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Phase I/II Trial of the Combination of Midostaurin (PKC412) and 5-Azacytidine for Patients with Acute Myeloid Leukemia and Myelodysplastic Syndrome

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Abstract

We investigated the combination of midostaurin and azacitidine (AZA) in patients with AML and high risk MDS. Patients received AZA 75 mg/m^2 on days 1–7 and midostaurin 25 mg bid (in cohort 1 of phase I) or 50 mg bid (in cohort 2 of Phase I and in Phase II) orally on day 8–21 during the first cycle and continuously thereafter. Fourteen patients were enrolled in the phase I and 40 in the phase II. Overall response rate was 26%. The median remission duration (RD) was 20 weeks and was significantly longer in patients with FLT3 mutations not previously exposed to other FLT3 inhibitors (p=0.05) and in patients not previously transplanted (p=0.01). Thirty-two (59%) patients have died, all of complications related to disease progression. G3-4 non-hematological toxicity was reported in 38 (70%) patients, most frequently infections (56%), ejection fraction reduction (11%), and diarrhea or nausea/vomiting (9% each). The combination of midostaurin and AZA is an effective and safe regimen in patients with AML and high-risk MDS. Patients with FLT3 mutations but not previously exposed to other FLT3 inhibitors and patients not previously transplanted derived the greatest benefit. Further studies with this combination are warranted.

Keywords

AML; MDS; AZA; midostaurin

Introduction

FMS-like tyrosine kinase III (FLT3) is a transmembrane tyrosine kinase which stimulates the survival and proliferation of myeloid progenitors.(1) FLT3 is expressed on the leukemic cells of 70–100% of patients with AML and it can be mutated in up to 30% of cases.(2, 3) Mutations include internal tandem duplications (ITD) in the juxta-membrane domain (17–

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34%) and mutations in the tyrosine kinase domain (D835) activation loop (7%).(4) These mutations, particularly FLT3 ITD, have been associated with an unfavorable outcome in AML.(5, 6) Midostaurin (PKC-412) is a broad-spectrum tyrosine kinase inhibitor of both wild type and mutated FLT3.(7) Phase I(8) and phase II trials of midostaurin have shown a significant but usually transient reduction in blast percentage in the peripheral blood and/or the bone marrow of patients with relapsing refractory AML or high-risk MDS, but no complete remissions.(9, 10) Other FLT3 inhibitors currently in clinical trials similarly induce usually transient decrease in blast counts.(11–13) Combination strategies of FLT3 inhibitors are being investigated to explore whether deeper and more durable responses can be achieved.(14, 15)

We present here the results of a phase I/II study of the combination of midostaurin and azacitidine (AZA) for both untreated and previously treated patients with AML or high-risk MDS, irrespective of FLT3 mutational status.

Methods

Patients selection

This was a single-institution, phase I/II single-arm open-label study. Eligible patients were aged 18 years or older with MDS or AML diagnosed according to the WHO classification.(16) Both untreated patients who were not able or refused to receive standard therapy and patients with refractory or relapsed AML were eligible. As midostaurin inhibits both mutated and wild-type FLT3, patients were enrolled in this study regardless of their FLT3 mutational status. Patients could have received prior therapy with other FLT3 inhibitors but, after an amendment of the protocol, should have not been primary refractory to such therapy. Patients should have been off chemotherapy for 2 weeks and must have recovered from the toxic effects of such therapy to at least grade 1. In case of rapidly proliferative disease, hydroxyurea was allowed before the start of study therapy and for the first four weeks on therapy. Additional eligibility criteria included: adequate liver (bilirubin <2x and ALT ≤2.5x upper limit of normal –ULN-) and renal (creatinine <2x ULN) function, and Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2. Sexually active patients were required to practice contraception. Patients were excluded if they had any coexisting medical condition that in the judgment of the treating physician was likely to interfere with study procedures or results, or if they had any active uncontrolled infection. Patients with acute promyelocytic leukemia and core binding factor leukemia were also excluded.

The study was approved by the institutional review board (IRB) of the University of Texas, M. D. Anderson Cancer Center and was conducted in accordance with the principles of the declaration of Helsinki. All patients signed informed consent prior to participation in the trial.

