The mutational landscape of chronic neutrophilic leukemia: Case report and literature review

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Introduction

Chronic neutrophilic leukemia (CNL) is a rare myeloproliferative neoplasm characterised by mature neutrophil leucocytosis, a hypercellular bone marrow with minimal dysplasia and myeloblasts, and the presence of CSF3R mutations [1-2]. Historically, the overall survival of CNL patients is poor with transformation to blast crisis frequent [3]. The discovery of CSF3R mutations in this neoplasm, most frequently the T618I, has provided a rationale for targeted therapy with inhibitors of the JAK-STAT or SRC signalling pathways [4] borne out by some in vivo evidence [5,6]. However, some case reports suggest that a clinical response to JAK2 inhibition may be dependent on the underlying mutational heterogeneity [7]. Despite these advances, allogeneic stem cell transplantation (ASCT) remains the only potentially curative option but is limited to those eligible patients [8]. Therefore in order to stratify CNL patients into those who may benefit from JAK2 inhibitors or ASCT, evaluation of the individual patients’ mutational landscape may be increasingly necessary. Here we describe the results of a targeted next-generation sequencing panel in a patient presenting with suspected CNL and summarize the current literature regarding the mutational landscape of this malignancy.

Case report

A 54 year-old male presented with a history of weight loss, a white cell count of 78.8 x 10^9/L (of which neutrophils 68.3 x 10^9/L), hemoglobin of 13.0 g/dL and platelets of 211 x 10^9/L. The bone marrow aspirate was markedly hypercellular with increased, dysplastic megakaryocytes noted. There was a marked myeloid hyperplasia, left shift, prominent eosinophils with less than 5% myeloblasts, consistent with a myeloproliferative neoplasm (Figure 1). The patient had a normal karyotype, no PDGFRα or PDGFRβ rearrangements, no BCR-ABL1 transcripts and the JAK2 V617F mutation was not detected, all consistent with a diagnosis of CNL. Mutations were sought in diagnostic peripheral blood DNA using a targeted next-generation sequencing panel incorporating 27 genes commonly mutated in myeloid malignancies. This approach revealed mutations in CSF3R (p.Thr618Ile), ASXL1 (p.Val807Phefs*11), SETBP1 (p.Gly870Ser), and SRSF2 (p.Pro95Leu) consistent with a diagnosis of CNL (Table 1).

The patient commenced hydroxyurea (1g every third day and 500mg alternate days), then ruxolitinib (10mg bd) and allopurinol (300mg daily) but has not achieved any appreciable reduction in white cell count after eight months. The patient has continual weight loss and has subsequently developed splenomegaly (20cm). In the absence of any sibling donors, a non-related donor search has been activated.

Discussion

CSF3R mutations represent a recurrent element of CNL cases with detection now a diagnostic criterion [1]. In addition to the CSF3R T618I, this patient also evidence of mutations in SETBP1, ASXL1, and SRSF2 reflecting the underlying, complex clonal architecture. A review of previous molecular profiling studies [9-13] has shown that these mutations are common co-operating events in CNL patients (Table 1). The clinical implications of these additional mutations remains poorly understood, largely due to the small number of CNL patients studied. As in the case described herein, a SETBP1 mutation has been previously associated with ruxolitinib unresponsiveness [7] with ASXL1 mutations a poor prognostic factor [10] hence the decision to proceed with an unrelated donor search with a view to ASCT.

This case further underscores the complexity of the mutational landscape of patients with CNL. Targeted NGS profiling is likely to play...
an integral role in the future prognostic and therapeutic stratification of CNL patients.

**Authorship and contributorship**

SEL managed molecular studies. EE provided patient care and clinical information. Both authors contributed to manuscript preparation and approved the final submission.

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None

**Competing interests**

The authors declare no competing interests.

**References**


Table 1. Summary of targeted sequencing studies in chronic neutrophilic leukemia depicting number of cases with the relevant mutated genes

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<th>CSF3R</th>
<th>SETBP1</th>
<th>SRSF2</th>
<th>TET2</th>
<th>ASXL1</th>
<th>CALR</th>
<th>CBL</th>
<th>NRAS</th>
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<td>Meggendorfer, et al. [9]</td>
<td>8/14</td>
<td>(57%)</td>
<td>2/14 (14%)</td>
<td>3/14 (21%)</td>
<td>4/14 (29%)</td>
<td>4/6 (67%)</td>
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<td>Elliott, et al. [10]</td>
<td>14/14</td>
<td>(100%)</td>
<td>5/13 (38%)</td>
<td></td>
<td>8/14 (57%)</td>
<td>1/3 (8%)</td>
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<tr>
<td>Cui, et al. [11]</td>
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<td>6/8 (75%)</td>
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<td>1/8 (12%)</td>
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<td>Ouyang, et al. [12]</td>
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<td>(80%)</td>
<td>1/10 (10%)</td>
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<td>Langabeer, et al. [13]</td>
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Table 1. Summary of targeted sequencing studies in chronic neutrophilic leukemia depicting number of cases with the relevant mutated genes

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