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Sorafenib is tolerable and improves clinical outcomes in patients with FLT3-ITD acute myeloid leukemia prior to stem cell transplant and after relapse post-transplant

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To the Editor

Fms-like tyrosine kinase receptor 3 internal tandem duplication (FLT3-ITD) is one of the most common mutations in *de novo* acute myeloid leukemia (AML) at an incidence of about 20–30%. This mutation dictates significant decreases in overall survival and disease-free survival with only 30–40% survival even after hematopoietic stem cell transplantation (HSCT) [1]. It is recommended that patients with FLT3-ITD AML undergo allogeneic HSCT [2].

AML patients with medical comorbidities or poor performance status (PS) following remission induction are not candidates for aggressive consolidation chemotherapy pre-HSTC or HSCT itself. These patients are not generally candidates for clinical trials and there are few, if any, treatment options for these patients. Sorafenib is a tyrosine kinase inhibitor with activity against RAF, VEGF, and FLT3-ITD [3], which has been approved by the US Food and Drug Administration for treatment of unresectable hepatocellular carcinoma, advanced renal cell carcinoma, and locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine treatment [4]. Sorafenib has been used off-label in AML [5], and in several Phase 1 clinical trials [6–8]. There have been case reports on the use of sorafenib in FLT3-ITD AML with variable results [9–11].

Here, we report the successful use of sorafenib in 13 FLT3-ITD AML patients treated at University of Maryland (UMD) and Johns Hopkins (JHU). From the two tertiary cancer centers, we retrospectively included adult (>18-years-old) patients with FLT3-ITD AML at

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diagnosis who received sorafenib for >4 weeks anytime after induction chemotherapy. Patients with poor PS (>3) and severe medical comorbidities were included. Patients with acute promyelocytic leukemia were excluded. The use of patients information was approved by the UMD and JHU institutional review boards.

Table I summarizes demographics, cytogenetics, FLT3 mutational status and allelic burden, treatment regimens, relapse history, and survival until April 1, 2014. Thirteen patients (eight female and five male), with a median age of 52, were included. All patients had AML with FLT3-ITD mutations with median ITD allelic burden (ratio of the ITD allele to wild type allele) at diagnosis of 68.5%. AML in 11 patients had normal karyotype (NK).

Patient 1 is a 50-year-old woman with NK FLT3-ITD (unknown allelic burden) M5-AML. She received induction therapy with cytarabine plus daunorubicin (7+3) leading to complete remission (CR). Her postinduction course was complicated by sepsis, respiratory failure, cardiomyopathy, cerebral hemorrhage, and latent tuberculosis reactivation with a prolonged intensive care unit stay and ventilator-associated restrictive lung disease. Due to severe physical deconditioning, she was not a candidate for high-dose cytarabine (HiDAC) consolidation. Sorafenib was started postinduction and dose reduced due to elevation in liver enzymes. This successfully bridged her to a matched-related nonmyeloablative allogeneic HSCT on day 151 postinduction. She is currently in CR receiving sorafenib.

Patient 2 is a 56-year-old woman with treatment-related (cyclophosphamide, doxorubicin, and docetaxel for breast cancer) NK FLT3-ITD with 69% ITD allelic burden M1-AML. She received induction therapy with 7+3 and achieved CR. She developed cardiomyopathy (ejection fraction =15%) and several infectious episodes; all resulted in poor PS making her not an immediate candidate for consolidation chemotherapy. Her cardiomyopathy was treated and she underwent physical rehabilitation. She was on sorafenib until her cardiac function and PS have improved significantly. She received four cycles of HiDAC and remains in CR Day 331 postinduction. She is proceeding to a matched-unrelated nonmyeloablative HSCT.

Patient 3 is a 50-year-old woman with NK FLT3-ITD with 49% ITD allelic burden M5-AML. She received induction therapy with 7+3 and achieved CR. She received three cycles of HiDAC, which were complicated by MRSA bacteremia and thoracic spine osteomyelitis which was treated with vancomycin. Her HSCT was delayed due to vancomycin-associated acute kidney injury. During recovery of her kidney function, her AML was relapsed with FLT3 mutation with 39% ITD allelic burden. She was treated with sorafenib and azacitidine [12] for three cycles leading to achievement of the second CR. She underwent matched-unrelated nonmyeloablative HSCT. Her AML relapsed on Day 45 of HSCT with FLT3-ITD mutation with 69% allelic burden. She was reinduced with HiDAC, mitoxantrone, and L-asparaginase [13] and achieved the third CR. She remains in CR 456 days postinduction. Her chimerism study shows 100% donor. She is on sorafenib.