Treatment schedule

AZA was administered subcutaneously (SQ) or intravenously (IV) (at the discretion of the treating investigator) for 7 days of every cycle (Days 1–7). Midostaurin was administered

orally twice daily (bid) for 14 days on cycle 1 (Days 8–21). After the first 23 patients were enrolled, the protocol was amended to allow, starting with cycle 2, continuously (daily) administration of midostaurin with no interruptions unless there were adverse events. During phase I, the starting dose of midostaurin was 25 mg bid for the first 6 patients, with the target dose being 50 mg bid (provided no dose limiting toxicity –DLT- was identified in > 1 patient at the 25 mg bid dose level). The cycles were repeated every 4 weeks, up to a maximum of 12 cycles. Adequate anti-nausea and anti-infectious prophylaxis was provided during all cycles. Concomitant medications known to induce or inhibit CYP3A4, likely to interact with midostaurin, were not allowed. Toxicity was graded according to the CTCAE version 4. All clinically relevant non-hematological grade (G) 3-4 toxicities possibly related to the study drugs were considered DLTs during phase I. Grade 3-4 toxicities possibly related to the study drugs were managed with treatment interruptions and dose reductions in addition to appropriate medical management.

Correlative studies

For pharmacokinetic analysis, the median concentration of midostaurin and its metabolites (CGP62221 and CGP52421) were measured during the first cycle at day 8, 15, and 21.

The activity of midostaurin was evaluated through the Plasma Inhibitory Activity (PIA) assay for FLT3, as previously described.(17) Plasma was collected prior to therapy and on day 15 (1 week after starting treatment with midostaurin). Molm14 cells (expressing a FLT3 ITD mutant receptor) were exposed for 1 hour to the plasma samples, followed by lysis and immunoblot analysis for phosphorylated FLT3 and total FLT3. Densitometric analysis compared the day 15 sample to the pretreatment sample.

Response assessment

The pretreatment evaluation included history and physical examination, complete blood count with differential, a complete chemistry survey, a pregnancy test for women of childbearing potential, an electrocardiogram, an echocardiogram or multi-gated acquisition scan, and marrow aspiration with cytogenetic and FLT3 mutational status. Bone marrow aspirate and/or biopsy were performed on day 28 of the first cycle and then every 1–3 cycles. Response to therapy was defined according to the International Working Group criteria (18, 19). Responders were patients who obtained a complete remission (CR), a CR with incomplete bone marrow recovery (CRi), a morphologic leukemia-free status (MLFS), or a partial remission (PR). A CR was defined as ≤5% bone marrow blasts, neutrophil count ≥1.0 $\times 10^9$/L, and platelet count ≥100 $\times 10^9$/L. A CRi was defined as meeting all CR criteria except residual neutropenia (<1.0 $\times 10/L^9$) or thrombocytopenia (<100 $\times 10^9$/L). A MLFS was defined as <5% blasts in the bone marrow regardless of neutrophil and platelet count in the peripheral blood. A PR was defined as meeting all CR criteria, except a reduction ≥ 50% in bone marrow blasts, but still >5%.

Statistical considerations

Primary endpoints were CR and overall response rate (ORR). We chose dual endpoints since it was uncertain at the start of the trial what type of responses could be observed. This trial was conducted using a Bayesian design that jointly models toxicity and response outcomes.

Differences between variables were compared by the chi2 test and Mann-Whitney U test for categorical and non-categorical variables, respectively. Remission duration (RD) was calculated from the time of response achievement until the earlier of loss of response or death or last follow-up. Survival curves were estimated by the Kaplan-Meier method and compared by the log-rank test.

Results

Patient characteristics

Fifty-four patients were enrolled in this study, 14 in the phase I and 40 in the phase II. Patient characteristics are shown in Table 1. Fifty-nine percent of patients were male and 15% were 75 years or older. Sixty-nine percent of patients had primary AML, 26% secondary AML (sAML) and 5% had MDS. Seventy-four percent of patients had a FLT3 mutation: 68% ITD alone, with a median ITD ratio of 0.35 (range, 0.006–0.75), and 6% with associated D835, with a median D835 ratio of 0.46 (range, 0.32–0.50); no patient presented with isolated D835 mutation. Seventy-six percent of patients had been previously treated, with a median number of 2 (range, 1–8) prior regimens. Forty-three percent of patients had been previously exposed to a hypomethylating agent, including either azacitidine (n=9) or decitabine (n=11) or both (n=3), and 24% had previously received another FLT3 inhibitor (sorafenib in 10 patients and quizartinib in 3). None of the patients without FLT3 mutations had been exposed to prior FLT3 inhibitors. Thirty percent of patients had received a prior allogeneic stem cell transplant (SCT).

