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Phase I study of azacitidine and bortezomib in adults with relapsed or refractory acute myeloid leukemia

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Abstract

We previously reported that bortezomib indirectly modulates transcription of DNA methyltransferase 1 (DNMT). We designed a phase I study of azacitidine (a direct DNMT inhibitor) plus bortezomib in acute myeloid leukemia (AML) to determine safety and tolerability. Twenty-three adults with relapsed/refractory AML received azacitidine 75mg/m^2 daily on days 1-7. Bortezomib was dose escalated from 0.7mg/m^2 on days 2 and 5 to 1.3mg/m^2 on days 2, 5, 9, and 12. The target dose was reached without dose limiting toxicities. Infection and/or febrile neutropenia were frequent. Patients received a median of 2 cycles of therapy (range, 1-12+). Five of 23 patients achieved remission including two with morphologic and cytogenetic complete response (CR) and three with CR and incomplete count recovery (CRi). Of CR/CRi responders with cytogenetic abnormalities at baseline, three of four achieved cytogenetic CR. The combination of azacitidine and bortezomib was tolerable and active in this cohort of poor-risk previously-treated AML patients.

Keywords

Relapsed AML; bortezomib; velcade

Introduction

Adult acute myeloid leukemia (AML) patients who fail to respond to initial therapy or relapse after initial complete remission (CR) are unlikely to experience long term survival with currently available conventional therapies.[1] Innovative approaches with targeted

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agents that have a favorable toxicity profile are needed to improve outcomes in patients with poor risk AML.

Alterations in DNA methylation have been observed in patients with AML, and the recent discovery of somatic mutations in epigenetic modifiers that regulate this process underscores its importance in disease pathogenesis.[2] Epigenetic targeting with azanucleosides (decitabine and azacitidine) to reactivate aberrantly silenced genes and restore normal patterns of gene expression by inhibition of DNA methyltransferase (DNMT) enzymes has been explored in both myelodysplastic syndromes (MDS) and AML. Several groups have shown activity of each hypomethylating agent in AML, alone or in combination with other agents including histone deacetylase inhibitors.[3-7] However, the potential of such combinations remains to be fully explored.[4,8,9]

Our group has tested alternative ways to target DNMT enzymes. We previously demonstrated a novel hypomethylating activity for the proteasome inhibitor bortezomib via downregulation of *DNMT* expression, rather than by direct enzymatic inhibition.[10] Thus, we tested the feasibility of combining hypomethylating azanucleosides with bortezomib in AML. We recently reported a phase I trial of decitabine and escalating doses of bortezomib in patients with AML.[11] The combination was tolerable and the overall response rate of the cohort was 37%; 50% of previously untreated patients achieved a CR or CR with incomplete count recovery (CRi), and 22% of patients with relapsed or refractory disease achieved a CRi.

We now report a phase I trial of azacitidine and bortezomib in AML to determine the maximum tolerated dose (MTD), to describe toxicities of the combination, and to recommend a dose at which to explore the hypothesis that combining azacitidine with bortezomib will target DNA hypermethylation via effects on both transcription of *DNMT* isoforms and inhibition of enzyme activity.

Patients and methods

Eligibility criteria and study design

This study enrolled adult (≥18 years) patients with morphologic evidence of relapsed/refractory non-M3 AML. Patients were required to have total bilirubin ≤ 2 × upper limit normal (ULN), creatinine ≤ 2.0 mg/dL, ALT/AST ≤ 5 × ULN, left ventricular ejection fraction at least 40%, and Eastern Cooperative Oncology Group performance status ≤ 2. Active infection was permitted if controlled. Exclusion criteria included chemotherapy or radiotherapy within 2 weeks, active other malignancies (within 3 years), active central nervous system disease or granulocytic sarcoma as the sole site of disease, uncontrolled intercurrent illness, and pre-existing grade 2 or higher neuropathy or other serious neurologic toxicity that would significantly increase risk of complications from bortezomib therapy. The primary objective of this study was to determine the MTD and to define the specific toxicities and dose limiting toxicity (DLT) of bortezomib in combination with azacitidine. The secondary objectives were to determine the overall response rate and CR rate of this combination. Informed written consent approved by The Ohio State University

Human Studies Committee was obtained on all patients prior to study entry. This trial was registered with the NCI clinical trials network (NCT00624936).

