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Avapritinib treatment of KIT D816V-mutant atypical chronic myeloid leukemia

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ABSTRACT

Background: Atypical chronic myeloid leukemia (aCML) is a rare myelodysplastic/myeloproliferative neoplasm. There is no proven standard of care treatment and the only curative option available is hematopoietic stem cell transplant. In addition to traditional chemotherapy, targeted therapy has shown to be a promising. Avapritinib is a selective type 1 tyrosine kinase inhibitor with high potency for KIT D816V and was recently approved for treatment of systemic mastocytosis. Here we present a case of aCML with novel D816V mutation treated with avapritinib for 17 months leading to clonal extinction of the driver mutation.

Case presentation: An 80 year old man initially presented for evaluation of aCML. A bone marrow biopsy was completed, and next generation sequencing was notable for a novel KIT D816V mutation. Patient was started on avapritinib leading to significant improvement in leukocytosis and extinction of the D816V mutation over 17 months of treatment. The extinction was followed with serial next generation sequencing.

Conclusion: We present the first case of aCML with KIT D816V driver mutation. We also demonstrate two novel management strategies. First, we show that treatment with avapritinib does not need to be limited to cases of systemic mastocytosis and could be useful in other hematologic malignancies with this driver mutation. Furthermore, with the use of serial next generation sequencing we were able to identify new emerging clones. While none of the clones noted in this study were targetable, they could be in other patients with aCML and help guide treatment.

Background

Atypical chronic myeloid leukemia (aCML) is a rare myelodysplastic/myeloproliferative neoplasm, similar in clinical picture to classical CML, but differs in that it lacks the BCR::ABL1 rearrangement (classically characterized as the Philadelphia chromosome) [1]. In order to decrease confusion, the most recent WHO classification in 2022 renamed aCML as MDS/MPN neoplasm with neutrophilia however diagnostic criteria remained largely unchanged and this entity is characterized by persistent leukocytosis ($> 13 \times 10^9$/l), cytopenias, presence of immature circulating myeloid precursors (> 10% leukocytes), no or minimal absolute monocytosis (<10% of leukocytes), minimal basophilia (<2% of leukocytes), less than 20% blasts and dysgranulopoiesis [1]. Given the heterogeneity of aCML there is overlap with other MDS/MPN diseases, such as chronic myelomonocytic leukemia (CMML) and distinguishing between these entities is difficult as diagnosis is based in part on white blood cell differential counts which can change over time. In addition to laboratory criteria, next generation sequencing has offered insights to the common mutations, resulting in the addition of SETBP1 and ASXL1 mutations as part of the diagnostic criteria [1].

Treatment for aCML remains difficult with no proven standard of care. This is due to the rarity of the disease, clinical and molecular disease heterogeneity and absence of large clinical studies. Hematopoietic stem cell transplant (HSCT) is the only curative treatment for aCML although studies of transplant are limited [2,3]. Other options for treatment include, hypomethylating agents such as azacytidine or decitabine, interferon-alpha, hydroxyurea or targeted therapy. Targeted therapy serves as a promising frontier in treating aCML and next generation sequencing is currently being used to identify targetable mutations. JAK-STAT mutations, although infrequent, have been identified in aCML patients [4]. In murine studies the use of ruxolitinib (JAK 1/2 inhibitor) in aCML led to reduction in leukocytosis and spleen weight