Response to therapy

During the dose-finding portion of the study, 6 patients received midostaurin at a dose of 25 mg bid and 8 at a dose of 50 mg bid. No DLT was observed in any of these patients. Thus, 40 patients were enrolled in the phase II portion of the study with midostaurin at 50 mg bid. The first 23 patients received midostaurin on days 8–21 in all cycles, while 31 received midostaurin continuously after cycle 1. Patients received a median of 2 (range, 1–9) cycles, with 21 (39%) patients receiving only 1 cycle. Among the 54 patients, after a median time of 12 (range, 1–31) weeks, ORR was 26%. One (2%) patient achieved a CR, 6 (11%) achieved a CRi, 6 (11%) a MLFS, and 1 (2%) patient a PR. Forty (74%) patients were primary refractory to therapy. The response rate among the 27 patients with FLT3 ITD previously unexposed to FLT3 inhibitors was 33%; of those, 26 were treated at a midostaurin dose of 50 mg bid and 9 (35%) responded. A trend for a lower ORR (13%) was observed among the 23 patients with previous exposure to hypomethylating agents; of those, 9 (39%) had sAML, and 14 (61%) were FLT3 mutated. Other factors not significantly associated with ORR were: age, sex, diagnosis of AML, presence of FLT3 ITD or D835 mutation, FLT3 allele burden, previous therapy, previous SCT, previous exposure to FLT3i, and dose and schedule of midostaurin. Two (4%) patients (1 in CR and 1 with a reduction in bone marrow blasts >50% -from 27% to 7%-, but not meeting the criteria for response) received an allogeneic SCT after 4 and 2 cycles, respectively.

Forty-eight patients were evaluable for bone marrow response, whereas 6 patients did not have a bone marrow performed after the start of treatment. Median time to best bone

marrow response was 4 (range, 3–17) weeks. Thirty-eight (79%) patients had a reduction in bone marrow blasts from a median at baseline of 57% (range, 9–93%) to a median of 13% (range, 2–63%) as best response at any time. The median reduction in the percentage of bone marrow blasts was 68% (range, 18–97%) and 25 (53%) patients had a reduction ≥50% (Figure 1A). Ten (21%) patients had stable or worsening bone marrow disease, with a median increase in bone marrow blasts of 23% (range, 0–200%), from a median of 38% (range, 17–68%) to a median of 48% (range, 34–89%) (Figure 1A). Forty-nine patients had peripheral blood blasts before starting therapy. Median time to best peripheral blood response was 3 (range, 1–18) weeks. Forty-seven (96%) patients had a reduction in peripheral blasts from a median at baseline of 41 % (range, 2–100%) to a median of 1% (range, 0–98%) as best response at any time. The median reduction in the percentage of peripheral blood blasts was 89% (range, 2–100%) and 41 (84%) patients had a reduction ≥50% (Figure 1B). Two patients had a stable/worsening peripheral blood disease, with an increase from to 2% to 4%, and from 51 to 52%, respectively (Figure 1B).

Safety

Treatment emergent adverse events are presented in Table 2. Grade (G) 3-4 hematological adverse events were observed in all patients: neutropenia in 52 (96%) patients, thrombocytopenia in 51 (94%), and anemia in 33 (61%) patients. However, G 3-4 myelosuppression was already present in 44 (81%) patients before starting therapy. Neutropenia was associated with infections (documented by cultures and/or imaging) in 30 (56%) patients.

G3-4 non-hematological toxicity was reported in 38 (70%) patients: decreased left ventricular ejection fraction (EF) in 6 (11%), diarrhea in 5 (9%), nausea or vomiting in 5 (9%), hyperglycemia in 3 (5%), hyperuricemia in 2 (4%), hyperbilirubinemia in 2 (4%), skin rash in 2 (4%), hypokalemia in 2 (4%), QTc prolongation in 1 (2%), thrombosis in 1 (2%), bleeding (gastric hemorrhage) in 1 (2%), acute renal failure in 1 (2%), and hyponatremia in 1 (2%). None of the patients discontinued therapy because of adverse events.

Among the 6 patients who had a reduction in left ventricular EF reduction, 3 had previously received anthracyclines, and 3 had significant cardiac risk factors (including hypertension, heavy smoking, dyslipidemia, and previous cardiac event). The median EF reduction was 15% (range, 10–40%). Serial echocardiograms were available in 2 patients, and they both recovered to baseline despite continuation of study therapy.

