Sorafenib in Relapsed AML With FMS-Like Receptor Tyrosine Kinase-3 Internal Tandem Duplication Mutation

Smith Giri, MBBS^a; Shadi Hamdeh, MD^b; Vijaya Raj Bhatt, MBBS^c; and James K. Schwarz, MD^c

Abstract

Old age (≤ 65 years), relapsed or refractory disease, and the presence of FMS-like receptor tyrosine kinase-3 (*FLT3*) internal tandem duplication (ITD) mutation are poor prognostic factors in acute myeloid leukemia (AML). *FLT3* inhibitors such as sorafenib have been shown to have a potential role in treating relapsed or refractory AML with *FLT3* mutations. In the present report, the use of sorafenib in combination with cytarabine and idarubicin resulted in disease control for 7 months in an older patient with relapsed *FLT3*-positive AML. This case report and the existing literature indicate that sorafenib has disease activity against relapsed AML with the *FLT3*-ITD mutation in older patients. Larger multicenter studies should be conducted to confirm these findings, which have the potential to improve outcomes in this high-risk AML subgroup. (J Natl Compr Canc Netw 2015;13:508–514)

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Release date: May 13, 2015; Expiration date: May 13, 2016

Learning Objectives

Upon completion of this activity, participants will be able to:

- Describe the factors associated with poor prognosis for patients with AML
- Discuss the potential benefits of the use of several therapies to treat patients with *FLT3*-ITD mutations

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Submitted July 7, 2014; accepted for publication October 2, 2014.

The authors have disclosed that they have no financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products discussed in this article or their competitors.

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Acute myeloid leukemia (AML) is the most common form of acute leukemia in adults, with an estimated incidence of 3 cases per 100,000 people.¹ Factors associated with poor prognosis include advanced age, unfavorable cytogenetics, molecular markers (such as FMS-like receptor tyrosine kinase-3 [*FLT3*], internal tandem duplication [ITD] mutation, or absence of nucleophosmin [*NPM1*] mutation), poor performance status, multiple comorbidities, inability to tolerate chemotherapy, and multidrug resistance.² The management of patients with relapsed/refractory AML remains a huge clinical challenge with few therapeutic options available, particularly for older patients.³

Among the intermediate cytogenetic risk group with normal karyotype, the *FLT3*-ITD mutation portends poor disease-free and overall survivals.⁴ *FLT3* is normally expressed on the surface of hematopoietic stem cells and is important in the normal development of pluripotent stem cells.⁵ *FLT3* is mutated in approximately one-third of AML cases.⁴ Therapeutic options in cases of refractory or relapsed *FLT3*-positive AML are limited, particularly in the presence of poor performance status or prior allogeneic stem cell transplantation (alloSCT).³ *FLT3* inhibitors, such as sorafenib, may have some role in these situations.⁶ Sorafenib was initially designed as a small molecule inhibitor of c-Raf kinase but has demonstrated efficacy in inhibiting the activities of *FLT3*, vascular endothelial growth factor receptors 2 and 3, and members of the platelet-derived growth factor receptor family.⁷ This report presents a case of an older man with relapsed *FLT3*-positive AML who experienced disease control for 7 months with the combination of chemotherapy and sorafenib.

Case Presentation

A 65-year-old man presented to the emergency room who had experienced worsening pain in both calves during the past 2 to 3 weeks, fever and chills for 1 week, rectal bleeding, and weight loss. His past medical history was significant for prostate adenocarcinoma (Gleason 7) treated 4 years ago with intensity-modulated radiation therapy (8000 cGy in 40 fractions), diabetes mellitus, hypertension, hyperlipidemia, atrial fibrillation, gastroesophageal reflux disease complicated by Barrett esophagus, and glaucoma. Family history was significant for head and neck cancer in his father. The patient denied

smoking or drinking alcohol. Physical examination revealed a blood pressure reading of 130/70 mm Hg, heart rate of 77 beats per minute, temperature of 98.6°F, respiratory rate of 18 breaths per minute, and oxygen saturation of 96%. He had bilateral calf tenderness without erythema or edema. The remainder of the examination was unremarkable.

