaration of Helsinki. SWOG Study S0605 is registered at http://www.clinicaltrials.gov as NCT00352365.

Treatment schema

Patients were treated with lenalidomide at a dose of 50 mg daily for up to 28 days as induction therapy. This was the maximum tolerated dose in a phase 1 study of single-agent lenalidomide in relapsed/refractory AML.[25] Concomitant cytotoxic or growth factor therapies were not allowed, though hydroxyurea could be given to lower the white blood cell count to < 30 000/mL up to 24 hours before lenalidomide initiation. Bone marrow biopsies were performed as safety checks on days 14 and 21 of therapy, with discontinuation of study medication for a bone marrow cellularity of < 10%. The study drug was not supposed to be discontinued for persistent blasts at these bone marrow assessments.

Patients achieving stable disease or better on an efficacy bone marrow assessment performed on day 28 or later could receive maintenance lenalidomide at a dose of 10 mg daily for 21 days of a 28-day cycle. Neutrophil and platelet counts must have recovered to pretreatment levels and nonhematologic adverse events must have resolved to grade 2 or less. Postremission therapy could continue until disease progression or unacceptable adverse events.

Response and toxicity definitions

Responses were defined according to 2003 International Working Group (IWG) response criteria.[26] A CR was defined as having an absolute neutrophil count ≥ 1000/μL, a platelet count ≥ 100 000/μL, < 5% bone marrow blasts, no Auer rods, and no evidence of extramedullary disease. CR with incomplete blood count recovery (CRi) required the same results as CR, but the absolute neutrophil count (ANC) could be < 1000/μL and/or the platelet count could be < 100 000/μL. Partial response (PR) required an ANC > 1000/μL, a platelet count < 100 000/μL, and at least a 50% decrease in the percentage of marrow blasts to 5%-25% or marrow blasts < 5% with persistent Auer rods. Progressive disease was defined as a > 50% increase in blast percentage or development of extramedullary leukemia, with stable disease defined as not meeting the criteria of CR, CRi, PR, or progressive disease. Overall survival (OS) was measured from entry into the clinical trial until death from any cause, with observations censored for patients last known alive. Relapse-free survival (RFS) was measured from date the CR or CRi was established until relapse of leukemia or death from any cause, with observations censored for patients last known to be alive without report of relapse.

Cytogenetic studies and response evaluation

Metaphase cytogenetic studies were performed at previously approved laboratories for protocol eligibility and subsequently centrally reviewed by the SWOG Cytogenetics Committee. All eligible patients had the presence of the del(5q) cytogenetic abnormality confirmed at the treating institution. A major cytogenetic response was defined as no detectable cytogenetic abnormality, whereas a minor cytogenetic response required a 50% or more reduction in the proportion of abnormal metaphases with no new clones and no clonal evolution. FISH studies were not required for reporting to the Cytogenetics Committee and may not have been included in the review process. The National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 was used to determine severity of adverse events.

Statistical analysis

Enrollment from October 2006 through June 2010 was in 2 stages. Initially, 20 patients were registered; if at least 1 CR/CRi was observed using IWG criteria, an additional 20 patients could be enrolled. The study was designed with a critical level of 4.7% (erroneously concluding the regimen warrants further study if the true response rate is 5% or less) and power of 92% (probability of concluding that a response rate of 20% warrants further study).

The OS distribution was estimated by the method of Kaplan and Meier.[27] Confidence intervals (CIs) were calculated at the 95% confidence level and *P* values are 2-tailed. Baseline values and cytogenetic characteristics were examined in descriptive analyses. Results were based on data available as of November 2010.

Results

Baseline characteristics

Of 41 patients enrolled, 4 were excluded (2 without AML, 1 without del(5q), and 1 who died before receiving therapy), leaving 37 for adverse event and efficacy analyses. The median age was 74 years (range, 60-94), 21 (57%) were female, 33 (89%) were white, and 19 (51%) had a prior MDS diagnosis (Table 1). The median presenting white blood cell count was 2600/μL (range, 600-658 000), platelet count was 53 000/μL (range, 6000-4 000 000), and 30 patients (81%) had a performance status of 1. WHO classifications included AML with multilineage dysplasia (10 patients [27%]), secondary AML (4 patients [11%]), and AML not otherwise categorized (10 patients [27%]); whereas French-American-British classifications included myelomonocytic AML (4 patients [11%]), AML with maturation (4 patients [11%]), AML without maturation (3 patients [8%]), and 1 patient each with minimal differentiation and erythroleukemia (6%).