Patients were given azacitidine at 75mg/m^2 IV over 15-30 min daily on days 1-7 for all dose levels. Subcutaneous dosing was permitted if preferred. Bortezomib was administered immediately following azacitidine dose. Bortezomib was dose-escalated according to the following plan: dose level 1, 0.7mg/m^2 IVP on days 2 and 5; dose level 2, 0.7mg/m^2 IVP on days 2, 5, 9, 12; dose level 3, 1.0 mg/m^2 IVP on days 2, 5, 9, 12; and dose level 4, 1.3 mg/m^2 IVP on days 2, 5, 9, 12. Subsequent cycles of therapy were given every 4 weeks. Treatment delays of ≥ 10 days were permitted for patients with bone marrow (BM) cellularity of ≤ 10% and no evidence of disease in the marrow until at least partial restoration of hematopoiesis occurred (defined as BM cellularity > 10% or ANC ≥ 1000/ uL). A repeat BM aspiration and biopsy was required if treatment was delayed more than 4 weeks. In the absence of a hypoplastic marrow (≤10% cellularity), clearly progressive increase in bone marrow blasts, ongoing febrile neutropenia, unresolved systemic neutropenic infection, or serious hemorrhagic complications, dosing was to be continued every 4 weeks without delay. Hydroxyurea was permitted during cycle 1 to maintain WBC < 40,000/μL if necessary. Reponses were defined according to International Working Group criteria for AML.[12] Treatment continued indefinitely until disease progression or unacceptable toxicity occurred, except that bortezomib was discontinued after 3 cycles in patients with no evidence of clinical benefit (azacitidine was continued for a total of 6 cycles before discontinuation due to treatment failure). Six additional patients were treated at the MTD.

Adverse events were graded according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE), version 3.0. DLT was defined with cycle 1 of therapy. Drug related non-hematologic toxicity of grade 4 with the exception of alopecia, nausea and vomiting controllable with anti-emetic therapy, infection, and fatigue were considered DLT. If the toxicity occurred in two or more patients at a single dose level, 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 defined as: failure to recover neutrophil and/or platelet counts by day 42 in patients with < 5% blasts in the bone marrow, absence of myelodysplastic changes, and/or absence of evidence of disease by flow cytometry in the bone marrow.

Results

Twenty-three patients with a median age of 65 years (range, 42-81) were enrolled. Clinical and cytogenetic characteristics are summarized in Table 1. Median white blood cell count and bone marrow blast percentage were 3.7 × 10^3/μL (range, 0.5-59.1) and 26 (range, 2-93), respectively. Of the nine patients who enrolled with AML in untreated first relapse, seven had CR1 of < 1 year. Fourteen patients had not responded to the most recent therapy given prior to enrollment; four had primary refractory AML. Sixteen patients had received

intensive induction chemotherapy (ie. anthracycline/cytarabine or high dose cytarabine based) at the time of the initial AML diagnosis; four patients had previously undergone autologous or allogeneic bone marrow transplantation. Ten patients had received prior hypomethylating therapy with either decitabine or azacitidine, seven as their initial and only treatment.

Toxicities

Though no toxicities were considered to be DLT in this study, infection and/or febrile neutropenia were nearly universal. Death within 8 weeks occurred in 5 patients (22%) due to pneumonia (1), sepsis (1), or progressive disease (3). The median time to death in these patients was 39 days (range, 23-52). Two patients developed grade 3 neuropathy after 2 cycles. Fifteen of the 23 patients were platelet transfusion dependent at the time of study enrollment. Grade 3 or 4 thrombocytopenia, regardless of attribution, were common and occurred in 19/23 patients. There were five grade 3 bleeding events that occurred. Additional grade 3 or higher non-hematologic toxicities are noted in Table 2.

