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Final Report of Phase II Study of Sorafenib, Cytarabine, and Idarubicin for Initial Therapy in Younger Patients with Acute Myeloid Leukemia

Farhad Ravandi¹, Cecilia Arana Yi¹, Jorge E. Cortes¹, Mark Levis², Stefan Faderl¹, Guillermo Garcia-Manero¹, Elias Jabbour¹, Marina Konopleva¹, Susan O'Brien¹, Zeev Estrov¹, Gautam Borthakur¹, Deborah Thomas¹, Sherry Pierce¹, Mark Brandt¹, Keith Pratz², Rajyalakshmi Luthra³, Michael Andreeff¹, and Hagop Kantarjian¹

¹Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

²Division of Hematological Malignancies, Johns Hopkins Sidney Kimmel Cancer Center, Baltimore, MD, USA

³Division of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

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Sorafenib is a multikinase inhibitor and a potent *FLT3* inhibitor that inhibits tumor growth and angiogenesis by inhibiting intracellular *Raf* kinases and cell surface kinase receptors such as *VEGFR*, *PDGFR-beta*, *ckIT*, and *FLT-3*.¹ It has been approved by the U.S. Food and Drug Administration for the treatment of advanced renal cell carcinoma and hepatocellular carcinoma at a standard dose of 400 mg twice daily. The antileukemic activity of sorafenib has been evaluated in preclinical models and a number of recently reported clinical trials.²

In a phase I/II study, combination therapy with sorafenib, cytarabine, and idarubicin in younger patients with AML was able to induce a high complete response (CR) rate in those with *FLT3* mutations and a 1-year probability of survival of 74%.³ We here report long-term outcome for adults with newly diagnosed AML who were treated with a combination of sorafenib, cytarabine, and idarubicin. Details of the patient population and the treatment regimen have been previously published.³ Survival curves were plotted by the Kaplan-Meier method and compared using the log-rank test. Differences in subgroups by different covariates were evaluated using the χ^2 test for nominal values and Fisher's exact test for continuous variables.

Between February 1, 2008, and March 31, 2010, 62 patients with previously untreated AML were enrolled in this study. Patient characteristics are summarized in Table 1a. The median age of the patients was 53 years (range, 18 to 66 years); 12 were older than or equal to 60 years. Twenty-three had *FLT3* mutations, including 17 with *FLT3*-ITD (10 with low mutation burden), 4 with *D835* mutation, and 2 with both mutations; 11 patients had antecedent hematologic disorder and 10 had unfavorable cytogenetics. Herein, we will refer to the patients as *FLT3*-ITD-positive or negative including the 4 patients with sole *D835* mutation in the latter group and the 2 with both mutations in the former group.

The median white blood cell count (WBC) at presentation was $7.25 \times 10^9/L$ (range, 0.6 to $228.5 \times 10^9/L$). Eight patients were *FLT3*-ITD–positive/nucleophosmin-1 (*NPM1*)–negative. The median age of patients with *FLT3*-ITD mutation was 52 years (range, 20 to 66 years); one had adverse and 18 had intermediate cytogenetics (17 with normal karyotype) based on MRC criteria.

