Targeted FGFR inhibition results in a durable remission in an FGFR1-driven myeloid neoplasm with eosinophilia

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Key Points

- A novel PCM1-FGFR1 gene rearrangement was identified in a patient with a myeloid neoplasm with eosinophilia.
- Futibatinib, an oral selective small molecule inhibitor of FGFR1-4, resulted in a durable complete hematologic and cytogenetic remission.

Introduction

The myeloid/lymphoid neoplasms with eosinophilia are a rare group of diseases defined by rearrangements of PDGFRA, PDGFRB, or FGFR1 or by the fusion of PCM1-JAK2.1,2 Although neoplasms arising from rearrangements of PDGFRA and PDGFRB respond well to imatinib, those associated with FGFR1 are typically aggressive and do not respond to imatinib or to other available tyrosine kinase inhibitors.1 Therefore, allogeneic hematopoietic stem cell transplantation is recommended to achieve durable remissions.3,4 Here, we report the case of a patient with a novel fusion of PCM1 with FGFR1, presenting as a myeloid neoplasm with eosinophilia, treated with an oral selective small molecule inhibitor of FGFR1-4 (futibatinib [TAS-120]) under a single-patient protocol, resulting in the first reported case of complete hematologic and cytogenetic remission using futibatinib in an FGFR1-driven myeloid neoplasm.

Case description

A 55-year-old male with a history of heart failure with preserved ejection fraction and chronic obstructive pulmonary disease presented with progressive dyspnea on exertion of a 3-weeks duration. Initial management included prednisone for a possible chronic obstructive pulmonary disease exacerbation and diuretics for possible volume overload. The dyspnea improved over time and was ultimately thought to be multifactorial. During the prednisone taper, peripheral blood eosinophilia was noted, with an absolute eosinophil count (AEC) of 3.6 K/mm3. At that time, blood counts were as follows: white blood cell count, 16.64 K/mm3 (48% neutrophils, 9% lymphocytes, 10% monocytes, 22% eosinophils); hemoglobin, 13.8 g/dL; and platelets, 46 K/mm3. Review of the peripheral smear demonstrated left-shifted myeloid elements, eosinophilia, and thrombocytopenia.

A bone marrow biopsy revealed a hypercellular (cellularity >95%) erythroid-dominant marrow with increased eosinophilic forms and increased pronormoblasts (Figure 1A-C). Flow cytometric analysis did not show evidence of a clonal B- or T-cell population or increased myeloblasts. A clinical next-generation sequencing (NGS) assay to detect common single-nucleotide variants and insertions/deletions in hematological malignancies (heme SNaPshot)5 did not show any abnormalities. Of note, this assay does not detect fusion proteins.

Break-apart fluorescence in situ hybridization (FISH) studies (performed at NeoGenomics Laboratories) revealed an FGFR1 gene rearrangement in 11.3% of nuclei (normal <5.7%). The nature of the rearrangement was shown to be a paracentric inversion of chromosome 8p based on the distinct gap between the 5’ FGFR1 and 3’ FGFR1 probes seen in 12 of 20 metaphases on FISH (Figure 2B-C; performed at Brigham and Women’s Hospital Cytogenetics Laboratory). A targeted NGS assay for fusion transcript detection (heme fusion assay)5 revealed a PCM1-FGFR1 fusion transcript (40 unique fusion reads). The rearrangement was consistent with an in-frame fusion of PCM1 (exons 1-36) to FGFR1 (exons 14-24). The patient was then treated with futibatinib (a selective oral inhibitor of FGFRs 1-4) under a single-patient protocol (ClinicalTrials.gov identifier: NCT03468885). Therapy was well tolerated with transient grade 2 increase in liver enzymes and grade 2 postural hypotension. After 11 months of therapy, complete hematologic and cytogenetic remission was achieved, with a peripheral blood eosinophil count of 0.3 K/mm3, absence of left-shifted myeloid elements, and normalized liver enzyme levels.
FGFR1 (exons 11-18) (Figure 2A). Taken together, the findings established a diagnosis of a myeloid neoplasm with eosinophilia driven by rearrangement of FGFR1.

