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A Phase I Study of Midostaurin and Azacitidine in Relapsed and Elderly AML

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Abstract

Background—Midostaurin is a novel, orally available FLT3 tyrosine kinase inhibitor that induces cell cycle arrest and apoptosis of leukemic cells expressing both mutant and wild type FLT3 receptors, and has shown potential synergism with cytotoxic chemotherapy.

Methods—We conducted a phase I study of azacitidine (75 mg/m^2 iv daily for 7 days) with escalating doses of oral midostaurin (25 mg bid, 50 mg bid, and 75 mg bid) days 8–21 of a 28 day cycle in untreated AML in older patients and/or relapsed AML. Patients were eligible regardless of FLT3 mutation status. Trough blood samples for pharmacokinetics were obtained on days 8, 15, and 21 before midostaurin dosing.

Results—17 patients, median age 73 (range 57–83) years, were enrolled; 5 patients had prior conventional treatment and none of the patients had FLT3 mutations. Dose-limiting toxicities (DLT) were not observed. Hospitalizations, primarily for infections, occurred in one-third of treatment cycles. 14 patients were evaluable for response: 3 attained complete remission and 2 had hematologic improvement. Median (range) survival from enrollment was 6 (1–19+) months. 3 patients died within 60 days of enrollment (2 progressive disease, 1 non- DLT treatment-related). Pharmacokinetic data at 75 mg po bid showed increased trough levels of midostaurin during cycle 2 compared to cycle 1 as well as persistent and increasing levels of its active metabolite, CGP52421.

Conclusions—The combination of sequential azacitidine and midostaurin is safe and tolerable with response rates comparable to azacitidine alone and should be studied further in FLT3 mutation positive AML.

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Conflicts of Interest

Patient drug supply of midostaurin and azacitidine was provided by Novartis and Celgene, respectively. Dr. Brenda Cooper received research funding from Novartis and Celgene which was used to defray the costs of conducting the clinical trial. The other authors report no significant conflicts of interest.

Keywords

midostaurin; azacitidine; elderly AML

Introduction

A large proportion of elderly acute myeloid leukemia (AML) patients are not candidates for standard induction chemotherapy due to multiple comorbidities and significant treatment related morbidity and mortality (1, 2). For these patients, epigenetic therapy with agents such as azacitidine appears to be relatively well tolerated and may provide a survival benefit comparable to intensive chemotherapy (3, 4). Strategies to combine azacitidine with novel targeted agents has the potential to improve outcomes, potentially without causing significant additive toxicity (5–7).

The Fms-like tyrosine kinase 3 (FLT3) receptor is expressed on 80% of AML samples and activating mutations, which are associated with an adverse prognosis, are expressed in 20–25% of AML patients (8–10). FLT3 plays an important role in hematopoiesis by regulating proliferation, differentiation, and survival of hematopoietic cell progenitors (8). FLT3 mutations, particularly the internal tandem duplication (ITD), cause constitutive and unregulated growth of AML (11–13). Pharmacologic blockade of FLT3 autophosphorylation inhibits a number of downstream targets important in the pathogenesis of AML (14, 15). Several novel agents targeting FLT3 kinase recently have shown promising activity in patients with both wild type and mutated FLT3, but with few exceptions, single agent therapy does not result in durable clinical remissions (16–19). *In vitro* studies have shown that FLT3 inhibitors potentiate standard cytotoxic chemotherapy, particularly when administered sequentially (20, 21), and may possibly reverse multi-drug resistant phenotype (22). In contrast to standard induction chemotherapy, increased levels of FLT3 ligand (FL), a potential mechanism of drug resistance, have not been observed during azacitidine therapy (23).

Midostaurin, a novel orally available FLT3 inhibitor, is cytotoxic to both FLT3 wild-type and FLT3 mutant leukemic blasts (24, 25). Preliminary clinical data have shown safety and tolerability when given as a single agent or in combination with standard induction chemotherapy in patients regardless of FLT3 mutation status (16, 26). Herein, we report results of a phase I study of sequential azacitidine and midostaurin in relapsed and/or untreated AML in older patients.

