blood advances

TO THE EDITOR:

Gilteritinib combination therapies in pediatric patients with *FLT3*-mutated acute myeloid leukemia

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Pediatric acute myeloid leukemia (AML) is a rare and profoundly heterogeneous disease at the molecular and clinical levels, with an incidence of ~700 to 1000 cases per year.[1,2] Although in recent clinical trials, the 5-year event-free survival rates for childhood AML have ranged between 49% and 64%,[3,4] bone marrow relapse still occurs in up to one-third of cases, and the long-term outcomes of these patients continue to be dismal.[4] Newer therapies are desperately needed.

Mutations in the FMS-like tyrosine kinase-3 receptor gene (FLT3) occur in ~20% of children and are associated with poor prognosis.[5,6] FLT3 mutations with internal tandem duplications (ITDs) in the juxtamembrane and point mutations in the tyrosine kinase domain activation loop drive proliferation by phosphorylation of downstream targets, including STAT5, SHIP, and SHP-2, and signaling through critical oncogenic pathways such as Ras/Raf/MAPK and phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin.[7] Competitive inhibition of ATP-binding sites in the FLT3 receptor kinase domain with small-molecule FLT3 inhibitors represents a significant paradigm shift in AML.[8-13]

However, to date, FLT3 inhibition as a treatment strategy in pediatric AML has been hampered by limited potency and significant toxicity, mainly because of off-target effects. This is the case with FLT3 inhibitors that could be used for pediatric patients, such as sorafenib and midostaurin.[14,15] Sorafenib, although deemed effective and more tolerable than expected in pediatric patients, has been associated with significant toxicities.[14] Midostaurin, currently under more extensive evaluation, has shown limited clinical activity based on preliminary data.[15] Gilteritinib, a highly potent and selective oral FLT3 inhibitor, has shown promising results in adults with relapsed/refractory (R/R) FLT3-mutated AML and frontline in combination with induction therapy.[9,16] This has led to the incorporation of this agent in the new Children's Oncology Group frontline AAML1831 trial (registered at www.clinicaltrials.gov as #NCT04293562).

Given the lack of data on this approach in children, institutional review board approval was obtained to conduct a retrospective medical record review of patients who had received at least 1 dose of gilteritinib at The University of Texas MD Anderson Cancer Center and Texas Children's Hospital to describe the efficacy, adverse events (AEs), and toxicities of gilteritinib. The study was conducted in accordance wit the Declaration of Helsinki. Patient characteristics and treatment outcomes are summarized in Table 1. The date for data cutoff was 28 September 2020. Patients considered for the study were ≤21 years of age. Response criteria were established according to the revised recommendations of the International Working Group Response Criteria in Acute Leukemia.[17] Minimal residual disease was measured institutionally by multiparameter flow cytometry with a sensitivity of 0.01% to 0.1%. FLT3 detection was assessed using polymerase chain reaction–based DNA analysis to detect ITDs and codon 835/836 point mutations in FLT3. The lower limit of detection (analytical sensitivity) of this assay is ~1% of mutant DNA in a background of wild-type DNA. Gilteritinib toxicities were graded per the Common Terminology Criteria for Adverse Events (version 5.0)[18] based on clinical documentation. Eight pediatric patients with

Submitted 3 May 2021; accepted 2 August 2021; prepublished online on *Blood Advances* First Edition 30 September 2021; final version published online 7 December 2021. DOI 10.1182/bloodadvances.2021005164.

Requests for data sharing may be submitted to David McCall (dmccall1@mdanderson.org).