The patient was initially treated with prednisone, and the AEC was noted to decrease to 0.03 K/μL and subsequently fluctuate between 0.20 K/μL and 2.72 K/μL. He was also evaluated for hematopoietic stem cell transplantation; however, he was not a candidate because of comorbidities. Given the presence of the FGFR1 fusion transcript and the lack of an adequate steroid-sparing therapy, he enrolled (with informed consent) on a single-patient protocol in an expanded-access program for the selective FGFR inhibitor futibatinib (TAS-120; Taiho Oncology).

On day 175 of therapy, repeat bone marrow biopsy showed a moderately hypocellular marrow with maturing trilineage hematopoiesis and no pronormoblasts (Figure 1D-E). Blood counts showed white blood cell count, 5.0 K/μL (67% neutrophils, 21% lymphocytes, 9.6% monocytes, 1.4% eosinophils); hemoglobin, 13.2 g/dL; and platelets, 119 K/μL. The PCM1-FGFR1 fusion transcript was no longer detectable by heme fusion assay. Furthermore, the paracentric inversion of chromosome 8 was no longer observed on metaphase FISH (20 metaphases tested), consistent with cytogenetic remission. The patient continues on futibatinib, with ongoing evidence of hematologic and cytogenetic remission after >18 months of therapy.

Methods

Molecular testing

Two clinically validated NGS assays (heme SNaPshot and heme fusion) were used.5 The heme SNaPshot assay detects single-nucleotide variants and insertions/deletions in 103 gene targets commonly mutated in hematological malignancies. The heme fusion assay detects gene rearrangements in 89 commonly rearranged genes in hematologic malignancies. Briefly, genomic DNA (heme SNaPshot) or total nucleic acid (heme fusion) was isolated from bone marrow aspirates using standard protocols. Sequencing was performed with Illumina NextSeq using a validated anchored multiplex polymerase chain reaction assay.5

The patient enrolled in this study under an expanded-access program. The single-patient Investigational New Drug Application...
Results and discussion

Our patient presented with a myeloid neoplasm driven by an FGFR1 rearrangement, a rare and aggressive hematologic malignancy that is often accompanied by eosinophilia.²⁻⁹ A novel gene rearrangement, resulting in PCM1-FGFR1 fusion, was identified as the putative genetic driver of disease in this case. Similar to other fusion-driven neoplasms, no other clonal marker was identified, suggesting that the single-fusion event is sufficient to cause disease. Fewer than 20 FGFR1 fusion partners have been described,¹⁰⁻¹² with ZMYM2 and BCR being the most commonly observed.¹³ Although the fusion of PCM1 and FGFR1 has yet to be reported, PCM1 has been implicated in the pathogenesis of other myeloid/lymphoid neoplasms.¹⁴ Specifically, the PCM1-JAK2 rearrangement was added as a provisional entity in the 2016 World Health Organization classification of myeloid/lymphoid neoplasms with eosinophilia. A single case of a PCM1-PDGFRB fusion has also been reported.¹⁵ As with these analogous fusion proteins, the PCM1-FGFR1 fusion is expected to result in ligand-independent constitutive activation of FGFR1, with the coiled-coil motifs of PCM1 driving dimerization of the tyrosine kinase.¹⁶

The role of the FGFR1 fusion partner in driving constitutive activation of the tyrosine kinase is of clear importance in disease pathogenesis; however, little is known about the impact of different fusion partners on disease biology and clinical presentation. Importantly, there is evidence to suggest that different FGFR1 fusion partners result in varying clinical manifestations of disease. For example, the ZNF198-FGFR1 fusion and the BCR-FGFR1 fusion have been shown to induce distinct phenotypes via different signaling pathways in a mouse model.¹⁷