Patients and Methods

We conducted this phase I study at the Seidman Cancer Center, University Hospitals of Cleveland, Case Medical Center, Case Western Reserve University, Cleveland, OH and the Mary Babb Randolph Medical Cancer Center, West Virginia University, Morgantown, WV, between August 2009 and November 2012. Eligibility criteria included histologically confirmed AML regardless of FLT3 mutational status in therapy naive elderly patients (≥ 70 yrs), patients of any age who were not suitable for standard induction, or relapsed/refractory AML after no more than one prior conventional induction regimen. At enrollment, blood or

bone marrow samples were analyzed for FLT3 mutations by qualitative DNA-based PCR assay performed by certified commercial laboratories. Other requirements for enrollment included ECOG performance status of 0–2, anticipated life expectancy without active anti-leukemia treatment of at least 12 weeks, adequate hepatic function (AST, ALT, serum total bilirubin ≤ 1.5 times upper limit of normal [ULN]), and adequate renal function (serum creatinine ≤ 1.5 times ULN). Exclusion criteria included diagnosis of acute promyelocytic leukemia, prior hematopoietic stem cell transplant, prior treatment with demethylating agents or midostaurin, symptomatic cardiac disease or abnormal ECG (QTc interval > .450 millisecs or bradycardia < 50 beats per minute), impaired gastric function, pulmonary infiltrates, requirement for strong CYP3A inhibitors or inducers (fluconazole was allowed up to 200 mg/daily), concurrent active malignancy, or other severe uncontrolled medical conditions including infections. Lactating and pregnant females were excluded and all patients were required to use effective contraception. The study was approved by the Institutional Review Board at both institutions and all patients were required to be able to understand and give written informed consent.

Treatment Plan

Patients received azacitidine 75 mg/m^2 intravenous over 30 minutes daily for 7 consecutive days followed by escalating doses of oral midostaurin (25 mg bid, 50 mg bid, and 75 mg bid) days 8–21. Patients were entered in cohorts of 3 patients. Compliance with oral midostaurin was assessed by patient self-reported pill diaries and pill counts. Cycles were repeated every 28 days with allowed treatment delays of 2 weeks to recover from non-hematologic toxicities. Dose modifications for blood counts and QTc interval are provided in the Supplement. Clinical response was assessed after cycles 2 and 4 by bone marrow examination using standard morphologic and blood count response criteria (27) and verified by a hematopathologist. Patients who achieved a complete or partial response, stable disease, or hematologic improvement were eligible to receive additional courses of treatment every 4 or more weeks with treatment delays to allow for hematopoietic recovery and resolution of non-hematologic toxicities. Patients were allowed to continue treatment as long as they demonstrated clinical benefit.

Toxicity grading and Determination of Maximum Tolerated Dose

Toxicities were graded using CTC of the NCI version 3. Determination of the maximum tolerated dose (MTD) was based on dose-limiting toxicities (DLT) observed during the first cycle of treatment consistent with previously published guidelines and details are provided in the Supplement (28). Serious adverse events (SAEs) included any life-threatening grade 3 or 4 non-hematologic toxicity, or any toxicity that resulted in permanent disability or required inpatient hospitalization.

Pharmacokinetic testing

Pharmacokinetic samples for determination of midostaurin and its active metabolites CGP62221 (the desmethyl-metabolite) and CGP52421 (the monohydroxyl-metabolite) plasma levels were obtained before midostaurin dosing on days 8, 15 and 21 of the first two treatment cycles. The concentrations of midostaurin and the metabolites were determined using a high performance liquid chromatography method coupled with mass spectrometry

(HPLC/MS) at SGS (St Benoit, France). The limit of quantification of the method was 10 ng/ml (29)

Statistical Analysis

Patients were entered in cohorts of three per dose level and were monitored for a minimum of 28 days from the first day of treatment before dose escalation to the next cohort. Dose escalation proceeded if none of 3 patients or ≤ 1 of 6 patients experienced a DLT at a given level. Three additional patients were treated at a given dose level if 1 of 3 patients experienced a DLT. If a DLT was observed in 2 of 3, or ≥ 2 of 6 patients in a given dose level, the prior dose level was declared the MTD. A total of 9 patients were required to be treated at the MTD or 75 mg po bid, the maximum dose studied. Duration of clinical response as well as survival was calculated from initiation of protocol treatment.

Results

Patient Characteristics

Between August 2009 and November 2012, seventeen patients (11 females and 6 males) were enrolled. Median (range) age was 73 (57–83) years. Two previously untreated patients younger than 70 opted for protocol treatment. All subjects enrolled were FLT3-ITD or tyrosine kinase domain mutation (TKD) negative. Seven patients had intermediate-risk cytogenetics (5 normal; 2 patients with abnormalities of trisomy 8) and 10 patients had high-risk cytogenetics (30). Charleson comorbidity index was 0 in 10 patients, 2 in 4 patients and 3–4 in 2 patients (31). (Table 1)

Safety and Toxicity

Patients who received one or more doses of protocol treatment were evaluable for toxicity. No dose-limiting toxicities, as defined above, were observed during midostaurin dose escalation, nor in the expansion cohort at the MTD dose level of 75 mg po bid. Two patients treated at the expansion cohort were evaluable for toxicity, but not response, and were replaced, leaving a total of 11 patients at the 75 mg bid dose level.