Dose escalation and treatment

Patients were treated at each of the four planned dose levels as follows: dose level 1: 4 patients, no DLT, one patient replaced due to early progression without completing cycle 1 (non-evaluable for toxicity); dose level 2: 6 patients, no DLT, one patient died of sepsis that was also complicated by ventricular arrhythmias, one did not complete cycle 1 of treatment due to pneumonia, one patient was replaced due to early progression without completing cycle 1 (non-evaluable for toxicity); dose level 3: 4 patients, no DLT, one patient replaced due to death from pneumonia; dose level 4: 9 patients enrolled, no DLT, (includes 6 patient expansion at the MTD). No patient was replaced due to drug related toxicity. Patients received a median of 2 cycles of study therapy (range, 1-12+). However, only 1 patient received bortezomib beyond cycle 3. Two patients had bortezomib discontinued after 3 cycles due to neuropathy, the rest were discontinued per protocol given failure to achieve CR/CRi/PR by this time point.

Clinical Responses

The overall response rate was 26% (6/23 patients). Responses by IWG criteria were 2- CR, 3-CRi, 1- PR. One CRi patient (in cytogenetic remission also) who discontinued study treatment after 2 cycles due to unrelated trauma subsequently had complete count recovery meeting CR criteria, but a repeat marrow examination was not performed. The median number of prior therapies for CR/CRi patients was 3 (range 1-5). One CRi patient had achieved CR1 with decitabine but relapsed during the sixth cycle of chemotherapy, enrolling to this trial 2 weeks later. The sole PR patient had received two cycles of decitabine prior to developing progressive disease and enrolling.

Of the 4 CR/CRi patients with pretreatment cytogenetic abnormalities, 3 achieved cytogenetic CR. Both CR patients achieved cytogenetic CR. Although one of the CR patients had 2% blasts in the bone marrow at the time of relapse, there were 25% blasts circulating in the peripheral blood. Given the hypocellular and hemodilute nature of the bone marrow aspirate from this patient, it is likely that the lower blast percentage in the

aspirate at the time of enrollment represents sampling artifact. Response duration assessment is compromised due to three patients subsequently receiving allogeneic transplantation; none received maintenance therapy. One CR patient died in remission of transplant-related mortality 4 months after transplant. The other transplanted CR patient and one transplanted CRi patient relapsed 7 and 3 months after transplant, respectively. Another CRi patient had a response duration of 6 months (with full count recovery though marrow aspiration confirming CR was not done, as noted above).

Response followed the typical pattern of azanucleoside activity, requiring more than one cycle of therapy; the median number of cycles to initial response was 2 (range, 1-5). Five of six responders achieved response to combination therapy; one patient responded following 5 cycles of treatment, the last 2 with azacitidine as a single agent.

Discussion

Treatment of AML in relapse is associated with low response rates, and most patients do not experience durable benefit with currently available salvage therapies.[13] Older patients with AML are less able to tolerate intensive chemotherapy and are often not even offered therapy for relapsed disease due to low efficacy and high toxicity.[14-16] Novel/lower intensity therapies are particularly needed for these patients.

Current therapeutic approaches aimed at modifying DNMT activity in AML have focused on direct enzymatic inhibition with azanucleosides. Preclinical studies by our group have demonstrated that bortezomib inhibits *DNMT1* transcription and DNA methylation by interfering with SP1/NF-*k*B interplay, resulting in global hypomethylation of DNA *in vitro* and *in vivo*.[10] Thus, we designed studies to explore combining azanucleosides and bortezomib, agents with distinct mechanisms of hypomethylation, as a way to target aberrant hypermethylation in AML. We have previously reported results from a phase I study of decitabine and bortezomib in poor risk AML.[11] The Alliance conducted a follow up randomized study of decitabine vs. decitabine plus bortezomib in which the primary objective was to determine whether the combination significantly improved overall survival in previously untreated older AML patients; it was recently closed prematurely when the interim analysis demonstrated that the combination was unlikely to be superior with respect to this outcome. A complete analysis of the data, inclusive of toxicities and response rates to each of these regimens, has yet to be reported.