Table 1. Patient characteristics

Age/sex	FLT3 mutation	Other mutations	CNS status	Upfront chemotherapy regimen	Time from diagnosis to first relapse, mo	Gilteritinib regimen (line of therapy)	Gilteritinib dosing schedule	Cycles	Response to gilteritinib and cycle of MRD	Toxicity	Status	Follow-up, mo
6/M	FLT3 non-ITD p.N676K missense variant of TKD	RUNX1, GATA2, CREBBP	CNS3	ADE + GO	Refractory	FLAG-Ida + gilteritinib	40 mg (2 mg/kg) daily d 1-14	1	NR	Alanine aminotransferase increased, febrile neutropenia, creatinine elevation, seizure, anemia, thrombocytopenia	Alive	7
21/F	FLT3 ITD, ITD ratio of 0.27	NPM1	CNS1	CLIA + VEN	NA	CLIA + gilteritinib consolidation	80 mg daily	4	CR; MRD^- first cycle	Febrile neutropenia, constipation, abdominal pain, dysuria, bacteremia, acidosis, anemia, thrombocytopenia	Alive	10
21/F	FLT3-ITD, ITD ratio of 0.10	NPM1	CNS1	7 + 3 and midostaurin	Refractory	CLIA + VEN + gilteritinib	120 mg daily ×14 d/cycle ×2 cycles; 40 mg daily post-SCT maintenance ×3 mo and then increased to 80 mg daily	3, then post-SCT maintenance	CR; MRD^- third cycle	Febrile neutropenia, anemia, thrombocytopenia, bacteremia, colitis, HTN	Alive	14
17/F	FLT3 ITD, ITD ratio of 0.02	Negative	CNS1	ADE + sorafenib	Refractory	Cytarabine + GO + gilteritinib	120 mg daily ×1 cycle; post-SCT maintenance 40, 80, 120 mg daily (adjusted because of AEs)	5, then post-SCT maintenance	CR; MRD^- after SCT	Febrile neutropenia, nausea, hypomagnesemia, neuropathy, thrombocytopenia, anemia, paresthesia, rhabdomyolysis, lung infection	Alive	18
19/M	FLT3 ITD and D835 point mutation; ITD ratio of 0.625 and D835 ratio of 0.062	Mosaic germ line GATA2 deletion, KIT	CNS3	ADE	Refractory	(1) Mitoxantrone + cytarabine; (2) AZA, fludarabine, cytarabine; (3) DAC; (4) AMG330 (BiTE CD33/CD3); (5) CAR T-cell infusion; (6) Ox40 mAb; (7) S64315 (MCL-1 inhibitor); (8) DAC + VEN + midostaurin; (9) DCLL9718S (anti-CLL1) + AZA; (10) DAC + VEN + sorafenib; (10) DAC + VEN + gilteritinib + ponatinib; (11) fludarabine + cytarabine + vorinostat + ponatinib + gilteritinib	120 mg daily	7	NR	Alanine aminotransferase increased, febrile neutropenia, fungal pneumonia, bacteremia, intracranial hemorrhage, acidosis	Dead	8
20/F	FLT3-ITD then FLT3-TKD (ratios unknown)	CUX1, WT1	CNS1	ADE + sorafenib	27 mo; day +700 from SCT	(1) FLAG + midostaurin; (2) cytarabine + mitoxantrone + midostaurin; (3) second SCT; (4) DAC + vorinostat + sunitinib; (5) DAC + VEN + sunitinib; (6) DAC + sunitinib + AZA + gilteritinib + VEN	120 mg daily continuous	1	NR	Febrile neutropenia, anemia, thrombocytopenia	Dead	2

ADE, cytarabine, daunorubicin, etoposide; AZA, azacitidine; BiTE, bispecific T-cell engager; CAR, chimeric antigen receptor; CLIA, cladribine, idarubicin, cytarabine; CNS, central nervous system; CR, complete response; DAC, decitabine; FLAG, fludarabine, cytarabine, granulocyte colony-stimulating factor; GO, gemtuzumab ozogamicin; HSCT, hematopoietic stem cell transplantation; HTN, hypertension; Ida, idarubicin; mAb, monoclonal antibody; MRD, minimal residual disease; NA, not applicable; NR, no response; PEG, pegaspargase; SCT, stem cell transplantation; TKD, tyrosine kinase domain; VEN, venetoclax.