Correlative studies

Pharmacokinetic studies were conducted during the first cycle of therapy. The median concentration of midostaurin and its two metabolites (CGP62221 and CGP52421) was measured during the first cycle of therapy: on 33 patients on day 8, and 29 patients on day 15 and day 21. Their levels rose rapidly over one week of treatment. Then the median concentrations of midostaurin and CGP62221 reached steady state, whereas concentrations of CGP52421 continued to increase (Figure 2).

To evaluate the activity of midostaurin and its metabolites, a PIA assay was conducted. A decrease of in phosphorylated FLT3 was observed on day 15 (1 week after starting treatment

with midostaurin) (Figure 3A). This corresponded to a considerable reduction in the mean level of FLT3 phosphorylation (49%, range 21–74%) when compared to baseline (Figure 3B).

Response duration and survival

Among the 14 patients who responded to therapy, 6 (43%) have relapsed, whereas 8 (57%) have an ongoing response. After a median follow-up of 15 weeks (range, 1–85 weeks), the median response duration (RD) was 20 weeks (95% confidence interval [CI], 10–30 weeks). A significantly longer RD was observed for patients with FLT3 mutations who had not been previously exposed to other FLT3 inhibitors (31 vs 16 weeks, p=0.05) (Figure 4A) and for patients who had not previously received a SCT (31 vs 6 weeks, p=0.01) (Figure 4B). A trend for a longer RD was observed for patients 65 years or older (31 vs 11 weeks, p=0.06) and for all patients previously unexposed to FLT3 inhibitors (31 vs 16 weeks, p=0.09). Other factors not significantly associated with RD (p>0.05) were: sex, AML vs MDS, cytogenetics, FLT3 ITD or D835 mutation, FLT3 allele burden, prior therapy, prior exposure to HMT, and dose and schedule of midoasturin.

Thirty-two (59%) patients died, 5 (9%) of them while on study. All patients died of complications related to disease progression. After a median follow up of 15 (range, 1–85) weeks, the median overall survival (OS) was 22 weeks (95% CI, 15–29 weeks)

Discussion

The major cause of treatment failure in AML is represented by resistance (primary or secondary) to treatment (20), emphasizing the need to investigate new effective regimens. This applies particularly to elderly patients, the majority of affected patients(21, 22), for whom hypomethylating agents, such as AZA, are associated with similar survival rates as intensive chemotherapy (23, 24). A poor outcome is also classically observed in patients with adverse prognostic factors, such as FLT3 mutation. Several FLT3 inhibitors have been investigated in this setting, including sorafenib, quizartinib, crenolanib, CEP-701 and others in earlier stages of development. None of these agents has received regulatory approval for use in FLT3-mutated AML.

We present here the first results of a phase I/II study of the combination of midostaurin and AZA for both untreated and previously treated patients with AML or high-risk MDS. As outlined in Table 1, this study enrolled a high-risk population, including mostly older patients, 74% harboring a FLT3 mutation, and 76% had relapse after previous therapy. Prospective studies assessing the outcome of patients older than 65 years treated with standard anthracycline-based induction-consolidation chemotherapy have reported poor outcomes, with a median OS of 21 weeks and a 2-years OS of 27%.(25, 26) For patients with normal karyotype and FLT3 mutation receiving induction chemotherapy, a median OS of 10 months has been observed, significantly shorter than that of patients not harboring such mutation.(27) Patients with relapsed AML, particularly if occurring after SCT (a scenario observed in up to 30% of patients in our study), carry a very poor prognosis with less than 29% survival at 1 year.(28) Among patients with FLT3 mutations who have experienced failure of induction chemotherapy, the response rate with standard

chemotherapy is 24%, and the median survival is 13 weeks.(29) The population included in the study described in this manuscript included mostly patients who had failed at least 1 prior regimen. A retrospective analysis of patients with relapsed or refractory leukemia with FLT3 mutations suggested that those treated with FLT3 inhibitor-based combinations may have a better outcome compared to those treated with standard chemotherapy regimens, particularly if their initial remission duration was shorter than 12 months.(30)

In the present study, the combination of AZA and midostaurin produced an ORR of 26%, with 6 patients achieving a CRi, 6 a MLFS, 1 a CR and 1 a PR. Of interest, 79% of patients had a reduction in bone marrow blasts and up to 53% had a reduction ≥50%, including 15 (31%) with a reduction to <10% blasts. Although not considered as responders, patients with significant reduction of blasts in the bone marrow may be considered to derive clinical benefit as they may become candidates for SCT which may offer the potential for long-term remission and possible cure. The outcome for patients with relapse leukemia who receive a stem cell transplant is better if they are transplanted in remission or at least with a lower percentage of blasts, ideally less than 20%.(31) Thus, achieving this goal, particularly if done with a treatment strategy associated with minimal morbidity, is desirable to increase this potential. Few patients (2) in our study eventually received a stem cell transplant. The fact that 30% of them had already received a stem cell transplant and that half of the patients were aged 65 years or older decreased the potential for stem cell transplant in this series. However, it is conceivable that using this approach at earlier stages and in younger patients might improve this potential.