Treatment outcome: adverse events

Fourteen patients (38%) completed protocol induction therapy, and 8 (57% of those completing induction therapy, 21% of total) initiated postremission (maintenance) lenalidomide. Of the remaining 23 patients who did not complete induction therapy, 7 died during induction therapy; 3 of these deaths were due to adverse events (1 respiratory, 1 cardiac, and 1 febrile neutropenia) thought to be at least possibly related to therapy, 2 to disease progression,

Table 1. Baseline characteristics of subjects

Characteristic	Median (range or %), n = 37
Age (y)	74 (60-94)
Sex, female/male	21/16
Race, white/black or non-white	33/4
Prior MDS diagnosis	19 (51%)
Baseline:	
WBC, $\times 10^3$/mL	2.6 (0.6-658)
Platelet count, $\times 10^3$/mL	53 (6-4000)
Peripheral blasts, %	4 (0-72)
Marrow blasts, %	38 (17-90)
Zubrod performance status	
0	7 (19%)
1	30 (81%)
2	0
WHO or FAB classification	
AML with multilineage dysplasia	10 (27%)
AML not otherwise specified	10 (27%)
Secondary AML (prior MDS or therapy-related)	4 (11%)
Myelomonocytic leukemia	4 (11%)
AML with maturation	4 (11%)
AML without maturation	3 (8%)
AML with minimal differentiation	1 (3%)
Acute erythroid leukemia	1 (3%)
Cytogenetic abnormalities, 30 (81%)	
Isolated del(5q) by FISH	1 (3%)
Isolated del(5q) by MC	5 (17%)
Isolated trisomy 8 by MC, del(5q) by FISH	1 (3%)
Complex	23 (77%)

WBC indicates white blood cell count; FAB, French-American-British; and MC, metaphase cytogenetics.

and 2 to adverse events not related to therapy (1 respiratory and 1 cardiac; Table 2). One of the 14 patients who completed induction therapy also died of an induction-related adverse event (respiratory) 34 days after study registration. Eight patients were removed from induction therapy because of disease progression at a median of 28 days (range, 18-29 days) after the initiation of induction therapy, with 2 patients removed on days 18 and 19 and the remaining 6 between days 26 and 29. One other patient was removed from induction therapy due to declining health and opted for hospice care on day 24 after therapy initiation. Seven patients were removed from protocol therapy due to nonfatal adverse events (infection, renal, respiratory, gastrointestinal, and rash) during the induction cycle, with a median treatment duration of 20 days (range, 11-28 days). In addition to the 4 patients with fatal adverse events (3 during and 1 after completion of induction), 5 patients had grade 4 nonhematologic adverse events: hypocalcemia (2), fatigue (2), and infection (1; Table 2). Four of the 8 patients receiving maintenance therapy experienced 4 grade 3 adverse events (Table 3).

Treatment outcome: efficacy

Patients were followed for a median of 2 months (range, 0-27). Five (14%: 95% CI 5%-29%) of the 37 evaluable patients achieved CR/CRi/PR, all of whom completed the induction therapy course; 3 of the 5 relapsed after 0, 2, and 5 months; 1 died 15 months after CR without a report of relapse; and 1 is alive without a report of relapse 19 months after achieving a PR during maintenance therapy (Table 4). The median duration of RFS for responders was 5 months (range, 0-19 months) and the median OS was 15 months (range, 2-23 months). Thirteen patients (35%) had stable disease after induction of therapy, 8 of whom completed the induction course. Of the 4 CR/CRi patients who completed induction therapy per protocol, 3 went onto protocol maintenance therapy. Five additional patients with stable disease went on to protocol maintenance therapy. One patient achieved a PR during maintenance therapy, 3 patients did not have further decrease of marrow blasts, and 1 patient did not have any reports of marrow examinations during or after maintenance therapy. Thirty-four of the 37 patients have died, and the median OS was 2 months (95% CI, 1 to 4 months). The follow-up time of the 3 survivors was 6, 23, and 24 months.