Table 1. (continued)

Age/sex	FLT3 mutation	Other mutations	CNS statusregimen	Upfront CNS chemotherapy	Time from diagnosis to first relapse, mo	Gilteritinib regimen (line of therapy)	Gilteritinib dosing schedule	Cycles	Response to gilteritinib and cycle of MRD	Toxicity	Status	Follow-up, mo
19/F	FLT3 ITD, ITD ratio of 0.46	NPM1, TP53, WT1	CNS1	ADE + sorafenib	10 mo	(1) CPX-351 + FLAG; (2) cytarabine + PEG + midostaurin; (2) DAC + VEN + sorafenib; (3) SCT + post-SCT maintenance with sorafenib; (4) azacitidine + VEN + gilteritinib; (5) second SCT + post-SCT maintenance AZA + gilteritinib	80 mg daily continuous	3, then post-SCT maintenance	CR; MRD^- third cycle	Febrile neutropenia, anemia, bacteremia, neuropathy, thrombocytopenia, hypomagnesemia, thromboembolic event, paresthesia, alanine aminotransferase increased, creatinine increase	Alive	12
14/M	FLT3-ITD allelic ratio of 0.67 (N609_L610ins)	NUP98-NSD1, WT1 S118fs*81	CNS1	ADE	Refractory	AZA-FLA + gilteritinib ×2 cycles, HSCT, post-HSCT gilteritinib	AZA-FLA + gilteritinib ×2 cycles, HSCT, post-HSCT gilteritinib	2, then post-SCT maintenance	CR; MRD^- first cycle	Tooth discoloration, febrile neutropenia with *S mitis* bacteremia, anemia, thrombocytopenia	Alive	7

ADE, cytarabine, daunorubicin, etoposide; AZA, azacitidine; BiTE, bispecific T-cell engager; CAR, chimeric antigen receptor; CLIA, cladribine, idarubicin, cytarabine; CNS, central nervous system; CR, complete response; DAC, decitabine; FLAG, fludarabine, cytarabine, granulocyte colony-stimulating factor; GO, gemtuzumab ozogamicin; HSCT, hematopoietic stem cell transplantation; HTN, hypertension; Ida, idarubicin; mAb, monoclonal antibody; MRD, minimal residual disease; NA, not applicable; NR, no response; PEG, pegaspargase; SCT, stem cell transplantation; TKD, tyrosine kinase domain; VEN, venetoclax.

FLT3-mutated AML were included, with ages ranging from 6 to 21 (median, 19) years. None of the patients received upfront gilteritinib, but 1 patient received it as consolidation therapy, achieved complete response, and remains in remission. The other 7 patients received it after their disease proved refractive to at least 1 line of treatment, including a median of 2 (range, 2-9) prior salvage treatments and a median of 1 (range, 1-2) prior FLT3 inhibitors. All 7 patients received gilteritinib-based combinations (Table 1). Seven patients had FLT3-ITD (median allelic frequency, 0.27; range, 0.02-0.67), and 1 had a noncanonical mutation, including the tyrosine kinase domain mutation p.N676K.

For the older pediatric patients (age >17 years), flat dosing was used, starting at 120 mg and then reducing to 80 mg for maintenance as needed for myelosuppression or toxicity. Weight-based dosing was 2 mg/kg for the 6-year-old patient and 1.73 mg/kg for the 14-year-old patient given the available tablet size of 80 mg.

All 8 patients developed grade 3 febrile neutropenia, grade 3 anemia, and grade 4 thrombocytopenia. The median time to onset was 15 days (range, 2 days to 1 month). One patient had grade 4 acidosis and intracranial hemorrhage at the end of life. One patient with leptomeningeal disease had grade 3 seizures. He was found to have increased opening pressure on lumbar puncture, and although there was concern for posterior reversible encephalopathy syndrome given its association with gilteritinib, his clinical team attributed this AE to leptomeningeal disease. Grade 3 or 4 AEs considered at least possibly related to gilteritinib included febrile neutropenia and thrombocytopenia in all patients. Other reported grade 1 to 2 AEs included creatine elevation (n = 2), constipation, abdominal pain, dysuria, bacteremia (n = 3), acidosis, hypertension, colitis, nausea, hypomagnesemia (n = 2), peripheral neuropathy (n = 2), paresthesia (n = 2), rhabdomyolysis, lung infection (n = 2), thromboembolic event, alanine aminotransferase increase (n = 3), headache, and tooth discoloration. Of these, creatine elevation, abdominal pain, constipation, bacteremia, nausea, peripheral neuropathy, paresthesias, rhabdomyolysis, lung infection, alanine aminotransferase increase, headache, and tooth discoloration were considered possibly related gilteritinib. Notable grade 1 to 2 AEs occurring after stem cell transplantation included paresthesia and creatine kinase elevation. Both cases resolved with dose reduction. There was no reported association with or worsening of graft-versus-host disease. No sudden death, arrhythmia, or persistent seizures were recorded.