A 4% ORR and a median OS of 3.1 months (12 weeks) has been reported for patients with relapsing AML receiving single agent AZA.(32) Similar data have been observed with the use of single agent midostaurin.(10) Thus, with the limitations dictated by an inter-study comparison, the combination of these two drugs seems to be more effective than their use as single agents. This concept is further supported by the encouraging data deriving from a phase I trial combining midostaurin to another hypomethylating agent, decitabine.(33) Our correlative studies showed that midostaurin and its metabolites were active. Moreover, the pharmacokinetics (PK) were similar to those using midostaurin alone, suggesting no interference of the combination with the kinetic of midostaurin. Unfortunately in our study PK data were limited by the sampling time, so that the concentration of the active metabolite beyond day 21 is not known. Likewise, the PIA assay was performed early, after only 1 week of therapy with AZA and 1 week of combination therapy. Pharmacodynamics assays were further limited by the complex PK profile of midostaurin. Although in this study the inhibition of FLT3 appears to be less profound than what has been reported with other inhibitors (e.g., sorafenib or quizartinib) (34), the combination of midostaurin with AZA could still be synergistic and resulted in clinical benefit in many patients.

Analogous results have been observed for other FLT3 inhibitors.(35) In elderly patients with relapsed and/or refractory AML, AC220 at the dose of 135 mg daily (90 mg for women) produced an ORR of 43% and a median RD of 17 months.(36) However, at the time of this writing, no combination data are available for this compound. In the same clinical setting, a 31% ORR was reported with the use of sorafenib monotherapy at the dose of 400 mg twice a day.(37) This increased up to 84%, with a 74% 1-year OS, when sorafenib was combined

with cytarabine and idarubicin in younger patients with newly diagnosed, previously untreated AML.(38) The combination of AZA with sorafenib in patients with relapsed and refractory disease resulted in an ORR (among evaluable patients) of 43% and a median OS was 6.2 months.(15)

Midostaurin showed to be a safe drug in comparison to other FLT3 inhibitors, even in association with AZA. The main toxicity was hematological, but severe cytopenia was already present at baseline in this high-risk population. The most common non-hematological toxicity was represented by infections and EF reduction. As outlined above, the latter could have been justified by individual cardiac risk factors and previous exposure to cardio-toxic agents, and it did not cause any of the observed deaths.

In our study, a longer RD was observed for patients FLT3 mutated not previously exposed to other FLT3 inhibitors and for patients not previously treated with SCT. The latter finding is not surprising, as together with age, cytogenetic, and duration of remission, previous SCT inevitably associates with poor prognosis in patients with relapsed AML. The former finding, instead, raises major considerations. During the phase IIb trial of single agent midostaurin, the reduction in bone marrow blasts was more pronounced in the presence of FLT3 mutation.(10) However, in our study, FLT3 mutation did not associate with a longer RD, unless combined with the absence of previous exposure to other FLT3 inhibitors. Sorafenib and quizartinib were the FLT3 inhibitors most commonly used previously by patients included in the present study. The main potential mechanism of resistance to FLT3 inhibitors described at present is the onset of concomitant D835 mutation.(39–41) However, the latter was described in only 6% of patients enrolled in our study and its presence did not correlate with ORR or RD. Other mutations associated with resistance to FLT3 inhibitors, particularly those in gate-keeping residues, were not assessed in our patient population. It is possible that such mutations were present in some patients and could explain resistance to therapy, as midostaurin (like sorafenib and quizartinib) does not have inhibitory activity in the presence of these mutations.