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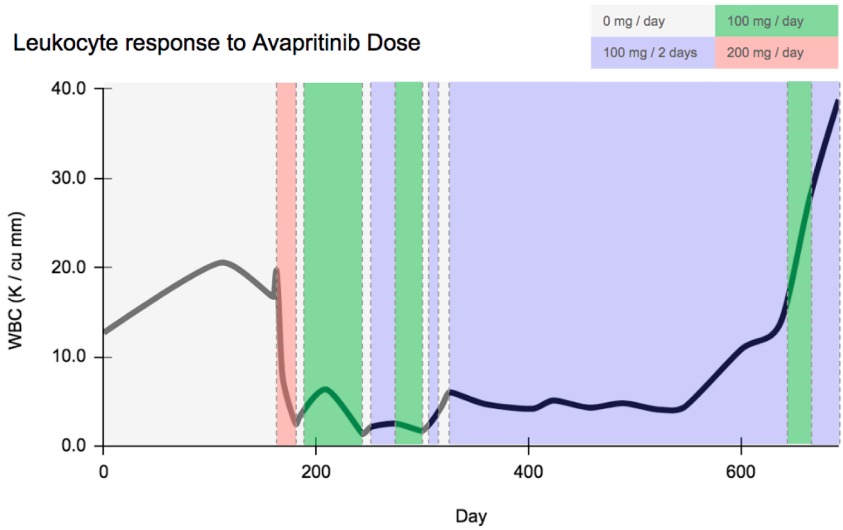

Fig. 1. Total WBC count vs. time. The vertically shaded regions show the dose and schedule of avapritinib over time.

[5]. Because of these results, ruxolitinib has been used in a few case reports with promising results [6,7].

Avapritinib is a selective type 1 KIT tyrosine kinase inhibitor with high potency for KIT D816V [8,9]. This medication was approved in June of 2021 for advanced systemic mastocytosis, aggressive systemic mastocytosis, systemic mastocytoisis with hematologic neoplasm, and