Among the 8 patients treated with gilteritinib, 5 (63%) had a CR, and 4 of these had refractory disease to prior therapies. Of the 7 patients with R/R disease, 4 (57%) had a CR after initiation of gilteritinib. Four patients underwent allotransplantation directly after combination treatment with gilteritinib; all are in CR, and all are continuing to use gilteritinib (at 40, 80, or 120 mg once daily) as stem cell transplantation maintenance. The maintenance dosing varies based on tolerability.

With a median follow-up of 9 (range, 2-18) months from the start of gilteritinib, as depicted in the Kaplan-Meier curve in Figure 1, 6-month overall survival (OS) was 87.5% and 1-year OS was 70%. Among responders (n = 5), the median number of gilteritinib cycles to best response was 1 (range, 1-2). None of the 5 responders subsequently relapsed. It is worth noting, however, that 3 of the responders had NPM1 mutations with a low FLT3-ITD allelic ratio, which has been found to be a favorable mutation in some

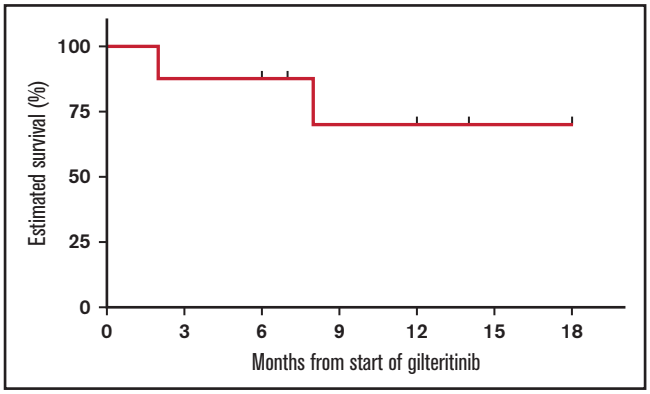

Figure 1. Survival from start of gilteritinib.

patients.[19,20] Six patients (including 5 with R/R disease and 1 receiving consolidation with gilteritinib) remain alive.

This case series, the largest to date in pediatrics using gilteritinib in AML, involves 2 of the largest pediatric cancer institutes in the United States. This review, although limited in patient number and length of follow-up, illustrates a 62% remission rate (5 of 8), with 6 of 8 patients alive at a median follow-up of 9 months. It is important to note the responders are all continuing to receive gilteritinib. Historically, FLT3 mutations confer an OS of 50% to 60%.[5] We acknowledge the limitation of this retrospective review, but despite the small sample size and limited follow-up, the survival in pediatric patients receiving gilteritinib is encouraging.

This case series demonstrates that gilteritinib is safe to consider for use in pediatric and young adult patients with FLT3-mutated AML. Pediatric studies (registered at www.clinicaltrials.gov as #NCT03730012, along with Children's Oncology Group AAML1831) are underway to evaluate the use of gilteritinib in patients with relapsed disease and as upfront therapy.

Authorship

Contribution: All authors contributed significantly to the body of work; D.M. and B.C. designed research, performed research, contributed vital analytical tools, analyzed data, and wrote the paper; L.T. and J.S.Y. performed research, contributed vital analytical tools, and analyzed data; M.R., K.M.M., C.N., N.J.S., N.D., T.M.K., and C.D. contributed vital analytical tools and analyzed data.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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