Given that this is the first report of a PCM1 and FGFR1 fusion, the specific effect of PCM1 in this patient’s disease is unclear; however, features of the PCM1-JAK2 rearrangement provide hypotheses. Notably, the PCM1-JAK2 rearrangement has been associated with large aggregates of immature erythroid precursors on bone marrow biopsy.¹⁸ Interestingly, evaluation of our patient’s bone marrow revealed an unusual and striking increase in immature erythroid elements, with 25% pronormoblasts; it is possible that this observation is an effect of PCM1. Nevertheless, it is currently unknown how the identity of the FGFR1 fusion partner may affect clinical response to therapies; as such, treatment of these myeloid/lymphoid neoplasms is guided by the identification of an FGFR1 rearrangement by karyotype and FISH.

In our case, the identification of the FGFR1 rearrangement suggested that selective tyrosine kinase inhibition would be a viable treatment strategy.¹⁹,²⁰ Therefore, we treated our patient with

Figure 2. Fusion of PCM1 to FGFR1 as the genetic driver for this myeloid neoplasm with eosinophilia. (A) Illustration of the in-frame fusion of PCM1 (exons 1-36) to FGFR1 (exons 11-18), resulting in amino acid 1947 of PCM1 juxtaposed to amino acid 429 of FGFR1. The coiled-coil motifs (blue, shown with corresponding amino acid numbers) of PCM1 are thought to drive dimerization of the FGFR1 tyrosine kinase domain (red, shown with corresponding amino acid numbers). (B) Partial GTG banded karyotype demonstrating both chromosomes 8. The normal chromosome (left) and the abnormal chromosome with a distinctly abnormal 8p region pattern caused by inv(8)(p11.2p22) (right). (C) Corresponding partial metaphase FISH karyotype using a home-brew break-apart FGFR1 probe set. A distinct gap between the 5′ FGFR1 centromeric (green) probe and the 3′ FGFR1 telomeric (red) probe is clearly observed on the abnormal chromosome 8 (right), consistent with paracentric inversion between the 8p11 and 8p22 bands.
futibatinib, a potent second-generation irreversible inhibitor of FGFR1-4 that has been used in the treatment of cholangiocarcinoma driven by FGFR2 gene fusions and rearrangements.\textsuperscript{21,22}

With futibatinib, our patient achieved and maintained hematologic and cytogenetic remission. These observations share similarities with a recent case report demonstrating complete remission of a myeloid/lymphoid neoplasm with eosinophilia using an FGFR inhibitor; however, in that case, the neoplasm was driven by a \textit{CEP110-FGFR1} rearrangement, and treatment involved pemigatinib, an inhibitor of FGFR1/2/3.\textsuperscript{23}

To our knowledge, this case represents the first use of futibatinib to achieve a durable hematologic and cytogenetic remission in a patient with a myeloid neoplasm and \textit{FGFR1} rearrangement. Hematologic malignancies driven by \textit{FGFR1} rearrangement are aggressive and, historically, have been unresponsive to chemotherapeutic regimens. Just as imatinib revolutionized the treatment of \textit{BCR-ABL}-driven chronic myelogenous leukemia, the use of new selective tyrosine kinase inhibitors has the potential to dramatically affect outcomes in patients with \textit{FGFR1}-driven neoplasms. Our findings support the use of these inhibitors as a therapeutic strategy, and ongoing clinical trials may establish the utility of FGFR inhibitors as first-line therapy for patients with myeloid/lymphoid neoplasms with \textit{FGFR1} rearrangement.

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Authorship

Contribution: M.K. and G.S.H. wrote the manuscript; G.S.H. developed the treatment concept and wrote the clinical trial; V.N. and P.D.C. edited the manuscript and assisted with methods and figures; and A.M.B., M.B., Y.-B.C., C.C., A.T.F., J.F., M.M., S.L.M., K.M., R.N., A.Y.R., T.T.S., M.V., R.S.F., and K.A.B. edited the manuscript.

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