Patient 4 was a 35-year-old man with NK FLT3-ITD (unknown allelic burden) M5-AML, who received induction with 7+3 and achieved CR, followed by a matched-unrelated myeloablative HSCT. His AML relapsed on Day 38 of HSCT with FLT3 mutation with 60%

ITD allelic burden. He was treated with HiDAC and topotecan [14], followed by donor lymphocyte and stem cell infusion. He was treated with sorafenib after count recovery, which after 2 months was discontinued due to elevated liver enzymes and drug–drug interaction with antigraft versus host disease (GVHD) medications. He remained in remission for approximately 1 year until his AML relapsed with FLT3-ITD with 55% allelic burden. His immunosuppressants were discontinued and he was treated with five cycles of sorafenib and azacitidine [12] leading to achievement of the third CR with incomplete platelet recovery. Unfortunately, he developed multiple infectious episodes including meningitis, gram negative bacteremia, and fungal pneumonia as well as severe GVHD. The patient died with severe respiratory failure, while bone marrow biopsy showed no residual leukemia.

Patient 5 was a 52-year-old woman with NK FLT3-ITD with 94% ITD allelic burden M1-AML. Her leukemia was refractory to initial induction chemotherapy with 7+3. Her ejection fraction decreased to 30%. Significant residual leukemia was present after reinduction with HiDAC and topotecan [14]. Surprisingly, treatment with single agent sorafenib resulted in CR. She remained on sorafenib until 1 week prior to matched-unrelated nonmyeloablative HSCT. Unfortunately her AML relapsed on Day 50 of transplant with FLT3-ITD with 84% allelic burden. Patient died from multiorgan failure with refractory AML post-HSCT.

Patient 6 is a 50-year-old man with NK FLT3-ITD with 68% ITD allelic burden M1-AML. He received 7+3 and achieved CR, followed by two cycles of HiDAC. He underwent matched-unrelated nonmyeloablative allogeneic HSTC. He was started on sorafenib post-HSCT and is currently in CR.

Patients 7 and 8 were treated with sorafenib before and after HCST. Both patients died after their leukemia relapsed post-HSCT. Relapsed leukemia in Patient 7 did not carry FLT3-ITD.

Patients 9 and 12 received single agent sorafenib after achievement of CR postinduction therapy while awaiting HSCT. Patient 10 was a 69-year-old man, not HSCT candidate, who was on single agent sorafenib for 1 year after CR and before dying due to AML relapse, which surprisingly occurred without FLT3-ITD mutation.

Patients 11 and 13 were placed on sorafenib after AML relapsed with FLT3-ITD post-HSCT. Both patients are alive at least 3 years post-HSCT relapse.

In summary, we report the successful use of sorafenib in several diverse and challenging clinical situations involving patients with FLT3-ITD AML. AML remained in remission by sorafenib, as a single agent, in medically unfit patients who were not candidate to receive cytotoxic chemotherapy prior to HSCT. After organ function improvement, patients were able to proceed to HSCT. We also used sorafenib in patients whose leukemia with FLT3-ITD relapsed after HSCT and observed meaningful clinical outcomes in this extremely poor prognostic situation. Metzelder et al. demonstrated high activity of sorafenib in FLT3-ITD AML post-HSCT possibly secondary to synergizing allo-immune effects leading to sustained regression in this specific population [9]. We also used sorafenib as maintenance therapy pre- and post-HSCT with durable complete response. Sorafenib was tolerated well with occasional dose reductions due to adverse events including elevated liver enzymes.

Further prospective clinical trials are needed to evaluate the use of sorafenib in FLT3-ITD AML as single and/or adjunctive therapy.