Laboratory evaluation revealed a WBC count of 59,000/mcL with 93% blasts, hemoglobin level of 9.2 g/dL, platelet count of 83,000/mcL (Table 1), and normal glucose and electrolyte levels, coagulation profile, and renal and liver function tests. Bone marrow biopsy revealed blasts with high nuclear-to-cytoplasmic ratio, occasional nucleoli, and some folded or bilobed nuclei. Most blasts appeared agranular; however, rare cytoplasmic granules and Auer rods were seen. Blasts expressed CD33, CD45, partial CD38, partial CD71, partial CD117, and cytoplasmic myeloperoxidase, consistent with AML. The blasts were negative for CD34, HLA-DR, terminal deoxynucleotidyl transferase, and lymphoid markers. Cytogenetics demonstrated normal male chromosomes, 46,XY[20]. Fluorescence in situ hybridization was negative for t(15;17) translocation. Deoxyribonucleic acid amplification showed *FLT*-ITD and *NPM1* mutations.

The patient received induction chemotherapy with 7-day infusional cytarabine (100 mg/m²/d) and 3-day daunorubicin (60 mg/m²/d). A repeat bone marrow biopsy at day 14 demonstrated residual leukemia with 15% blasts. After a lengthy discussion regarding different options, including alloSCT in the future, the patient chose to be treated with low-intensity therapy. Hence, he was started on subcutaneous azacytidine (75 mg/m²/d for 7 days) with a repeat cycle every 4 weeks. The patient received 9 cycles of azacytidine, and showed an improvement in his hemogram.

Ten months after his first presentation, the patient presented with dyspepsia and was feeling unwell. His CBC count was 20,700/mcL with 80% blasts. The patient was started on intermediate-dose cytarabine (1.5 g/m²/d for 3 days), idarubicin (12 mg/m²/d for 3 days), and sorafenib (400 mg twice daily for 7 days).⁸ The patient also received prophylactic filgrastim and prophylactic antibiotic, antifungal, and antiviral agents. A repeat bone marrow biopsy at day 28 showed 50% cellularity and 5% blasts. Cytogenetics demonstrated normal male chromosomes, 46,XY[19]. The patient tolerated

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Table 1 Hemogram Results During Different Stages of Disease

	WBC (per mL)	Blasts (% of WBC)	Hemoglobin (g/dL)	Platelet Count (per mL)
At diagnosis	59,000	93%	9.2	83,000
After 1 month of first induction therapy with cytarabine and daunorubicin	1700	0%	10.1	185,000
Before 9th cycle of azacytidine	3300	0%	14.4	307,000
At first relapse	20,700	80%	14.7	158,000
After 1 month of second induction with idarubicin, cytarabine, and sorafenib	5200	3%	10.1	416,000
After 1 month of consolidation with idarubicin, cytarabine, and sorafenib	5400	0%	11.8	245,000
One month before second relapse	5800	0%	15.0	194,000
At second relapse	110,000	93%	11.9	16,000

induction chemotherapy well, experiencing grade 1 skin rash, grade 1 transaminitis, and one episode of neutropenic fever. However, he presented 2 weeks after discharge with pleuritic chest pain and was found to have pulmonary embolism. This was managed with outpatient therapy with enoxaparin. The patient subsequently received one cycle of consolidation therapy with cytarabine, 0.75 g/m²/d for 3 days; idarubicin, 8 mg/m²/d for 2 days; and sorafenib, 400 mg twice daily for 28 days.⁸ This was complicated by prolonged myelosuppression, sepsis, clostridium difficile infection, weakness, and anorexia. On recovery, the patient was maintained on single-agent sorafenib, 400 mg twice daily,⁸ which was well tolerated. Seven months after the first relapse, he experienced disease relapse with elevation of his WBC count to 110,000/mL with 93% blasts. At this point, he was started on hydroxyurea, low-dose cytarabine, and sorafenib, 400 mg twice daily. The patient expired 3 months after his second relapse and 17 months after his initial diagnosis.