An important observation is that, although not significant, a lower ORR (13%) was observed for patients previously exposed to hypomethylating agents. Whereas decitabine is primarily incorporated in DNA, AZA is incorporated into both DNA and RNA, and the two show different patterns of gene induction and repression.(42) Moreover, in vitro there is a lack of cross resistance between the two.(43) In our study, 12 patients had been previously exposed to AZA, possibly explaining the finding above. Combination of midostaurin with cytarabine-based therapy has been explored and recently reported(44), although using a regimen more commonly employed in younger patients. Combination with lower-dose cytarabine, similar to what has been reported by Burnett et al (45) is warranted to determine whether a better response rate might be expected with such combination for patients previously exposed to hypomethylating agents.

In conclusion, the combination of midostaurin and AZA is an effective and safe regimen in patients with AML and high-risk MDS. Patients FLT3 mutated but not previously exposed to other FLT3 inhibitors and patients not previously transplanted may benefit the most from this combination. Further studies of this combination in these patients are warranted.

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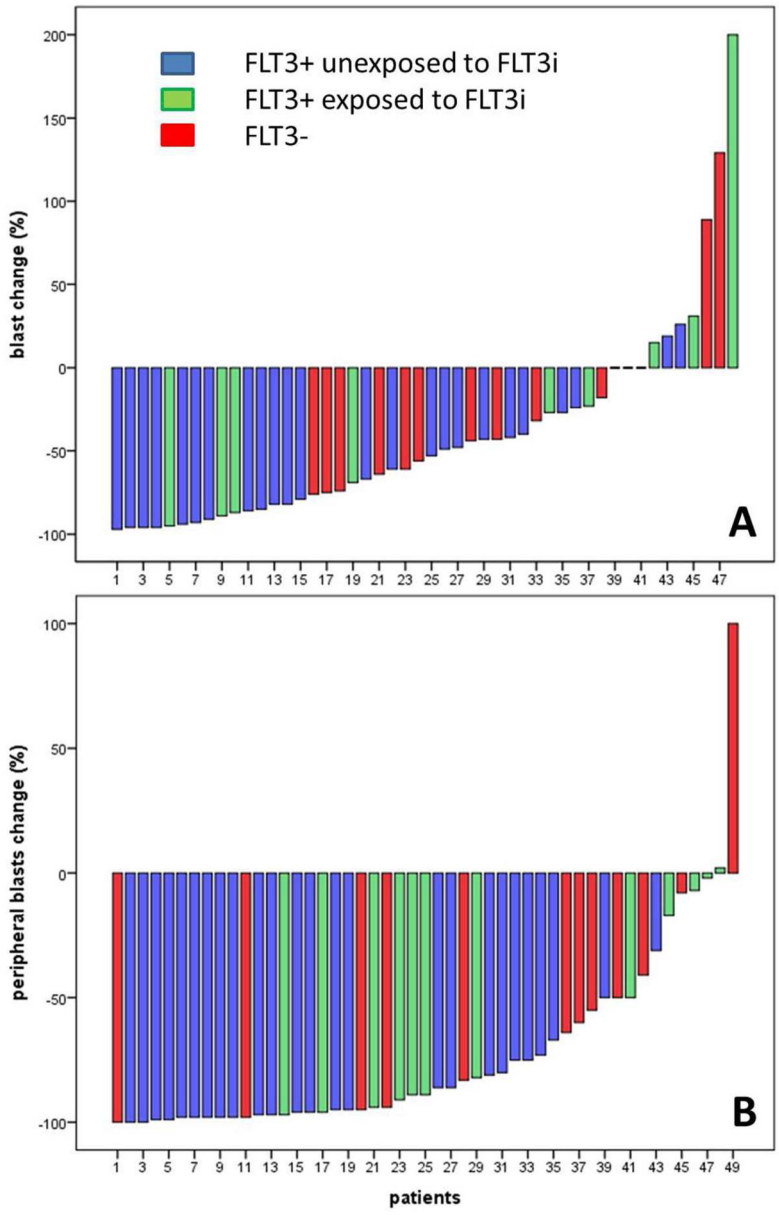

Figure 1.

Bone marrow and peripheral blood blast change. A. Median change in bone marrow blasts at time of best response to therapy. Thirty-eight patients had a reduction in BM blasts from median 57% (range, 9–93%) to 13% (range, 2–63%) and 25 (53%) patients had a ≥50% reduction. Ten patients had stable or increasing BM blasts from 38% (range, 7–68%) to 48% (range, 34–89%). B. Median change in peripheral blasts at time of best response to therapy. Forty-seven (96%) patients had a reduction in peripheral blasts from a median at baseline of 41 % (range, 1–100%) to a median of 1% (range, 0–98%) and 41 (84%) patients had a reduction ≥50%. Two patients had a stable/worsening peripheral blood disease, with an increase from to 2% to 4%, and from 51 to 52%, respectively.