A complete list of SAEs for the first 6 cycles at all dose levels is provided in the Supplement. Three grade 3 intestinal toxicities occurred after cycle 1 and included 1 episode of ischemic bowel, a diverticular abscess, and a small bowel obstruction in the setting of progressive AML. Hospitalization was required in 17 of 51 (33%) treatment cycles, usually for infectious complications. Three deaths occurred within the first 60 days of study treatment, 2 from disease progression and 1 during cycle 2 at dose level 3 due to infectious pneumonia and grade 3 hepatotoxicity which was a non-DLT, serious adverse event. As expected, grade 3 and 4 neutropenia and thrombocytopenia were observed in the majority of cycles.

Because midostaurin and its metabolites have the potential to cause QTc prolongation, electrocardiograms were obtained for QTc analysis on day 8 of each of the first four treatment cycles, before initiating midostaurin. No significant changes in QTc were observed throughout the course of treatment in any patient (data not shown)

Response and Outcomes

Seventeen patients received a median (range) of 2 (1–11) cycles of treatment. Treatment responses were assessed after cycles 2 and 4 by bone marrow biopsy. Disease progression occurred within the first 2 cycles in 4 patients. Median survival was 6 months in our entire cohort and ranged from 1–19+ months. Remarkably, this result did not differ between the 5 previously treated and the 12 previously untreated patients (range 2–12 months and 1–19+ months, respectively). Two patients achieved hematologic improvement: one recovered ANC ≥ 500/μL and became platelet transfusion independent for 3 months, one had clearing of circulating blasts. Three treatment naïve patients treated at the MTD achieved a complete remission of 7, 12, and 12 months and survived 8, 17 and 19+ months. Baseline bone marrow blast counts were 30, 28% and 60% and two of these patients had complex cytogenetics. One of these patients had morphologic CR with persistent cytogenetic abnormalities.

Drug Compliance and Dose Modifications

Midostaurin compliance was assessed by self reported pill diaries and pill counts. Sixteen of 17 patients received > 75% of their assigned midostaurin dose during cycle 1. One patient enrolled on dose level 3 misunderstood dosing instructions and inadvertently took 25 mg twice daily (33% of prescribed dose). 70% of patients received > 75% of their assigned midostaurin doses during cycles 2 and 3. The main reasons for incomplete dosing of midostaurin cycles were infections (3 pts), disease progression (1 pt) and decline in performance status (1 pt). Only one patient required a reduction in azacitidine due to neutropenia.

Pharmacokinetics

Samples were available for trough midostaurin plasma concentrations and its metabolites CGP62221 and CGP52421 for 4 patients (cycle 1) and 6 patients (cycle 2) treated at the maximum tested dose of 75 mg bid. All patients analyzed were receiving fluconazole, a moderate CYP3A inhibitor. Midostaurin levels accumulated significantly during the first week of administration and then decreased despite continued dosing by approximately 2-fold following 2 weeks of dosing. However, the hydroxyl-metabolite CGP52421 concentrations increased continuously with time and remained detectable (median 1665 ng/ml day 8 cycle 2, compared to 1990 ng/ml day 21 cycle 1), indicating a prolonged half life of this metabolite. The median plasma trough concentration of midostaurin on days 15 and 21 of cycle 2 (6440, 5850 ng/ml) appeared to be significantly higher than the corresponding days of cycle 1 (median 3780, 2055 ng/ml), although there was significant variability of plasma levels in this relatively limited patient sample. (Figure 1) See also Table 3 in Supplement.

Discussion

We describe a novel regimen of azacitidine and midostaurin, a FLT3 kinase inhibitor, as induction therapy for untreated older patients and/or relapsed acute myelogenous leukemia. In our population with a median age of 73 years, we found the regimen to be well tolerated with excellent compliance at all doses studied. Our pharmacokinetic studies at the MTD (75

mg po bid) suggest that trough levels of midostaurin and its metabolites have the potential to contribute significantly to cytotoxicity of the regimen (25, 32).

In our phase I study, we did not observe any dose-limiting toxicities during the dose-escalation phase in this generally older and/or previously treated patient population, and were able to administer our target dose of 75 mg bid for 14 days. In contrast, Stone and colleagues reported a study undertaken in untreated younger patients (ages 18–60 years) combining midostaurin 50–100 mg twice daily either concurrently or sequentially with standard dose daunorubicin and cytarabine, and found intolerable grade 3–4 nausea and vomiting at the higher dosing schedule (26). Midostaurin at a dose of 50 mg bid in combination with azacitidine was the dose selected for testing in a recent study by Strati and colleagues (6).