Table 2. Adverse events during the induction phase

	Lenalidomide (n = 37) Grade		
Adverse event	**3**	**4**	**5**
Alanine aminotransferase	0	1	0
Acute respiratory distress syndrome	0	1	0
Aspartate transaminase	0	1	0
Anorexia	1	0	0
Bilirubin	1	0	0
Cardiac ischemia/infarction	0	0	1
Cough	1	0	0
Creatinine	3	0	0
Dermatology-other	1	0	0
Diarrhea	2	0	0
Dyspnea	1	0	1
Fatigue	9	2	0
Febrile neutropenia	12	2	1
Gastrointestinal infection, 3-4 ANC: esophagus	1	0	0
Gastrointestinal infection, 3-4 ANC: gums	1	0	0
Hyperglycemia	2	0	0
Hypernatremia	1	0	0
Hypocalcemia	1	2	0
Hypokalemia	3	0	0
Hyponatremia	1	0	0
Lung infection, 3-4 ANC: lung	4	1	0
Muscle weakness: whole body	2	1	0
Nausea	1	0	0
Neuropathy-motor	1	0	0
Pneumonitis	3	1	0
Pulmonary-other	1	0	1
Rash	2	0	0
Renal failure	1	0	0
Skin infection, 3-4 ANC: lip/perioral	1	0	0
Skin infection, 3-4 ANC: skin	1	0	0
Vomiting	1	0	0
Maximum grade any adverse event, n	20	5	4

Grade 3 or higher nonhematologic adverse events. Events not likely or not related to treatment were excluded.

Table 3. Adverse events during the maintenance phase

	Maintenance lenalidomide (n = 8) Grade		
Adverse event	**3**	**4**	**5**
Febrile neutropenia	2	0	0
Induration	1	0	0
Infection, 0-2 ANC: blood	1	0	0
Maximum grade any adverse event, n	4	0	0

Events not likely or not related to treatment were excluded.

Table 4. Baseline characteristics by responders (CR, CRi, and PR) and nonresponders

Characteristic	Responders (n = 5)	Nonresponders (n = 32)
Median age in years (range)	68 (60-79)	74 (60-94)
Sex, female/male	2/3	19/13
Race (white/black or nonwhite)	5/0	28/4
Prior MDS diagnosis, %	3 (60%)	16 (50%)
Median baseline laboratory measurements (range)		
WBC, $\times 10^3$/mL	2.1 (0.6-11.1)	2.7 (0.7-658.0)
Platelets, $\times 10^3$/mL	73 (28-166)	51 (6-4000)
Peripheral blasts, %	0 (0-58)	6 (0-72)
Marrow blasts, %	45 (27-90)	36 (17-70)
Zubrod performance status, n (%)		
0	2 (40%)	5 (16%)
1	3 (60%)	18 (56%)
2	0	7 (22%)
3	0	2 (6%)
Cytogenetics		
Number of abnormalities, median n (range)	8 (1-20)	8 (0-31)
Normal cells within patient, median % (range)	30 (25-60)	5 (0-100)
del(5q) cells within patient, median % (range)*	70 (30-75)	95 (0-100)
Patients with 100% of tumor cells w/ del(5q), %*	3 (60%)	21 (84%)
−5 abnormality, n (%)	1 (20%)	2 (8%)
−7 abnormality, n (%)	2 (40%)	6 (24%)
del(7q) abnormality, n (%)	1 (20%)	2 (8%)

WBC indicates white blood cell count; and MC, metaphase cytogenetics.
*Excluding cells with monosomy 5 (−5).

Cytogenetics

Of the 37 evaluable patients, 30 (81%) had pretreatment cytogenetic studies evaluated centrally. The other 7 patients had the presence of del(5q) confirmed at the treating institution. One patient displayed no demonstrable abnormalities via metaphase karyotyping but had del(5q) as shown by interphase FISH in 134 of 200 cells examined. One patient had a trisomy 8 and no other abnormality via metaphase karyotyping but had del(5q) as shown by interphase FISH in 86 of 200 cells examined with loss of 1 allele and in 76 of 200 cells examined with loss of both alleles. Five patients had an isolated del(5q) lesion and 23 patients (77%) had complex karyotypes (≥ 3 abnormalities) that included a del(5q) abnormality. Of the 5 patients who achieved CR/CRi/PR, 2 had only the deletion of 5q, whereas 3 displayed complex karyotypes that included this abnormality (Table 5). Loss (monosomy) of a chromosome 7 was present in 2 of these complex karyotypes. No other abnormalities common to more than 1 patient were observed, and only 1 patient—a nonresponder—had a 17p deletion. Among the 5 responding patients, follow-up cytogenetics were available on 2. One patient with complex cytogenetics who achieved a CRi retained the complex abnormalities, including −5. The other patient with complex cytogenetics who achieved a CR reverted to normal cytogenetics. Information about median numbers of abnormalities, the percentage of normal and del(5q) cells for each patient, and the numbers of patients with −5, −7, and del(7q) abnormalities are shown in Table 4. There were no statistically significant differences between responders and nonresponders with respect to these abnormalities; however, such results are inconclusive given the small sample size.