Discussion

The presence of an *FLT3*-ITD mutation in AML has been associated with higher rates of relapse and shorter disease-free and overall survivals.⁹ A previous study had reported a relapse rate of 74% and a 5-year overall survival rate of 32% in individuals with these mutations.¹⁰ The outcomes are significantly worse in patients with *FLT3*-mutated AML with

relapsed disease, advanced age, or poor performance status. However, in patients with *NPM1*-mutated AML, the presence of low-allelic burden *FLT3*-ITD mutation, compared with wild-type *FLT3*, does not confer poor outcomes.¹¹ Although this patient had an *NPM1* mutation, the allelic burden of the *FLT3*-ITD mutation was not available. Increasing recognition of the *FLT3*-ITD mutation as an adverse prognostic factor in patients with AML has led to the development of potent tyrosine kinase inhibitors targeting this mutation. Several *FLT3* inhibitors, such as sorafenib, quizartinib, crenolanib, midostaurin, lestaurtinib, sunitinib, and tandutinib, have shown promising results in these subgroups of patients.⁵ Limited phase I/II studies on the different *FLT3* inhibitors have suggested a potential benefit of these agents; however, benefits had a short duration in most of these studies.^{8,12–16} The long-term utility of these agents has been hampered by the development of drug resistance. Possible mechanisms of drug resistance include point mutations in the *FLT3* tyrosine kinase domain, upregulation of the antiapoptotic protein MCL-1, or constitutive activation of *FLT3*.¹⁷ Newer-generation *FLT3*-ITD inhibitors may be effective in these patients. Newer agents such as crenolanib and quizartinib, individually or in combination with sorafenib, have been shown to be useful in such resistant cases.^{18–20} Similarly, ponatinib is a multikinase inhibitor that has been shown to be effective in cases of acquired *FLT3* tyrosine kinase domain mutations.^{21,22}

Sorafenib in Relapsed AML

Sorafenib has been tested in patients with AML both as a monotherapy and in combination with other chemotherapies (Table 2). Pratz et al²³ conducted a phase I dose-escalation trial evaluating sorafenib as a monotherapy in relapsed/refractory advanced leukemia. Although marked *FLT3*-ITD inhibition was achieved, the clinical response was only modest, with 11 of 15 patients experiencing stable disease as the best response. Metzelder et al⁶ studied the compassionate use of sorafenib among 6 cases of patients with relapsed/refractory *FLT3*-ITD-mutated AML before and after alloSCT. Sorafenib induced clinically meaningful responses (ranging from a hematologic response to complete remission) in 100% of patients. Similarly, Zhang et al⁷ reported a clinical response in all 6 patients, who carried solely an *FLT3*-ITD mutation. A marked reduction in median percentage of blasts in peripheral blood and bone marrow was reported after initiating sorafenib monotherapy in these patients (reduction from 81% to 7% in peripheral blood, and from 75% to 34% in bone marrow, respectively).⁷ Similarly, a phase I dose-escalation study of sorafenib monotherapy in patients with refractory/relapsed acute leukemia showed complete remission in 5 of 50 patients (10%), but in all patients (100%) with *FLT3*-ITD mutations.²⁴ Hence, sorafenib has single-agent activity in patients with relapsed/refractory AML with *FLT3*-ITD mutations.

Few studies have investigated the role of sorafenib in combination with chemotherapy in patients with AML. Inaba et al²⁵ conducted a phase I pharmacokinetic and pharmacodynamic study of sorafenib in combination with clofarabine and cytarabine in pediatric relapsed/refractory leukemia. Overall response was seen in 9 of 11 patients (82%), but in all 5 patients with *FLT3*-ITD mutations (100%). A dose of 150 mg/m² seemed to be safer than a dose of 200 mg/m², with no dose-limiting toxicities noted with the former dosing. In a phase I/II study of sorafenib in combination with cytarabine and idarubicin (regimen used in this case report), a complete remission rate of 75% and 93% was achieved among the entire cohort and patients with *FLT3*-mutated AML. This resulted in the probability of survival of 74% at 1 year, thus suggesting a high response rate with the combination of sorafenib with chemotherapy in patients with *FLT3*-mutated AML.⁸ Another phase I/II study of sorafenib in combination with low-dose cytarabine in older patients, otherwise unsuitable for

intensive chemotherapy, showed an overall response of 10%. This could be explained by underrepresentation of *FLT3*-ITD mutations in the study population, which was only seen in 3 of 21 patients (14%).²⁶ Another phase II trial tested the combination of azacitidine and sorafenib in 37 patients with refractory/relapsed AML with *FLT3*-ITD mutations. The overall response rate was 46%, with 64% achieving greater than 85% *FLT3* inhibition during the first cycle of chemotherapy.²⁷ A recent randomized controlled trial showed that the addition of sorafenib to cytarabine and daunorubicin is not beneficial among older patients with AML (including in a subgroup with *FLT3*-ITD mutations). Because the trial included only 28 patients with *FLT3*-ITD mutations, the study may not have adequate power to detect the difference in outcomes in this subgroup.²⁸