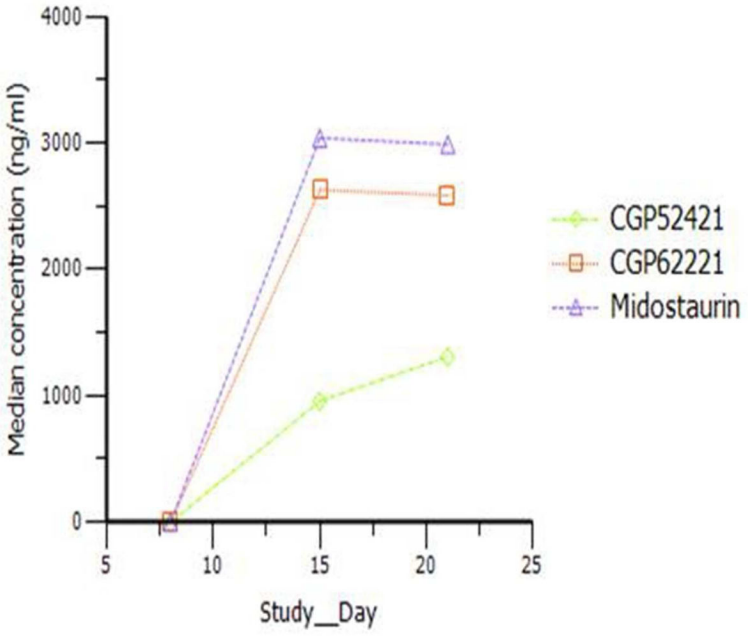

Figure 2.

Pharmacokinetics of midostaurin and its metabolites during cycle 1. Midostaurin and the metabolites levels rose rapidly over one week of treatment. Then the concentrations of midostaurin and CGP62221 reached steady state, whereas concentrations of CGP52421 continued to increase.

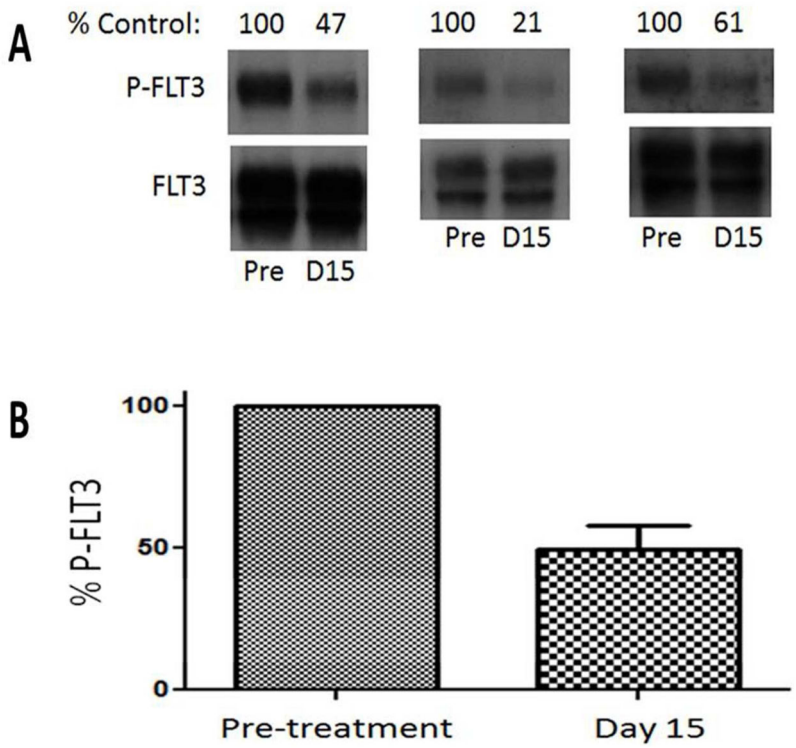

Figure 3.

Plasma Inhibitory Assay (PIA). A. Plasma was collected prior to therapy and on day 15. Molm14 cells were exposed for 1 hour to the plasma samples, followed by lysis and immunoblot analysis for phosphorylated FLT3 (upper gels) and total FLT3 (lower gels). Shown are the results from three different patients on the study. B. Densitometric analysis compared the day 15 sample to the pretreatment sample. The mean level of FLT phosphorylation (49%, range 21–74%) is shown relative to baseline. P-FLT3, phosphorylated FLT3.

