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SHORT REPORT

Haematological Malignancy – Clinical

Durable responses in acute lymphoblastic leukaemia with the use of FLT3 and IDH inhibitors

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Summary
Data regarding the use of FMS-like tyrosine kinase 3 (FLT3) and isocitrate dehydrogenase 1/2 (IDH1/2) inhibitors in acute lymphoblastic leukaemia (ALL) are lacking. We identified 14 patients with *FLT3*- or *IDH1/2*-mutated ALL. Three early T-cell precursor-ALL patients received FLT3 or IDH2 inhibitors. Patient 1 maintains a complete remission (CR) with enasidenib after intolerance to chemotherapy. Patient 2 maintained a CR for 27 months after treatment with enasidenib for relapsed disease. Patient 3 was treated with venetoclax and gilteritinib at the time of relapse and maintained a CR with gilteritinib for 8 months. These cases suggest that FLT3 and IDH inhibitors could represent a viable therapeutic option for ALL patients with these mutations.

KEYWORDS
ALL, FLT3, IDH1, IDH2, targeted

INTRODUCTION

Treatment of relapsed/refractory (R/R) B-cell acute lymphoblastic leukaemia (B-ALL) has significantly improved with the introduction of targeted therapies.[1] However, despite promising results using targeted therapies in early-phase clinical trials,[2] nelarabine is currently the only FDA-approved drug for the management of R/R T-ALL.[3,4] With salvage chemotherapy response rates ranging from 15% to 25% and a 5-year survival <30%, R/R T-ALL represents a major unmet need for drug development.[5] Agents approved for R/R ALL are now being incorporated into front-line therapy,[6–8] which highlights the need for new treatment options if these patients subsequently relapse or prove refractory.

An improved understanding of the pathogenesis of acute myeloid leukaemia (AML) has led to the development and subsequent approval of inhibitors of FMS-like tyrosine kinase 3 (FLT3) and isocitrate dehydrogenase (IDH) in patients with *FLT3* mutations and *IDH1/2* mutations respectively.[9] Data regarding use of these therapies in ALL are lacking. However, early T-cell precursor ALL (ETP-ALL) has a gene expression profile similar to that of AML, lending a rationale for the use of these therapies in patients with ALL that also have *FLT3* and or *IDH1/2* mutations.[10] ETP-ALL is diagnosed by its unique immunophenotypic makeup, indicating early T-cell differentiation in addition to myeloid and stem cell characteristics.[11]

PATIENT SELECTION/STUDY DESIGN

We searched our institutional database for patients with a diagnosis of ALL and *IDH1*, *IDH2* or *FLT3* mutations. We then conducted a retrospective chart review to evaluate the clinical outcomes of these patients. Response rates were assessed according to the National Comprehensive Cancer Network (NCCN) guidelines. Measurable residual disease (MRD) was measured using either flow cytometry and/or

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TABLE 1 Demographics and disease characteristics of patients who received FLT3 or IDH inhibitors.

Patient no.	Diagnosis	Targetable mutation	Sex	Age at diagnosis	ECOG at diagnosis	Race/ethnicity	WBC at diagnosis (K/μL)	Karyotype at diagnosis	Mutations at diagnosis	FLT3/IDH inhibitor
1	ETP-ALL	*IDH2*	M	65	1	Black	1.8	Normal	*IDH2*, *IKZF1*, *NOTCH1*, *DNMT3A*, *PTPN11*, *NRAS G12S*, *NRAS G12D*	Enasidenib
2	ETP-ALL	*IDH2*	F	60	1	Black	2.9	del (X)	*NRAS*, *IDH2*	Enasidenib
3	ETP-ALL	*FLT3*-TKD	M	34	0	Hispanic	9	Normal	NA[a]	Gilteritinib

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ETP-ALL, early T-cell precursor acute lymphoblastic leukaemia; FLT3-TKD, FMS-like tyrosine kinase 3-tyrosine kinase domain; IDH2, isocitrate dehydrogenase 2; NA, not available.

[a]Patient was found to have a FLT3-TKD mutation at the time of relapse.

next-generation sequencing via clonoSEQ® with sensitivities of 10^{-4} and 10^{-6} respectively.