The optimal role of sorafenib in patients with AML remains unanswered. For example, sorafenib monotherapy has not been compared with the combination of sorafenib and chemotherapy in patients with AML and the *FLT3*-ITD mutation, and therefore the role of combination therapy versus sorafenib monotherapy remains unclear. Despite promising results of sorafenib in these clinical trials, the development of resistance during the course of therapy is a major clinical challenge. Given their short-term efficacy and relatively few adverse effects, these agents seem to be particularly helpful as monotherapy in medically unfit patients with relapsed/refractory AML with *FLT3*-ITD mutations, who otherwise are poor candidates to receive cytotoxic chemotherapy (because of prior therapy). Thus, in select patients, sorafenib may be used as a bridge to alloSCT.²⁹ The 2015 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for AML acknowledge the poor prognosis associated with the presence of *FLT3*-ITD mutations in patients with AML with normal karyotype. Although data are considered inadequate to support the use of sorafenib during induction, it may be considered in relapsed AML. Importantly, NCCN Guidelines recommend clinical trials as the standard therapy for patients with *FLT3* abnormalities or other poor prognostic features. (to view the most recent version of these guidelines, visit NCCN.org).³⁰ Conversely, in clinical practice, sorafenib is frequently used as an off-label indication in patients with relapsed/refractory AML with the *FLT3*-ITD mutation.²⁹

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Table 2 Trials of Sorafenib in Patients With Relapsed/Refractory AML

Phase	Number of Patients (<i>FLT3</i> -ITD–Mutated)	Median Age (Range), y	Study Population	Dose and Schedule of Sorafenib	Combination Chemotherapy	Outcomes for Overall Population (Outcomes for <i>FLT3</i> -ITD–Mutated)	Common Adverse Events
Zhang et al, ⁷ 2008	I	61 (48–81)	Relapsed/refractory AML	Starting dose of 200 mg bid for 14 or 21 days	None	Clinical response 56% (100% in <i>FLT3</i> -ITD–positive cases)	No DLTs observed
Metzelder et al, ⁶ 2009	N/A	50 (42–62)	Relapsed/refractory <i>FLT3</i> -ITD–positive AML	400 mg bid adjusted for side effects	None	100% clinically meaningful response (1 of the following: HR, BMR, or CR)	Not mentioned
Pratz et al, ²³ 2010	I	63 (37–85)	Relapsed/refractory ALL and AML	400–600 mg bid for 14 or 21 days	None	Stable disease (73%) as the best response	Fatigue, weakness most common (various frequency depending on dose)
Ravandi et al, ⁸ 2010	I and II	34 (21–59) and 53 (18–65)	Relapsed/refractory AML	400 mg alternate day to bid for 7 days; Repeated if necessary	Cytarabine and idarubicin	CR rate 75% (92% in patients with <i>FLT3</i> -ITD mutations)	Diarrhea (44%), nausea/vomiting (29%), skin rash (27%)
Borthakur et al, ²⁴ 2011	I	61 (21–88)	Relapsed/refractory ALL, MDS	200 mg po bid for 14 or 21 days	None	Complete response rate 10%	Fatigue (58%), nausea/vomiting (44%), diarrhea (36%)
Inaba et al, ²⁵ 2011	I	9 (6–17)	Relapsed/refractory pediatric AML	150–200 mg/m ² bid for 7 days and continued concurrent with chemotherapy	Clofarabine and cytarabine	50% CR (100% in patients with <i>FLT3</i> -ITD mutations)	DLTs at a dose of 200 mg/m ² consisted of hand-foot skin reaction and rash
Ravandi et al, ²⁷ 2013	II	64 (24–87)	Relapsed/refractory AML	200–400 mg bid in combination with azacytidine	Azacytidine	Overall remission in 46%	Fatigue (47%), diarrhea (28%), rash (22%)
Macdonald et al, ²⁶ 2013	I/II	77 (63–83)	Older patients with AML or high-risk MDS	200 mg bid on day 2–28 of chemotherapy cycle	Cytarabine	Overall response rate of 10% (PR seen in 1 patient with an <i>FLT3</i> -ITD mutation)	Hypertension (38%), fatigue (38%), diarrhea (33%)
Serve et al, ²⁸ 2013	II	67 (61–78)	Older patients with AML	400 mg bid day +3 after end of chemotherapy until 3 days before the next chemotherapy during induction and consolidation, followed by 400 mg bid for a total of 1 year from induction	Cytarabine/daunorubicin (induction); cytarabine (consolidation)	Overall response rate of 57% ^a	Febrile neutropenia (58%), pneumonia (39%), diarrhea (14%), sepsis (13%)

