CSF3R truncation mutations in a patient with B-cell acute lymphoblastic leukemia and a favorable response to chemotherapy plus dasatinib

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ABSTRACT

Activating mutations in the gene encoding for receptor of colony stimulating factor 3 (CSF3R) are drivers of pathogenesis in chronic neutrophilic leukemia (CNL) and atypical chronic myeloid leukemia (aCML). We describe a patient with newly diagnosed B-cell acute lymphoblastic leukemia (ALL) and three unique CSF3R truncating mutations which are predicted to be activating. After a slow early response to induction chemotherapy, dasatinib was added based on data from \textit{in vitro} experiments demonstrating that dasatinib effectively targets key downstream kinases in CSF3R-mutated CNL/aCML. The patient subsequently achieved complete remission with minimal residual disease negativity that has been durable.

1. Introduction

Activating mutations in the gene encoding for the receptor of colony stimulating factor 3 (CSF3R) have been identified as drivers of pathogenesis in neoplastic myeloid disorders such as chronic neutrophilic leukemia (CNL) and atypical chronic myeloid leukemia (aCML). Previously published data suggests a rationale for using the tyrosine kinase inhibitor (TKI) dasatinib to target downstream dysregulation of SRC family-TNK2 kinases in patients with CNL/aCML and truncating mutations of CSF3R [1,6]. We describe a patient with B-cell acute lymphoblastic leukemia (ALL) and three unique CSF3R truncating mutations identified with comprehensive molecular profiling at diagnosis who was treated with chemotherapy and dasatinib with a favorable response.

2. Case description

A 24-year old previously healthy man was referred for pancytopenia with a white blood cell (WBC) count of 1300/mm$^3$, hemoglobin of 7.3 g/dL, and platelet count of 8000/mm$^3$. Bone marrow biopsy showed 80–90% B-lineage lymphoblasts (Immunophenotype: CD10+, CD19+, sCD22+, TdT+). Standard cytogenetic studies showed a normal male karyotype with no identifiable chromosomal abnormalities by fluorescence \textit{in situ} hybridization (FISH) for recurrent ALL abnormalities. Comprehensive molecular profiling by next generation sequencing (Foundation One Heme) was performed on the bone marrow aspirate and revealed three truncation mutations in CSF3R (D748fs*2, Q749X, Y752fs*1), CRLF2-P2RY8 fusion, CDKN2A loss, and ETV6 loss of exon 6. Prior to receiving results of molecular studies, the patient began induction with multiagent chemotherapy including rituximab, daunorubicin, cyclophosphamide, vincristine, prednisone, and pegylated asparaginase [4]. A day 14 bone marrow biopsy showed a 30% cellular marrow with 20–30% B-lymphoblasts. Dasatinib 140 mg daily was added on day 15 of induction. Bone marrow evaluation after completion of induction showed a complete response with partial hematologic recovery (CRh) with absence of minimal residual disease (MRD) by multiparameter flow cytometry. The patient continues on consolidation/maintenance chemotherapy plus dasatinib and remains in an MRD-negative complete remission at 10 months. NGS testing was repeated from a marrow aspirate sample after remission was achieved and showed that all mutations present at diagnosis including the CSF3R variants were no longer present.

3. Discussion

To our knowledge, this is the first detailed reported case of a patient with B-cell ALL and activating mutations of CSF3R. Maxson et al. [1] identified CSF3R mutations in samples obtained from 16/27 (59%) patients with CNL/aCML, 3/292 (1%) of patients with acute myeloid leukemia, 0/8 patients with T-cell ALL and 0/41 patients with B-cell ALL. CSF3R mutations identified in this cohort were categorized into two groups: membrane proximal mutations, and frameshift or nonsense
mutations that resulted in truncation of the CSF3R cytoplasmic tail. The leukemogenic potential of the latter type of CSF3R truncating mutations depended on expression of tyrosine kinase non-receptor 2 (TNK2) and SRC family kinases, both of which are potently inhibited by dasatinib. Primary CNL/aCML patient samples and leukemia cell models characterized by CSF3R truncating mutations were sensitive to inhibition of TNK2 or the SRC kinase FGR by small interfering RNAs (siRNA) specific to these kinases, or by administration of dasatinib. In contrast, CSF3R truncating mutations were resistant to the JAK kinase family inhibitor ruxolitinib. Extrapolating from this data, we reasoned that targeting SRC kinase/TNK2 signaling with dasatinib would improve the outcome of our patient with CSF3R-mutated Philadelphia chromosome-like (Ph-like) B-cell ALL. In the setting of a slow early response 14 days into intensive induction with conventional chemotherapy, the patient attained a MRD-negative CRh at the completion of induction after adding dasatinib. We acknowledge the limitation of not being able to assess the relative impact of dasatinib in terms of achieving remission at end-induction. However, the presence of significant morphologic residual disease (>20% narrow lymphoblasts) at the mid-way point of induction suggested that the likelihood of achieving remission with polychemotherapy alone was low.

Combination therapy with a TKI such as dasatinib plus chemotherapy is a standard treatment approach for patients with B-ALL characterized by the BCR-ABL1 gene fusion, or so-called Philadelphia chromosome-positive (Ph-positive) ALL. A subgroup of B-ALL referred to as Ph-like ALL includes cases without the BCR-ABL1 fusion but with gene expression profiling similar to patients with Ph-positive disease [2,3]. Ph-like ALL accounts for approximately 20–30% of adult B-ALL and is frequently characterized by genomic alterations that result in constitutive kinase and cytokine receptor signaling such as CRLF2 translocations, which this patient had (see Table 1). JAK inhibitors have demonstrated in vitro efficacy in patient-derived xenograft models of CRLF2-rearranged ALL, which is also the most common Ph-like alteration. [7] ABL-class fusions comprise the second most common Ph-like alteration and are sensitive to SRC/ABL-inhibitors in vitro. [8] Regardless of the specific kinase alteration, Ph-like ALL is associated with poor outcomes when treated with standard B-ALL chemotherapy regimens [5]. A strategy of adding dasatinib or ruxolitinib to chemotherapy in Ph-like ALL is currently being explored in clinical trials (NCT02883049), with the decision to use either SRC/ABL-inhibitor or JAK-inhibitor depending on the specific genomic alteration. As dasatinib is not known to have a significant inhibitory effect on the JAK/STAT pathway [2], it’s unlikely that the effect of dasatinib was mediated by blocking signals downstream of the CRLF2 rearrangement in our patient.

Fig. 1 CSF3R truncating mutations may represent a novel mechanism of kinase activation in B-ALL with Ph-like genetics and may respond favorably to the addition of dasatinib to chemotherapy. This case also highlights the role of comprehensive mutational profiling to identify actionable genomic alterations in leukemia patients with no other significant chromosomal or molecular abnormalities identified with standard testing methods.

Authorship

M.S. and M.W. designed and conceived the study and prepared the manuscript.
Declaration of Competing Interests

None.

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