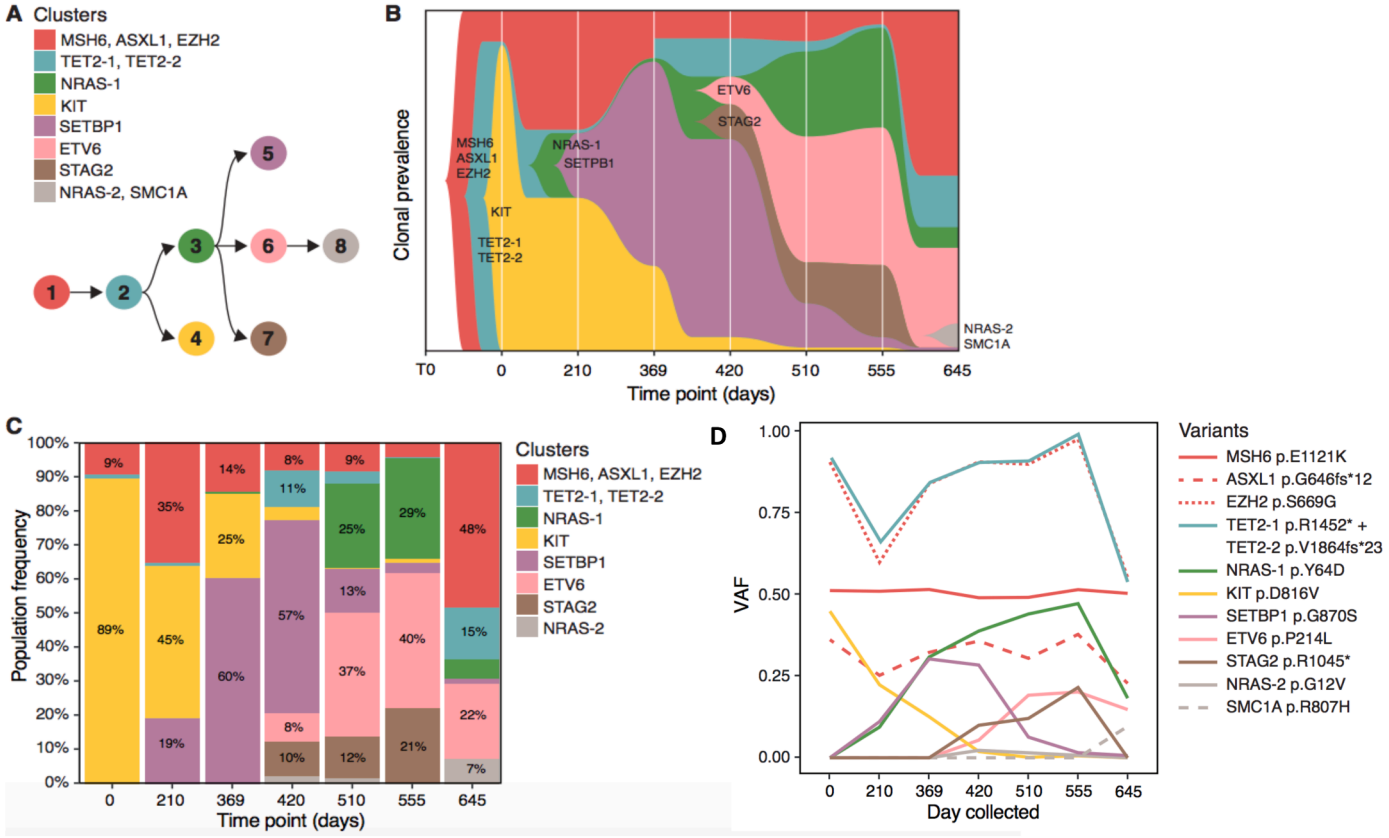

Fig. 2. Panel A-C. The patients NGS data was clustered using Pairtree, a clone tree reconstruction algorithm. Variants were clustered using the pairwise clustering model. Clusters were visualized using the R package "Timescape".Time 0 = date of first NGS data. This analysis identified 8 distinct clusters that emerged over time. The original myeloproliferative clone had mutations of MSH6 (likely a benign germline polymorphism), ASXL1 and EZH2 (Clone 1). Subsequently, this clone developed presumed bi-allelic inactivating mutations of TET2 (Clone2). Clone 2 underwent branched evolution with acquisition of a NRAS Y64D mutation in clone 3 and a KIT D816V mutation in clone 4. Avapritinib treatment eradicated clone 4, with the NRAS Y64D clone undergoing additional branched evolution with acquisition of SETBP1 (clone 5), ETV6 (clone 6), or STAG2 mutations (clone 7). Ultimately, the STAG2 clone became extinguished and the NRAS mutant/ETV6 clone acquired additional NRAS and SMC1A mutations.

Panel D. Variant allele frequency over time with avapritinib treatment. Specific mutations identified: MSH6 p.E1121K, ASXL1 p.G646fs*12, EZH2 p.S669G, TET2 −1 p.R1452*, TET2–2 p.V1864fs*23, NRAS-1 p.Y64D, KIT p.D816V, SETBP1 p.G870S, ETV6 p.P214L, STAG2 p.R1045*, NRAS-2 p.G12V, SMC1A p.R807H. TET2–1 and TET2–2 VAFs were added together to model presumed bi-allelic inactivation of TET-2 and the combined VAF value was plotted.

mast cell leukemia following two multi-center, single arm clinical trials: EXPLORER (NCT 02,561,988) and PATHFINDER (NCT03580655) [8, 10]. Advanced systemic mastocytosis is driven by the KIT D816V mutation and treatment with this drug showed an overall response rate of 75% and molecular remission of KIT D816V in the EXPLORER trial [8]. Similar results were seen in the PATHFINDER trial [10]. We report the first use of avapritinib in a patient with aCML associated with a KIT D816V mutation.