RESULTS

We identified 212 B-ALL patients, 52 T-ALL patients and 8 ALL patients without a specified subtype in our institutional molecular database. Fourteen of these patients had *FLT3*, *IDH1* or *IDH2* mutations. All T-ALL patients were classified as ETP-ALL. Four patients had a *FLT3*-internal tandem duplication (ITD) mutation (three with B-ALL and one with ETP-ALL) while four patients had a *FLT3*-tyrosine kinase domain (TKD) mutation (three B-ALL and one ETP-ALL). Two patients with B-ALL had *IDH1* mutations and four patients with ETP-ALL had *IDH2* mutations. One *IDH1* mutant B-ALL patient harboured *BCR::ABL-1* and one *FLT3*-ITD mutant ALL patient was diagnosed with *BCR::ABL*-1-like B-ALL due to a *CRLF2* rearrangement. Median overall survival was 39.5 months for the entire cohort (range, 1–160), 41.5 months for patients with B-ALL (range, 1–123) and 37 months for patients with T-ALL (range, 15–160). One B-ALL patient was lost to follow-up 4 years after diagnosis. Three ETP-ALL patients subsequently received FLT3 or IDH inhibitors. Detailed characteristics for these three patients can be found in Table 1, their molecular mutational patterns can be visualized in Figure 1, their clinical course has been summarized in Figure S1, and baseline demographics and characteristics for the entire cohort can be found in Table S1. Out of the three ETP-ALL patients that did not receive targeted therapy, one patient maintained remission after standard of care treatment, one patient died due to infectious complications after allogeneic stem cell transplantation, and one patient was deemed unfit for treatment due to a poor performance status and an active infection. None of the eight patients with B-ALL received FLT3 or IDH inhibitors: four patients maintained a complete remission (CR) after standard of care treatment, two patients responded to CD19- or CD22-targeted therapies at the time of relapse, one patient was lost to follow-up and one patient with known cardiomyopathy experienced sudden cardiac death shortly after treatment initiation.

Patient 1

A 65-year-old male was diagnosed with therapy-related ETP-ALL. He had a past medical history of colon cancer treated with surgical resection and chemotherapy 4 years prior to his leukaemia diagnosis. He initially presented with pancytopenia and circulating blasts. He also had significant cervical, supraclavicular and mediastinal lymphadenopathy. Genetic sequencing at diagnosis revealed mutations in *DNMT3A*, *PTPN11*, *NRAS*, *NOTCH1*, *IDH2* and *IKZF1*. He received induction chemotherapy according to the CALGB10403 regimen, with the PEG-asparaginase dose reduced to 500 iu/m^2 due to his age; he achieved a CR with measurable disease (MRD) by both flow cytometry