It should be noted that the pharmacologic effects of azacitidine vs. decitabine may be quite different, despite similarities in their structure and that this may play a role in each agent's activity. While decitabine is a reduced metabolite of azacitidine and is almost completely incorporated into DNA, only 20% of azacitidine is converted into decitabine by ribonucleotide reductase; 80% is incorporated into RNA.[17] We have reported that azacitidine downregulates ribonucleotide reductase (RR), self-limiting its conversion to decitabine, in turn altering its DNA hypomethylating activity.[18] We have also shown that azacitidine-mediated inhibition of RR leads to a dose-dependent decrease in the formation of deoxyribonucleotides necessary for DNA synthesis within leukemic cells, which may contribute to the agent's activity. Azacitidine has been explored as a single agent at different

doses and in varying schedules in patients with relapsed or refractory AML with CR/CRi rates of 0 to 11%.[19,20] In combination with other agents such as histone deacetylases inhibitors, all trans retinoic acid and others, response rates appear to be slightly improved with CR/CRi occurring in 3 to 22% of patients with relapsed or refractory AML.[21-24]

In this phase I study we evaluated the combination of azacitidine and bortezomib in a cohort of mostly older patients with relapsed or refractory AML (median age, 65 years). The treatment was generally well tolerated, and there were no dose limiting toxicities. Infectious complications and myelosuppression were common, though less severe than would be expected with conventional intensive reinduction treatment. With regard to bortezomib-related neurotoxicity, two patients developed reversible grade 3 peripheral neuropathy, but only one patient received bortezomib beyond cycle 3 per protocol guidelines. It is possible that repetitive cycles of azacitidine and bortezomib could result in a higher incidence of neurotoxicity; we had similar conclusions regarding neurotoxicity in the earlier phase I study of decitabine and bortezomib.[11] Strategies to decrease the risk for developing bortezomib-related neurotoxicity while maintaining efficacy with either once weekly or subcutaneous administration should be considered in future trials with these agents.[25-28]

The combination of azacitidine and bortezomib resulted in CR/CRi in 5 patients, and the overall response rate was 26%. Three of the four CR/CRi patients with pretreatment cytogenetic abnormalities achieved complete cytogenetic response. Prior hypomethylating agent therapy did not exclude patients from enrolling in this study, and, interestingly, two of six responding patients had either relapsed or developed progressive disease while receiving decitabine. Both of these patients were naïve to conventional chemotherapy and had only received decitabine treatment prior to enrollment. Although the small number of patients limits the interpretation of this finding, it may suggest that prior hypomethylating agent failure does not preclude the possibility of response to the combination. Three patients were able to proceed to allogeneic transplantation following azacitidine and bortezomib treatment; one had primary refractory AML and the two others with relapsed AML had received a total of 3 and 5 prior induction regimens, respectively. Of the 23 patients treated, 60% (14/23) were refractory to the most recent therapy given prior to enrollment. Despite the overall advanced age and poor risk nature of the cohort, the combination was active and tolerable; further testing in patients with relapsed or refractory AML, focusing on those who are not candidates for intensive re-induction, may be considered.