^aNo improvement in response rate or survival with the combination of sorafenib and chemotherapy compared with placebo and chemotherapy. Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; BMR, bone marrow response; CR, complete remission; DLTs, dose-limiting toxicities; *FLT3*-ITD, *FLT3*-like receptor tyrosine kinase-3 internal tandem duplication mutation; HR, hematological response; MDS, myelodysplastic syndromes; PR, partial response.

Sorafenib in Relapsed AML

The present patient received initial standard chemotherapy with cytarabine and daunorubicin, followed by azacytidine. Although this patient was a potential candidate for alloSCT, he declined this option. Relapse at 10 months was managed with sorafenib in combination with cytarabine and idarubicin, followed by consolidation therapy and sorafenib maintenance, which resulted in disease control for 7 months. The response duration of 7 months in an older patient with relapsed AML and the *FLT3*-ITD mutation indicates a good response to the sorafenib-based therapy. This patient was able to tolerate induction therapy without major toxicity but developed complications during consolidation therapy. Hence, he was maintained on single-agent sorafenib. Several studies discussed previously^{6-8,25} demonstrated a role for sorafenib in patients with relapsed/refractory AML and the *FLT3*-ITD mutation. Sorafenib monotherapy is often easily tolerated, even by heavily pretreated older patients,^{6,7,23,24} as illustrated in this case. Hence, it can be used as a palliative option or a bridge to alloSCT in eligible patients.²⁹ Larger phase II/III trials are indicated to compare the outcomes of sorafenib monotherapy versus its combination with chemotherapy in patients with relapsed/refractory AML with the *FLT3*-ITD mutation. Future studies should also focus on management of AML in patients who develop resistance to first-line *FLT3* inhibitors.

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Posttest Questions

1. *FLT3*-ITD mutation is a frequent molecular abnormality noted in approximately one-third of adults with AML. Which of the following statements is NOT true about *FLT3* or AML with the *FLT3*-ITD mutation?
 - a. *FLT3* is normally expressed on the surface of hematopoietic stem cells and is important in the normal development of pluripotent stem cells.
 - b. Among adult patients with AML with normal karyotype, the presence of the *FLT3*-ITD mutation, compared with wild-type *FLT3*, portends a worse overall survival.
 - c. FLT-3 inhibitors such as sorafenib have activity against AML with the *FLT3*-ITD mutation; however, the long-term utility of these agents has been hampered by the development of drug resistance.
 - d. In patients with AML with *NPM1* mutation, the presence of a high-allelic burden *FLT3*-ITD mutation, compared with wild-type *FLT3*, does not confer worse outcomes.
2. FLT3 inhibitor studies using sorafenib suggest:
 - a. Single-agent sorafenib is preferred to combination chemotherapy followed by allogeneic hematopoietic stem cell transplant in the management of patients with relapsed AML with the *FLT3*-ITD mutation
 - b. Promise as a therapeutic option because of the long duration of response in most studies
 - c. Drug resistance may result from point mutations in the FLT3 tyrosine kinase domain, upregulation of MCL-1, or constitutive *FLT3* activation
 - d. Single-agent sorafenib is not recommended for medically unfit patients with AML with the *FLT3*-ITD mutation
3. True or False: Sorafenib in combination with other chemotherapy has been studied in both adult and pediatric patients with the *FLT3*-ITD mutation.