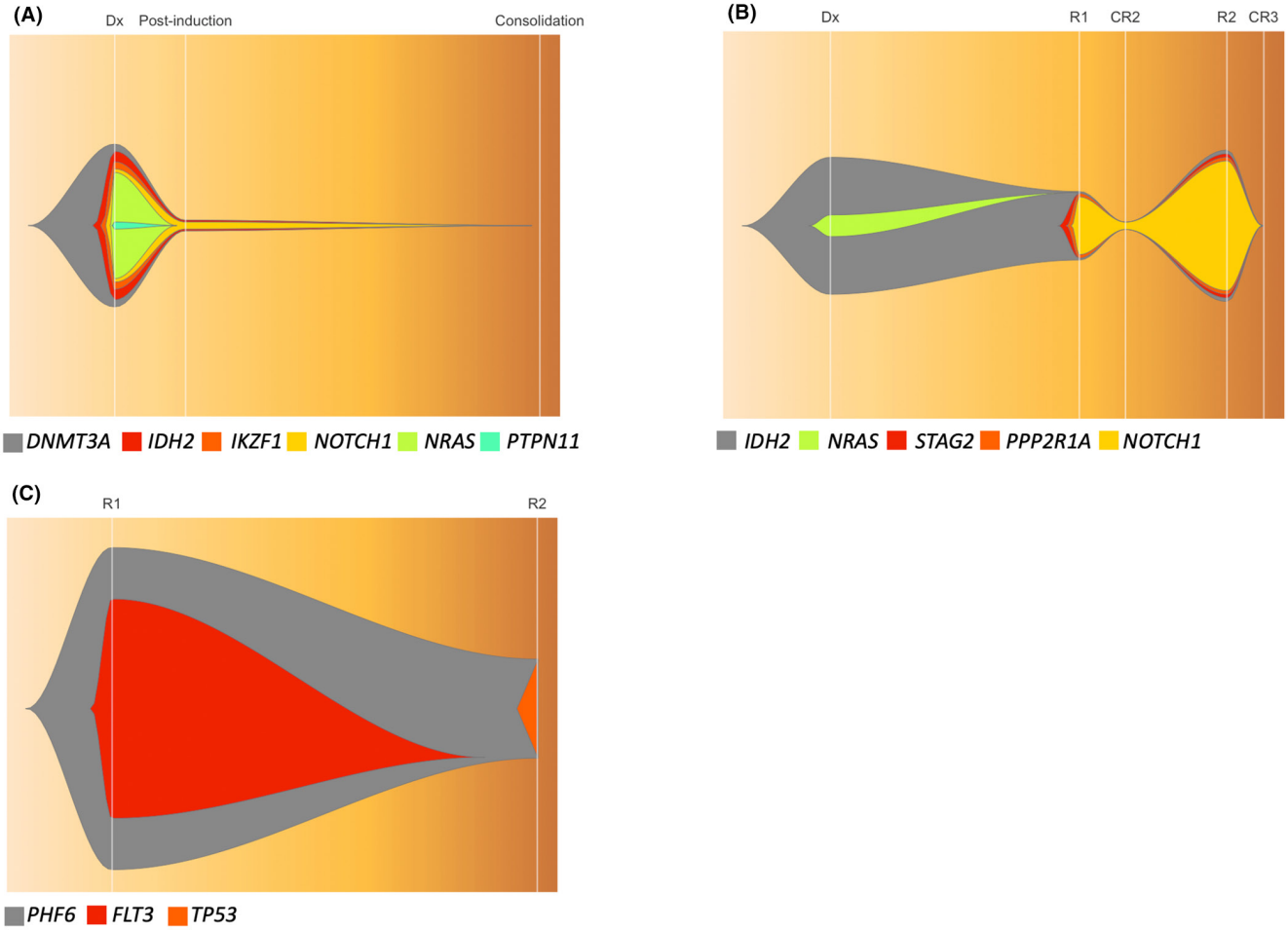

FIGURE 1 Clonal evolution in patients who received FLT3 or IDH inhibitors. (A) Clonal evolution of Patient 1 over the course of 5 months, with elimination of the mutated clone during consolidation chemotherapy. (B) Clonal evolution of Patient 2 over the course of 88 months, showing expansion of the *IDH2* clone on R2 and clearance of the mutated clone on CR3. Of note, limited diagnostic sequencing was performed at the time of diagnosis that did not include *PPP2R1A* or *STAG2* testing. (C) Clonal evolution of Patient 3 over the course of 12 months, revealing an emergence of a *TP53* clone and clearance of the *FLT3* clone at the time of R2. Of note, *BLM* was not included since it is suspected to be a germline mutation. CR2, second complete remission; CR3, third complete remission; Dx, diagnosis; FLT3, FMS-like tyrosine kinase 3; IDH, isocitrate dehydrogenase; R1, first relapse; R2, second relapse.

and clonoSEQ.[12] He then received three doses of nelarabine 1500 mg/m^2, as used in the CALGB19801 regimen.[13] However, this consolidation chemotherapy was complicated by neutropenic fever and gastrointestinal bleeding requiring hospitalization. He was transitioned to consolidation chemotherapy with cytarabine and methotrexate as used in the mini-Hyper CVD protocol together with venetoclax.[14] His course was complicated by another episode of gastrointestinal bleeding and haemorrhagic shock, but his *IDH2* mutation became undetectable at a sensitivity of 1%. He transitioned to maintenance chemotherapy with 6-mercaptopurine, vincristine, methotrexate and prednisone (POMP), but developed persistent thrombocytopenia. Given the presence of *IDH2* mutation at diagnosis, he was started on 100 mg of enasidenib daily along with ongoing intrathecal chemotherapy and has remained in CR for >18 months. Despite persistent MRD positivity by clonoSEQ, he achieved MRD negativity by flow cytometry.

Patient 2

A 60-year-old female was diagnosed with *IDH2*-mutated ETP-ALL. She initially presented with circulating blasts, anaemia, leukopenia, generalized lymphadenopathy and pneumonia. She achieved CR1 and completed 3 years of chemotherapy as per dose-adjusted CALGB10403.[12] Her ALL relapsed 18 months after the end of maintenance chemotherapy. Genetic sequencing at that time revealed a mutation in *IDH2*, with a variant allele frequency (VAF) of 19%, as well as mutations in *NRAS*, *NOTCH1*, *PPP2R1A* and *STAG2*. Treatment was started with 100 mg of enasidenib daily and she achieved CR2 with MRD positivity by flow cytometry. The patient then experienced a second relapse 27 months later. Enasidenib was continued, and she received six cycles of nelarabine 1500 mg/m^2 on Days 1, 3 and 5 of each cycle. She achieved CR3 with MRD positivity by both flow cytometry and clonoSEQ, although her *IDH2* mutation

became undetectable. Seven months after her last cycle of nelarabine, the patient experienced a third relapse. Flow cytometry characterization at that time revealed $CD34^+$, TdT^+, $CD117^+$, MPO^+, $CD33^+$, $cCD3^-$, $CD2^-$ and $CD19^-$ leukaemia. Thus, she developed a myeloid phenotype arising from her previously diagnosed ETP-ALL. She was treated with azacitidine and venetoclax and achieved CR4 with MRD positivity by clonoSEQ.