Sixty-one patients had response assessment; one patient died before response assessment could be performed. Among these, 49 (79%) achieved CR, and 5 (8%) CRp. Seven (11%) patients were non-responders. Among the 54 responders, 51 patients received consolidation and maintenance courses; 3 proceeded to allogeneic stem cell transplant straight after induction. Patients with *FLT3*-ITD were more likely to achieve a CR/CRp than were patients without *FLT3*-ITD [18 of 19 patients (95%) vs. 36 of 43 (84%), respectively ($P = 0.23$)] (Table 1b). Seventeen *FLT3*-ITD patients achieved CR and one had CRp, three *FLT3*-*D835* patients achieved a CR and one had CRp, and 32 of 43 patients without *FLT3*-ITD achieved a CR and four had CRp; one died at induction, and six were resistant to therapy. CR was achieved after one induction cycle in 44 patients and after two induction cycles in five patients. Sixteen patients with the *FLT3*-ITD mutation achieved CR/CRp after one induction cycle, and two achieved it after two cycles. Altogether, sixteen patients proceeded to allogeneic stem-cell transplantation in first CR/CRp, including nine with a *FLT3* mutation (six with *FLT3*-ITD, three with *FLT3*-*D835*). To date, 35 (65%) of the responders have experienced relapse including 11 of 18 patients (61%) with *FLT3*-ITD and 24 of 36 (67%) without *FLT3*-ITD ($P = 0.69$); 33 patients received salvage therapy: 2 died while receiving first salvage therapy, 11 achieved a second CR, 2 CRp, 1 PR and 17 had refractory disease. Ultimately 22 of these 33 patients died after their first or subsequent salvage therapies.

With a median follow-up of 52 months (range, 2.3-62.9 months) for all patients, the median OS and DFS were 29 and 13.8 months, respectively (Figure 1a and 1b). Figure 1c and 1d demonstrates the OS and DFS for all patients and for patients with *FLT3*-ITD. Among patients with *FLT3*-ITD who achieved CR/CRp, 11 have relapsed and 5 remain in CR; 2 patients died in CR. The median OS and DFS among the 19 patients with *FLT3*-ITD was 15.5 and 9.9 months, respectively (Figure 1c and 1d).

Hematopoietic stem cell transplantation was performed in first CR in 16 of 54 patients who achieved a CR/CRp (30%); six of the 16 relapsed and 7 died following the SCT. The 3-year disease-free survival (DFS) rate (in 54 patients achieving CR/CRp) was 34%; the 3-year OS rate for all patients was 48% (Figure 1a and 1b).

The regimen was generally well tolerated, the adverse events being those expected in patients receiving induction chemotherapy with the combination of cytarabine and idarubicin. The most common grade 3 and 4 adverse events possibly associated with the addition of sorafenib to the induction regimen occurred in 15 patients and included nausea and vomiting (7), cardiac/hypertension (6), diarrhea (5), infections (5), hand and foot syndrome (4), liver toxicity (5), and pancreatitis (2). One patient died of massive myocardial infarction during induction; this was not considered to be related to sorafenib (Table 1c).

Mutations in *FLT3* are well-established indicators of poor prognosis in AML⁴⁵ and occur in approximately 20% to 30% of patients. Small-molecule *FLT3* kinase inhibitors have been developed with different efficacies against *FLT3*-mutant cell lines. They also have been evaluated in *FLT3*-ITD+ primary leukemia cells, alone or in combination with cytarabine and anthracyclines such as idarubicin.⁶⁷⁸⁹

This study reports on the long-term follow-up of patients with newly diagnosed AML who received upfront treatment consisting of sorafenib combined with cytarabine and idarubicin. Nineteen patients had the *FLT3*-ITD mutation. The response rates (CR and CRp) for patients with *FLT3*-ITD were higher than that for patients without *FLT3*-ITD including those with *FLT3*-D835 mutants and those with wild-type *FLT3* (18/19 patients [95%] vs. 36/43 [83%], respectively) although this was not statistically significant ($P = 0.23$). Similarly, there was no significant difference in OS or DFS when comparing patients with and without *FLT3*-ITD (Figure 1c and 1d). This is in contrast to previous studies reporting significantly shorter DFS and OS for patients with *FLT3*-ITD and can potentially be attributable to the addition of sorafenib to the regimen. This may be due to the possible increased likelihood of the patients to be able to undergo an allogeneic stem cell transplant as a result of the addition of sorafenib. We also analyzed the outcomes censoring patients at the time of allogeneic stem cell transplant ($n=16$) and found no significant difference between the groups' outcomes (data not shown).