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Table 1

Patient characteristics

Age in years/Sex	No. of Prior Inductions	Pretreatment Karyotype	Presenting WBC count × 10^3/uL	% BM blasts	Response
45/M	2	46,XY,t(6;11)(q27;q23)/46,XY	2.7	4	PD
71/M	4	46, XY	12.3	84	PD
66/M	3	46,XY,t(9;17;10)(q34;p12;q22)/46,XY	1.3	81	CR
70/M	3	94<4n>,XXYY,+13,+13/46,XY	1.6	8	CRi**
75/F	1*	73-87<4n>, XXXX,-7,-7,t(8;21)(q22;q22)x2,-11,-14,-16, -20	3.6	93	CRi**
50/M	3	48,XX,t(6;11)(q27;q23),+21,+21/46,XX	17.2	90	PD
58/F	2*	46,XX,t(6;9)(p23;q24)/47,sl,+i(13)(q10)/ 47,sl,+mar	19.1	87	PD
51/M	3	47,XY+8/46,XY	0.5	11	PD
65/M	1	46,XY,t(4;12)(q12;p13)/46,XY	4.1	2	CR**
72/M	1*	46,XY,t(4;21)(q33;q22)/46,idem,der(3)t(3;4)(p22;q12) -4, add(8)(p12),+mar /48,XY, +21,+21	1.0	42	PR
49/F	2	46,XX,t(6;11)(q27;q23)/46,XX	6.3	85	PD
68/F	2*	43,XX,add(1)(q32),add(5)(q13),-6,-7, der(8) t(8;21)(p21;q11.2), add(12)(p11.2)13, dic(18;22)(q12;p12),der(19)t(6;19)(q11.2;p13.3) ins(19;?)(p13.3;?),der(19)t(13;19) (q14;q13.3), +20,del(20)(q11.2)x2, -21,+mar1[cp2]/46,XX	2.3	15-20	PD
76/M	1*	44,X,-Y,add(5)(q12),-7,del(8)(q?24),dic(?;12)(?;p11.2), der(16)t(16;17)(p13. 3;q12),-17,add(17)(p11.2),-18,-20, der(21) t(Y;21)(q11.23;p11.2),22,+r,+mar10, +mar11,+mar12/ 44,idem,del(3)(p11.2p21) +mar9, -mar12/46,XY	4.3	72	PD
62/F	1*	46, XX	2.5	35	PD
65/M	2	46,XY,del(11)(q13q23)/46,XY	39.1	8	PD
65M	1	46,XY,t(14;16)(q24;p13.3)/46,XY	24.5	10	PD
60/M	4	46,XY,t(9;22)(q34;q11.2)/46,XY,idem,del(6)(p23)	12.6	14	PD
75/M	5*	46,XY,dup(1)(q21q41)/46,XY	59.1	82	PD
50/M	3	46,XY	2.3	5-7	PD
77/F	2*	46,XX,del(5)(q22q35)/46,XX	1.8	26	PD
42/F	5	46,XX	3.7	23	CRi
81/F	1*	46,XX	3.1	3	PD

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Age in years/Sex	No. of Prior Inductions	Pretreatment Karyotype	Presenting WBC count × 10^3/uL	% BM blasts	Response
77/M	1*	46,XY	7.9	47	PD

PD (Progressive disease)

* Prior decitabine treatment

** Patient achieved cytogenetic remission

Table 2

Toxicities

Grade 3 or higher non-hematologic toxicities regardless of attribution*

TOXICITY	GRADE	# EVENTS
Metabolic		
Hyperglycemia	3	2
Acidosis	4	1
Low albumin	3	4
Tumor lysis	Present	1
Pulmonary		
ARDS	4	2
Bronchospasm	3	1
Infiltrates	3/4	2/1
Dyspnea	3/4	3/2
Other resp complaint	3	1
Cardiac		
Increased troponin I	3	1
Atrial fibrillation	4	1
Ventricular arrhythmia	5	1
Hypotension	4	1
Neurologic		
Peripheral neuropathy (sensory)	3	2
Limb pain NOS	3	1
Renal		
Insufficiency	3	1
Constitutional		
Fatigue	3	5
Other		
Increased AST/ALT	3	2
Hemorrhage	3	5
Thrombosis	3	2
Increased INR	3	1

*Clinically insignificant and correctable electrolyte abnormalities are not included in this list.