Both hematologic and non-hematologic toxicities appeared comparable to those that would be expected with azacitidine alone. Unique serious adverse events that potentially could be attributed to the midostaurin plus azacitidine combination included three subjects who experienced intestinal toxicities; investigators using this combination should monitor patients closely for this adverse event in future studies. Although we anticipated the majority of treatment would be outpatient, similar to other azacitidine studies, one-third of cycles required patient hospitalization, primarily for infectious complications (4, 23). Of the 3 deaths which occurred within the first 60 days of treatment, two were due to disease progression and one was a non DLT, treatment-related infectious complication during cycle 2 at the 75 mg dose level.

In our patient population, none of whom had FLT3 mutated AML, we observed a response rate of 18% (3 of 17) for the entire cohort and 25% (3 of 12) in previously untreated patients. These results are consistent with other studies of demethylating agents in this patient population (3, 4). In comparison, the impressive 35% response rate observed in previously treated FLT3 mutated patients in the phase I/II study of azacitidine and midostaurin by Strati and colleagues, suggests that the combination may prove even more effective in untreated FLT3 mutated AML (6).

The median trough midostaurin concentration of 3780 ng/ml in patients treated at the 75 mg bid dose on day 15 of cycle 1 on our study was comparable to the trough concentration profile of 3500 ng/ml at the 50 mg bid dose in the Dana-Farber study (26). However, due to variability of plasma levels, a direct comparison of drug-drug interactions between midostaurin and azacitidine, compared to standard chemotherapy is not possible. We observed a prolonged half-life and increasing trough levels of the hydroxyl-metabolite CGP52421 during cycle 2. In vitro studies show that this metabolite may be less selective and more cytotoxic in blasts isolated from AML patients than the parent compound at levels clinically achievable and has the potential to contribute significantly to activity in FLT3 wt AML (25, 32).

Conclusion

Our phase I study shows that the combination of azacitidine and midostaurin is safe and tolerable and has modest clinical activity in elderly patients who are not believed to benefit from standard induction chemotherapy. Evaluation of downstream targets of midostaurin in leukemia blasts during treatment will likely be important in understanding the activity of this regimen. A phase II study with pharmacodynamic studies evaluating downstream targets and FL ligand is in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Practice Points

- Our phase I study shows that midostaurin at a dose of 75 mg po bid for 14 days can be safety combined with standard-dose azacitidine in elderly patients with AML.
- Hospitalization occurred in 33% of treatment cycles, primarily for infectious complications, suggesting that these patients should be closely monitored.
- We observed a complete response rate of 25% in untreated patients, none of whom were FLT3 ITD mutated. We would recommend testing of the combination with a focus on this patient group.

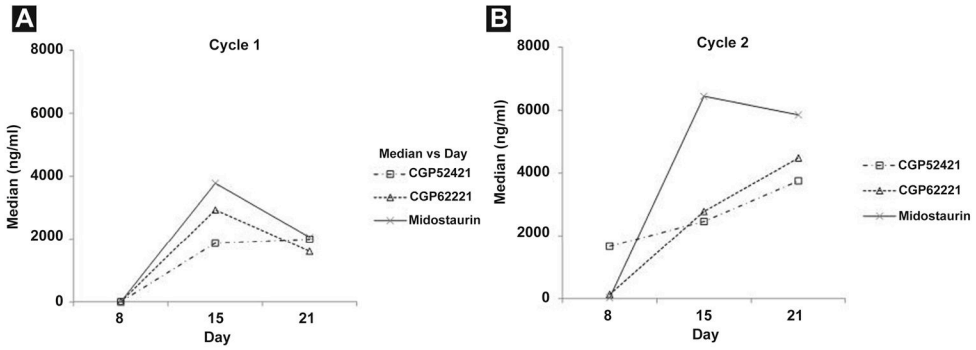

Figure 1.

Trough Levels of Midostaurin and Its Metabolites CGP52421 and CGP62221 at Maximal Tested Dose of 75 mg Oral Twice Per Day During (A) Cycle 1 and (B) Cycle 2

Table 1

Patient Characteristics N=17

Age	73 (57–84)
Gender M/F	5/12
Prior AML tx	5
No Prior tx	12
Secondary AML	6
Performance Status	
0	4
1	11
2	2
FLT 3 ITD positive	0
Cytogenetics [a]	
Favorable	0
Intermediate	7
Poor	10

[a] Favorable : t(15,17), t(8,21), inv 16 ; Intermediate : Normal, 11q23, +8, +22, Poor : complex, del 5q, −5, −7, abn 3q