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TABLE I

Characteristics of patients, their leukemia and their treatment

Patient	Age	AML	FAB	Cytogenetic	FLT3–ITD allelic burden at diagnosis/ relapse	Induction	Induction response	Reason for Sorafenib use	Sorafenib dose (mg), adverse events	Days on Sorafenib (pre- or post-HSCT)	HSCT	Sorafenib relation to HSCT	Most recent status	Follow-up days since induction
1	50	*de novo*	M5	46, XX	Unknown/NA	Dauno(90)+ ara-C	CR	Poor PS, multiple comorbidities	400 BID, dose reduced to 200 BID for transaminitis	108 (pre)	yes	Before and after	CR (alive)	325
2	56	Treatment related	M1	46, XX	69%/NA	Dauno(60)+ ara-C	CR	Non-ischemic cardiomyopathy, poor PS, multiple comorbidities	400 BID, dose reduced to 200 BID for transaminitis	168 (pre)	Awaiting	Before	CR (alive)	331
3	59	*de novo*	M5	46, XX	49%/39% (first relapse) and 69% (post-HSCT relapse)	Ida(12)+ ara-C	CR	Relapsed AML with poor PS; salvage therapy with azacitidine	400 BID plus azacitidine for three cycles	111 (pre)	Yes	Before	CR (alive)	456
4	35	*de novo*	M5	46, XY	Unknown/60% (first relapse, post- HSCT) & 55% (second relapse)	Dauno(60)+ ara-C	CR	Post-HSCT relapse salvage, and second salvage therapy with azacitidine	400 BID, then 400 BID plus azacitidine for five cycles	180 (post)	Yes	After	Deceased due to severe infections	765
5	52	*de novo*	M1	46, XX	94%/84%	Ida(12)+ ara-C	Ref	Single agent after not achieving CR after two induction therapies	400 BID until HSCT	61 (pre)	Yes	Before and after relapse post-HSCT	Deceased due to refractor leukemia	196
6	49	*de novo*	M1	46, XY	68%/NA	Ida(12)+ ara-C	CR	Post-HCST as maintenance	200 BID	83 (post)	Yes	After	CR (alive)	552
7	62	*de novo*	M1	46, XX, +21	Unknown/unknown	Dauno(60)+ ara-C	Ref	Pre-HSCT and Post- HSCT relapse salvage	400 BID	74 (pre)	Yes	Before and after	Relapsed without FLT3-ITD mutation 9 mo post-HSCT and deceased	510
8	55	*de novo*	M4	46, XX	Unknown/150%	Dauno(60)+ ara-C	Ref	Pre-HSCT and Post- HSCT relapse salvage	400 BID	84 (pre)	Yes	Before and after	Relapsed and deceased 137 days post-HSCT	219
9	47	*de novo*	M4	46, XX	180%/NA	Dauno(45), ara-c, etoposide	CR	Pre-HSCT maintenance	400 BID	35 (pre)	Yes	Before	CR (alive)	1,150
10	69	*de Novo*	M4	46, XY	57%/NA	Dauno(45), ara-c, etoposide	CR	Pre-HSCT maintenance	400 BID	328 (pre)	No	Before	Deceased after relapse without FLT3-ITD mutation	528
11	29	*de novo*	M4	47, XY, +21	Unknown/unknown	Dauno(45), ara-c, etoposide	CR	Post-HSCT relapse salvage	400 BID	769 (post)	Yes	After	CR (alive) [CNS relapse 223 days after stopping	1,790

Patient	Age	AML	FAB	Cytogenetic	FLT3–ITD allelic burden at diagnosis/ relapse	Induction	Induction response	Reason for Sorafenib use	Sorafenib dose (mg), adverse events	Days on Sorafenib (pre- or post-HSCT)	HSCT	Sorafenib relation to HSCT	Most recent status	Follow-up days since induction
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12	64	*de Novo*	M4	46, XY	Unknown/NA	Flavopiridol, ara-c, Mitoxantrone	CR	Pre-HSCT maintenance	400 BID	33 (pre)	Yes	Before	Deceased (in CR) 317d post-HSCT due to CMV pneumonitis	361
13	46	*de novo*	M4	46, XX	Unknown/unknown	Dauno(45), ara-c, etoposide	CR	Post-HSCT relapse salvage	400 BID × 22d then 200 BID × 2yrs post DLI	752 (post)	Yes	After	CR (alive)	1682d post-HSCT, 1614d post sorafenib

Abbreviation: ara-C, Cytarabine (100 mg/m^2/d ×7days); BID, twice daily; CR, complete remission; d, days; Dauno, daunorubicin (dose mg/m^2); DLI, Donor Lymphocyte Infusion; FAB, French American British classification of AML; HSCT, allogeneic hematopoietic stem cell transplant; Ida, idarubicin (dose per mg/m^2); ITD, internal tandem duplication; mo, months; NA, not applicable; PRES, posterior reversible encephalopathy syndrome; PS, performance status; Ref, refractory; WT, wild type.