In this study, the sorafenib containing induction regimen produced a high response rate but was associated with relapse in the majority of the patients. Man et al.¹⁰ reported activation of alternative survival pathways in sorafenib-resistant leukemic clones. In their study, 12 of 13 patients with AML and *FLT3*-ITD responded to treatment with sorafenib monotherapy but nine lost their response at a median of 72 days. We had a similar high response rate in this study but the median DFS was significantly longer at 9.9 months suggesting a potential benefit for combining sorafenib with chemotherapy, especially that overall, the treatment was well tolerated with limited grade 3 and 4 toxicity. A recent report, however, suggested that the addition of sorafenib to standard cytarabine and daunorubicin induction regimen did not improve EFS or OS and was associated with increased toxicity during induction.¹¹ However, the patients treated in that study were older than 60 which may account for the higher incidence of toxicity. Our study is limited due to the inability to discern the impact of other interventions such as allogeneic stem cell transplant, related to its non-randomized design and limited patient numbers.

Rollig and colleagues have reported preliminary results of SORAML trial in which patients received cytarabine 100 mg/m² for 7 days plus daunorubicin 60 mg/m² for 3 days followed

by high dose cytarabine consolidation.¹² Patients were randomized to receive Sorafenib at a dose of 800 mg/day or placebo during induction and consolidation and for a 12 months maintenance period after the end of consolidation. Among the 276 patients randomized, 264 were evaluable for event-free survival (EFS), 132 in each arm.¹² Patient and disease characteristics were similar between the two arms, with the *FLT3*-ITD incidence of 16%. The CR rates were 56% and 60% in the placebo and sorafenib arms, respectively (p=0.62). With a median follow-up of 18 months, the median EFS was 12.2 months in the placebo arm and was not reached in the sorafenib arm; the 2-year OS was 66% versus 72% in placebo and sorafenib arms, respectively (p=0.37). Although there was an increased risk of hepatotoxicity and bleeding events in the sorafenib arm, the authors concluded that the addition of sorafenib was associated with a prolongation of EFS which was most marked in the patients with *FLT3*-ITD.¹² The eventual result of this study will better clarify the potential role of sorafenib in the treatment of patients with AML and *FLT3*-ITD.

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Figure 1.

(a) OS for all patients; (b) DFS for all patients; (c) OS according to *FLT3*-ITD status; (d) DFS according to *FLT3*-ITD status.

Table 1a

Patient characteristics

Patient Characteristics	N	%
Patients Treated	62	100
Median age (range) in years	53	(18-66)
Patients > 60 years	12	19
Median WBC $\times 10^9/L$ (range)	7.25	(0.6-228.5)
Cytogenetics		
Adverse risk	10	16
Intermediate risk	48	77
Favorable risk	1	2
Insufficient Metaphases	3	5
<i>FLT3</i> mutation status		
Wild type	39	63
Mutated	23	37
ITD	17	27
D835	4	6
Both	2	3
<i>FLT3</i> -ITD allele burden		
High >25%	8	42
Low ≤25%	11	58

Table 1b
Response to induction according to FLT3 status

Response	<i>FLT3</i> -ITD mutation status			
	Negative	Low	High	Positive (Total)
	N (%)			
Patients (total)	43	11	8	19
CR	32 (74)	10	7	17 (89)
CRP	4 (9)	1	0	1 (5)
Died	1 (2)	0	0	0
Resistant	6 (14)	0	1	1 (5)

Table 1c

Toxicity	No of Patients with Grade	
	1 and 2	3 and 4
GI effects (nausea, vomiting)	9	7
Mucositis	6	1
Colitis	0	1
Anorexia	3	0
Bleeding	3	1
Diarrhea	22	5
Hand foot syndrome	8	4
Cardiac/hypertension	3	6
Elevated creatinine	1	0
Elevated liver enzymes	5	5
Weight gain/fluid overload	5	0
Infections	0	5
Pancreatitis	0	2