Discussion

In contrast to the successes achieved in pediatric acute leukemias, survival for older AML patients has changed little in the past 3 decades. This is despite attempts varying the types of anthracyclines being used, the addition of other agents, and dose intensification. Given the inherent biologic complexity of AML in these patients, inroads can probably best be made by identifying molecular subtypes of patients whose disease is susceptible to specific agents.

We report herein the results of a phase 2 study using such an approach: applying metaphase karyotype or FISH test results to target patients with the del(5q) abnormality and using a therapeutic agent that has demonstrated efficacy in this patient population (albeit in a less-aggressive disease). We show that lenalidomide, when used as a single agent, had modest activity in older AML patients with the del(5q) cytogenetic abnormality. The CR/CRi/PR rate was at least half that seen with cytarabine-based cytotoxic approaches in patients with similar cytogenetic abnormalities and of similar age.

The use of lenalidomide was also associated with significant adverse events in this unhealthy patient group. Indeed, almost uniformly, patients had to be hospitalized during the induction phase of the regimen and most could not complete all 28 days of therapy. This was likely due to inherent disease properties, because Medicare data show that the median survival rate for older AML patients is approximately 2 months.[11] This may also have been the result of the inclusion criteria, which stipulated that patients had to either decline intensive remission induction therapy or be deemed unlikely to tolerate or benefit from it. Eight patients were removed from the study for "disease progression" before completion of the full induction course, and in some cases this decision may have been made too early to observe a therapeutic effect. Whereas bone marrow assessments were stipulated at days 14 and 21 for safety reasons, to ensure that the high dose of lenalidomide was not continued in the setting of disease absence and low bone marrow cellularity, all of these patients stopped therapy for persistence of blasts: 6 of 8 patients based on a day 21 bone marrow biopsy and the other 2 patients based on a day 14 bone marrow biopsy, all with a > 50% increase in blast percentage. The induction dose of

Table 5. Characteristics and outcome of responding patients

WHO classification	Marrow blasts, %	Karyotype	Clinical response	Time to relapse, mo*	Survival time, mo†
AML without maturation (M1)	35	Pretreatment (no follow-up available): 46,XX,del(5)(q31q33)[14]/46,XX[6]	CRi	2.8	15.1 (died)
AML otherwise categorized	90	Pretreatment: 55,XY,+Y,+4,-5,add(7)(q11.2),+8, +9,+10, +11,+14,der(17)t(17;18) (p11.2;q11.2), +22, +marx2[5]/54~55,sl,-der(17)t(17;18), +17,+18, +20,+21,-22,-marx2[cp12] Follow-up: 55,XY,+Y,+4,-5,add(7)(q11.2),+8, +9,+10, +11,+14,der(17)t(17;18) (p11.2;q11.2), +22, +marx2[2]/54,sl,-mar[4]/46,XY[12]	CRi	0.9	2.8 (died)
AML otherwise categorized	80	Pretreatment (no follow-up available): 90–92, XXYY,del(5)(q13q33),-7,+13,+13,der(15) t(9;15)(q12;p11.2),-21,-21, +mar1, +mar2[6]/ 47,XY,+9[2]/46,XY[12]	CR	13.8 (no report of relapse)	15.6 (died)
AML otherwise categorized	27	Pretreatment: 44,XY,del(1)(p36.1),del(5) (q13q33),-7,-10,del(12)(p11.2p12),-20, +mar[11]/44,sl,del(11) (q14q23)[3]/46,XY[6] Follow-up: 46,XY[20] (only 1 process, inadequate for interpretation)	CR	5.3	6.7 (alive)
AML with multilineage dysplasia	45	Pretreatment (no follow-up available): 46,XX,del(5)(q15q33)[15]/46,XX[5]	PR	20.2 (no report of relapse)	23.6 (alive)