Patient 3

A 34-year-old male was diagnosed with ETP-ALL at another hospital. He was initially treated with Hyper-CVAD, followed by a paediatric-inspired regimen containing asparaginase with which he achieved a partial response. He received salvage chemotherapy with vinorelbine, topotecan, thiotepa and gemcitabine. Bone marrow biopsy revealed residual disease, but he achieved CR1 after a haploidentical donor stem cell transplant (SCT) following total body irradiation and etoposide conditioning. His post-transplant course was complicated by cytomegalovirus viremia, as well as skin and gastrointestinal graft-versus-host disease requiring treatment with steroids, rituximab and ruxolitinib. Twenty-nine months after SCT, he presented to our institution with altered mental status and shortness of breath. He was found to have relapsed disease with the central nervous system (CNS) involvement. Of note, he did not receive CNS-directed therapy prior to relapse. Genetic sequencing at that time revealed mutations in *BLM*, *PHF6* and a *FLT3*-TKD mutation with a VAF of 62%. He received one cycle of chemotherapy as per the AALL0434 regimen but had persistent disease. He then received treatment with venetoclax and 120 mg of gilteritinib daily for 4 weeks,[15] which was complicated by neutropenic fever and a subdural haemorrhage. Due to these adverse events, he restarted gilteritinib alone. Ommaya catheter placement was performed, and his CNS disease remitted after multiple cycles of intra-Ommaya cytarabine, methotrexate and hydrocortisone. He achieved CR2 with MRD negativity by flow cytometry 5 weeks after initiation of gilteritinib-based therapy. He experienced a third relapse 8 months later with *FLT3*-negative disease and enrolled in a clinical trial.

DISCUSSION

There are few data available regarding the use of FLT3 or IDH1/2 inhibitors for the treatment of T-ALL. Our study shows that despite the association of *IDH1/2* and *FLT3* mutations with myeloid malignancies, these mutations are also present in both B-cell and T-cell ALL. It is important to note that all T-ALL patients in this study had ETP-ALL, which is known to have a mutational pattern similar to myeloid neoplasms. The three ETP-ALL patients who received targeted therapy have achieved or maintained a significant clinical response, with Patient 2 maintaining CR for 27 months. No significant side effects were reported by these patients when treated with IDH2 or FLT3 inhibitor monotherapy. Two of these patients (1 and 3) were treated with IDH2 or FLT3 inhibitors after intolerance to alternative treatment regimens. These cases suggest that FLT3 and IDH1/2 inhibitors could represent a viable option for the treatment of ALL. These agents could be useful in R/R patients, as well as those unable to tolerate alternative regimens. Further prospective studies are required to confirm efficacy.

AUTHOR CONTRIBUTIONS

Rafael Madero-Marroquin collected and analysed the data, and drafted the initial manuscript; Anand Ashwin Patel conceptualized and supervised the project; Adam S. DuVall conceptualized the project; Peng Wang reviewed our molecular database; all authors reviewed and edited the final manuscript.

CONFLICT OF INTEREST STATEMENT

The authors have no competing interests. RM-M, CS and PW have no conflict of interest to disclose. ASD is a speaker for CE Concepts. SG is a consultant for AbbVie and Jazz pharmaceuticals; received royalties from UpToDate for contributions to various topics. RAL has acted as a consultant or advisor to AbbVie, Amgen, Ariad/Takeda, Astellas, Celgene/BMS, Curis, CVS/Caremark, Epizyme, ImmunoGen, Jazz Pharmaceuticals, Kling Biotherapeutics, Medpace, MorphoSys, Novartis and Servier, and has received clinical research support to his institution from Astellas, Celgene, Cellectis, Daiichi Sankyo, Forty Seven/Gilead, Novartis and Rafael Pharmaceuticals, and royalties from UpToDate. WS is an advisor for Kura, Servier, Newave and Asofarma. AAP received honoraria from AbbVie and BMS; research funding (institutional) from Pfizer and Kronos Bio.

DATA AVAILABILITY STATEMENT

For original data, please contact anand.patel@bsd.uchicago.edu.

ETHICS STATEMENT

Our leukaemia registry is approved by our Internal Review Board for its use in clinical research and adheres to the tenets of the Declaration of Helsinki.

PATIENT CONSENT STATEMENT

All patients provided consent to have clinical information reported via our institutional leukaemia registry.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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