Case presentation

An 80-year-old male was referred to our facility for evaluation of HSCT for aCML. The patient first became symptomatic in November of 2018. Following evaluation by his PCP, which was significant for leukocytosis, he underwent a bone marrow biopsy with findings notable for peripheral leukocytosis with absolute neutrophilia and monocytosis, atypical myeloid maturation and an absence of BCR-ABL1 fusion transcripts. A repeat bone marrow study was performed to obtain additional molecular markers; this marrow was notable for hypercellular marrow with myeloid dominant hematopoiesis and dysplastic maturation without increased blasts and lack of monocytosis, leading to the diagnosis of aCML. The patients next generation sequencing results were significant for mutations in ASXL1, TET2, EZH2, and KIT D816V. The patient was initiated on hydroxyurea; however, he was transitioned to avapritinib 200 mg daily based on his KIT D816V mutation. At 1 month follow up after initiation of avapritinib therapy, the patient's leukocytosis had resolved, however he had developed anemia and thrombocytopenia. His-avapritinib was held and restarted at a decreased dose of 100 mg daily, but he again developed neutropenia and thrombocytopenia leading to a brief dose holds and subsequent step wise dose reduction to 100 mg every other day (at that time, 100 mg tablets the smallest available formulation) (Fig. 1). During therapy, the leukemic cell mutational burden and clone diversity was monitored with next generation sequencing. The KIT D816V allele frequency decreased from 45% to 22% representing a 50% decline in frequency during the first 9 months of treatment with avapritinib. Patient remained stable on this dose for 8 more months with normalization of his white count and continued decrease in KIT D816 allele frequency from 22% to 13% and finally 2% (Figs. 2). After almost 17 total months of avapritinib therapy, he redeveloped leukocytosis, thrombocytopenia, and anemia and his avapritinib dose was increased to 100 mg daily. Follow up next generation sequencing was ordered to assess for KIT allele frequency. The results of this were notable for an undetectable KIT D816V allele and his avapritinib dose was decreased back to 100 mg every other day given that the KIT mutant clone was extinguished and he was started on hydroxyurea. He continued to have worsening anemia and progressive leukocytosis and the avapritinib was discontinued. Following the cessation of the avapritinib and in the setting of worsening leukocytosis the patient received a bone marrow biopsy. The results from this biopsy were significant for hypercellular marrow with myeloid dominant hematopoiesis and decreased erythropoiesis, continued extinction of KIT D816V and a continued rise in new clones suggestive of transition to chronic myelomonocytic leukemia. About two months later, patient developed blast crisis/acute myelogenous leukemia and transitioned to hospice.

Conclusion

Our patient demonstrates two novel management strategies for treatment of aCML. In this unique case, our patient presented with a KIT D816V mutation not previously reported in aCML. Based on the activity of avapritinib for KIT D816V mutant advanced systemic mastocytosis, the patient was treated with avapritinib. This led to clonal extinction of the KIT D816V mutation with stabilization of blood counts for almost 2 years. Thus, our patient shows treatment with avapritinib does not have to be limited to cases of systemic mastocytosis but could be potentially useful in other hematologic neoplasms with a KIT D816V driver mutation. Furthermore, with the use of serial next generation sequencing we were able to show extinction of the KIT D816V clone which corresponded to his clinical and laboratory improvement.

This case also demonstrates the clinical utility of monitoring responses to targeted drug administration using next generation sequencing. In addition to monitoring the response to treatment, serial next generation sequencing can also be used to monitor the dynamics of individual clones. Notably, while the patients KIT D816V mutation was rapidly extinguished, other clones began to increase in frequency and/or new clones emerged, and ultimately became the dominant clones. While none of these new clones in our patient were targetable at the current time, the use of next generation sequencing could potentially identify other targetable mutations as they emerge in other patients with aCML. In addition, this information can serve as an adjunct to radiologic and lab information for patient and monitoring guiding treatment.

Informed consent

Case report reviewed by Oregon Health and Science University IRB. No PHI was obtained or shared. No identifiable objects were included in the report. The HIPPA waiver and Request for Determination were approved by the OHSU IRB.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Michael Heinrich reports a relationship with Novartis that includes: consulting or advisory. Michael Heinrich reports a relationship with Deciphera Pharmaceuticals that includes: consulting or advisory. Michael Heinrich reports a relationship with Blueprint Medicines Corporation that includes: consulting or advisory. Michael Heinrich reports a relationship with Cogent that includes: consulting or advisory. Michael Heinrich reports a relationship with Theseus Pharmaceuticals Inc that includes: consulting or advisory.

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