*Time to relapse in months was measured from date of response until date of relapse or last contact.
†Survival time in months was measured from time of study entry until date of death or last contact.

lenalidomide was 5 times that used as standard therapy for MDS patients, resulting in cytotoxic effects and resultant profound cytopenias. This dose was chosen because AML was felt to be a more aggressive disease than lower-risk MDS (for which lenalidomide is approved by the Food and Drug Administration) and therefore would require a more ablative therapy.

This higher dose of lenalidomide, through its cytotoxicity, may have overcome some inherent disease resistance properties. In the Groupe Francophone des Myelodysplasies (GFM) study of lenalidomide in higher-risk MDS patients who harbored the del(5q) lesion, 20% of patients—all with an isolated del(5q) abnormality—achieved a CR. Conversely, in the present study, 3 of 5 responding patients had complex cytogenetic abnormalities, implying that the efficacy of the higher dose of lenalidomide may have been related to both specific and nonspecific cytotoxicities. One of these patients had a +8 abnormality among others. This lesion was also found in 1 patient in a previous report of patients who achieved a CR to azacitidine, lost their response, and then reachieved a CR with the addition of lenalidomide to azacitidine.[28] The +8 abnormality again surfaced in a study of MDS patients without del(5q) who responded to lenalidomide.[29] In that study, there did not appear to be major differences between responders and nonresponders in the numbers of cytogenetic abnormalities in patients who had 100% del(5q) expression or in patients with additional monosomy abnormalities. However, given the small sample size and overall modest response rate, these findings remain to be verified in a larger study.

Given that lenalidomide acts in part through inhibition of haplodeficient phosphatases coded in the 5q31 commonly deleted region, we also investigated whether there may be differential therapeutic effects in patients with high myeloblast proliferation or high total blast mass. There was no statistically significant association between response or OS and blast percentages or absolute blast counts. However, 2 patients with particularly high marrow blast percentages at baseline (80% and 90%) did achieve CR (1 CR and 1 CRi), giving some rationale to exploring this question in larger patient populations in the future.

To place this study's findings in context, our results should be compared with those of another set of agents that target genetic abnormalities found in a significant minority of AML patients: the FMS-like tyrosine kinase 3 (FLT3) inhibitors. Used as single agents, these drugs resulted in a reduction in blast percentages in older AML patients with the FLT3 abnormality, but not in formally defined objective responses. Lenalidomide, when used as a single agent, resulted in a CR/CRi/PR rate of 14% in the present study, 30% in a study of previously untreated older AML patients without the del(5q) abnormality,[30] and 16% in the relapsed/refractory setting using similar dosing regimens.[25] In the non-del(5q) up-front AML study, 2 of 10 responding patients also had complex cytogenetics. This is particularly significant because in some responders in the present study, the del(5q) abnormality was present in fewer than 50% of mitoses, bolstering the hypothesis that lenalidomide at higher doses may exert cytotoxic effects through non-del(5q)-mediated mechanisms. Responses may have been higher in that study compared with the present one because of: (1) differences in patient inclusion criteria, (2) prolonged treatment with lenalidomide at higher doses in that study (as opposed to decreasing the dose to 10 mg daily, as in the present study) for a second cycle of therapy, or (3) the single-center nature of that study. The results of the present study, combined with those of other groups, provide substantive rationale to combining lenalidomide with cytotoxic or hypomethylator therapies in older del(5q) AML patients, an approach that has been initiated in both the United States and Europe.[31,32]

In conclusion, lenalidomide, when used in high doses as a single agent in older AML patients with the del(5q) cytogenetic abnormality, has modest activity, supporting future trials exploring alternate dosing strategies and incorporating lenalidomide into combination drug strategies in AML patients.

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Authorship

Contribution: M.A.S., F.R.A., and A.F.L. helped design and perform the research, analyze the data, and write the manuscript; T.N. helped perform the research, analyze the data, and write the manuscript; and H.G., J.L., A.A., S.P., D.M., and C.L.W. helped perform the research and edit the manuscript.

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