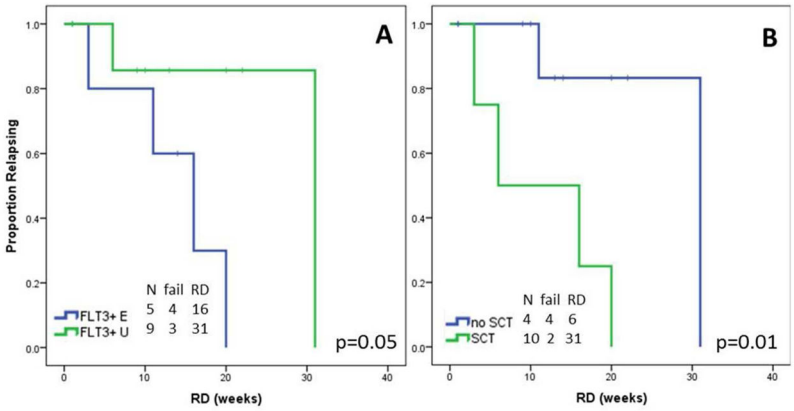

Figure 4.

Response duration (RD) among 14 patients responsive to therapy. A. A longer RD was observed for patients with FLT3 mutations previously unexposed to other FLT3 inhibitors (31 vs 16 weeks, p=0.05). B. A longer RD was observed for patients who had not previously received a SCT (31 vs 6 weeks, p=0.01). RD, response duration; n, number; U/E, previously unexposed/exposed to other FLT3 inhibitors; SCT, stem cell transplant; +, mutated.

Table 1

Patients characteristics. PB, peripheral blood; BM, bone marrow; AML, acute myeloid leukemia; sAML, secondary AML; MDS, myelodysplastic syndrome; SCT, stem cell transplant; FLT3i, FLT3 inhibitor; HMT, hypomethylating therapy; U, unexposed to previous FLT3 inhibitor

Baseline Characteristics (N=54)	Median [range]; number (percentage)
Males	32 (59)
Age ≥ 65 years	27 (50)
Age (years)	65 [21–85]
White blood count (x10^9/L)	4.3 [0–163]
PB blasts (%)	41 [0–100]
Hemoglobin (g/dL)	9.5 [6.6–14.3]
Platelets (x10^9/L)	41 [6–692]
BM blasts (%)	56 [4–100]
AML	37 (69)
sAML	14 (26)
MDS	3 (5)
Unfavorable cytogenetic	15 (28)
FLT3+	40 (74)
FLT3 ITD+/D835−	37 (68)
FLT3 ITD+/D835+	3 (6)
ITD ratio	0.35 [0.006–0.75]
D835 ratio	0.46 [0.32–0.50]
Previously treated	41 (76)
Previously treated sAML	10 (19)
Prior regimens	2 [1–8]
Prior SCT	16 (30)
Prior FLT3i	13 (24)
Prior HMT	23 (43)
FLT3+ U	27 (50)

Table 2

Treatment emergent toxicities. All patients experienced G3-4 hematological toxicity, whereas 70% of patients had G3-4 non-hematological toxicities. G, grade; EF, ejection fraction; ALT, alanine transferase; AST, aspartate transferase

	Number (%)	
	G3-4	**G1-2**
Hematological		
Neutropenia	52 (96)	2 (4)
Thrombocytopenia	51 (94)	3 (5)
Anemia	33 (61)	21 (39)
Non-Hematological		
Infections	30 (56)	5 (9)
EF reduction	6 (11)	2 (4)
Diarrhea	5 (9)	13 (24)
Nausea/vomiting	5 (9)	23 (43)
Hyperglycemia	3 (5)	0 (0)
Hyperuricemia	2 (4)	0 (0)
Hyperbilirubinemia	2 (4)	7 (13)
Skin rash	2 (4)	15 (28)
Hypokalemia	2 (4)	2 (4)
QTc prolongation	1 (2)	4 (8)
Thrombosis	1 (2)	6 (12)
Bleeding	1 (2)	5 (9)
Acute renal failure	1 (2)	1 (2)
Hyponatremia	1 (2)	0 (0)
Constipation	0 (0)	8 (16)
Tachycardia	0 (0)	6 (12)
Elevated ALT/AST	0 (0)	6 (12)
Hypomagnesaemia	0 (0)	2 (4)