Chronic Eosinophilic Leukemia: Diagnosis and Therapy

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Keywords
CEL, NOS, HES, NGS, JAK2, interferon-alfa

Introduction
In the 2017 World Health Organization (WHO) classification, chronic eosinophilic leukemia, not otherwise specified (CEL, NOS), is included as one of 7 distinct diagnostic entities under the major category of myeloproliferative neoplasms (MPNs). WHO defining criteria for CEL, NOS include: (a) peripheral blood eosinophilia >1.5x10^9/L; (b) evidence of clonal cytogenetic or molecular genetic abnormality, and/or (c) presence of excess myeloblasts (<20%) in the peripheral blood (≥2%) or bone marrow (≥5%). In addition, other eosinophilia-associated hematolymphoid neoplasms require exclusion, particularly myeloid malignancies associated with eosinophilia such as acute myeloid leukemia with inv(16)(p13.1q22) or t(16;16)(p13.1q22) [CBFB-MYH11], MPNs including chronic myeloid leukemia, myelodysplastic syndromes [MDS], MDS/MPNs, and myeloid/lymphoid neoplasms with eosinophilia and fusion genes involving tyrosine kinases (e.g., PDGFRα, PDGFRβ, FGFR1, or PCM1-JAK2; see SOHO abstract by Reiter et al). CEL, NOS is a very rare neoplasm among patients presenting with eosinophilia. For example, in a Mayo Clinic series of 1416 patients with peripheral blood eosinophilia who were evaluated between 2008 and 2019, only 17 patients (1.2%) fulfilled the WHO diagnostic criteria for CEL, NOS. An analysis of the Surveillance, Epidemiology, and End Results (SEER) data between 2004 and 2015 revealed a stable incidence rate of 0.4 cases/1,000,000 persons.

Histopathology
The US bone marrow morphology group and their colleagues evaluated whether bone marrow (BM) morphological features could be used to distinguish idiopathic hypereosinophilic syndrome (HES, n=122) from CEL, NOS (n=22). Abnormal BM histopathologic features (e.g., hypercellularity, abnormal eosinophils, MF-2 to MF-3 fibrosis, MDS- or MPN-like megakaryocytes, dyserythropoiesis/dysgranulopoiesis), resembling MDS, MPNs or MDS/MPNs, were identified in 40/139 (27%) patients: 16/17 (94%) of those with CEL, NOS and 24/122 (20%) of those with HES. Abnormal BM morphology significantly correlated with older age, constitutional symptoms, anemia, abnormal platelet count, organomegaly, elevated lactate dehydrogenase, abnormal karyotype, and the presence of myeloid mutations. Patients with abnormal BM features also had a significantly inferior median survival compared to patients without significantly abnormal BM morphology.

Cytogenetics/Molecular Genetics
In contrast to other MPNs, CEL, NOS is not characterized by a highly recurrent cytogenetic or molecular abnormality. Non-specific cytogenetic abnormalities have been identified in case reports or in small case series. In the Mayo cohort, cytogenetic abnormalities were found in 15 of 17 (88%) patients; these included trisomy 8 (n=4), complex karyotype (n=3), two patients each with del(13q), del(20q), and chromosome 1 abnormalities, and one patient each with monosomy 7 and del(3q). Next generation sequencing (NGS) multi-gene mutation panels are becoming increasingly employed as part of the diagnostic workflow for characterization of hematologic neoplasms, including those with associated eosinophilia. One study identified mutations in 14/51 patients with a diagnosis of HES, including a single mutated gene in seven patients and two or more mutated genes in another seven patients. The most commonly mutated genes included ASXL1 (43%), TET2 (36%), EZH2 (29%), SETBP1 (22%), CBL (14%), and NOTCH1 (14%). Patients with HES ultimately found to have positive sequencing results (and thus would be operationally re-defined as CEL, NOS) exhibited a prognosis that was inferior to HES patients without mutation findings, but similar to other patients with CEL, NOS. In another report, the activating STAT5B N642H variant, a driver mutation also found in lymphoproliferative disorders, was identified in 27/1715 (1.6%) cases referred for eosinophilia. In this series, patients with additional mutated genes (other than SF3B1) had an inferior overall survival compared to those with STAT5B mutations alone, or if the additional mutated genes included SF3B1 (median survival of 14 versus 65 months, respectively).

In the German Registry analysis of patients with hypereosinophilia of unknown significance, KIT D816V and JAK2 V617F mutations were respectively identified in 3% and 4% of such patients. All patients with KIT D816V were ultimately diagnosed with systemic mastocytosis with eosinophilia. Some controversy has surrounded the KIT M541L variant. One small case series identified the variant as a somatic, imatinib-response somatic mutation in 4 of 5 patients with CEL, NOS. However, a large study evaluating over 200 patients identified the variant in only 2 M541L cases with poor outcomes. The KIT M541L variant has been shown in vitro to be susceptible to imatinib and may be identified in patients with MLNs, myelodyplastic/myelo-lymphoid syndrome, and essential thrombocytopenia.
healthy controls and a similar number of patients with FIP1L1- PDGFRα-negative hypereosinophilia found a similar frequency of the variant in the two cohorts with a median variant allele burden of 50.2% (range 47.9–56.0%), consistent with KIT M541I being a benign germline polymorphism. Still, the possibility cannot be ruled out that it is acquired as a somatic mutation in rare cases. Somatic insertion/deletion mutations (p.L583_A586delinsS) within exon 13 of the pseudokinase domain of JAK2 have also been described in patients with CEL, NOS and a concomitant diagnosis of polycythemia vera. We have recently identified a JAK1 R629_ S632delinsSA mutation in a patient with chronic eosinophilia (submitted). The mutation is in close proximity to a heterozygous germine JAK1 A634D mutation described in a family with HES. Although initially characterized by NGS as a variant of unknown significance, functional interrogation found that the mutation leads to IL-3-independent growth of Ba/F3 cells and activation of the JAK-STAT pathway, which can be abrogated by the JAK1/JAK2 inhibitor ruxolitinib. When interpreting the results of NGS panels, it is important to consider whether variants are pathogenetically related to CEL, NOS or may alternatively represent clonal hematopoiesis of indeterminate potential (CHIP).

Prognosis and Treatment

The prognosis of WHO-defined CEL, NOS is dismal. In a cohort of 10 patients, the median survival was 22.2 months, and 5 of the 10 patients developed acute transformation after median of 20 months from diagnosis. Three of 5 patients who did not develop AML died with active disease; one patient underwent an allogeneic hematopoietic stem cell transplantation and maintained a long-term remission, and the remaining patient was reported as achieving a complete remission on imatinib and hydroxyurea. In the Mayo Clinic series of 17 patients, outcomes were similarly poor. At a median follow up of 13 months, nine patients died from infection, disease related organ failure, or leukemic transformation. The median overall survival was 16 months (range, 1–49 months) and 3 (17.6%) patients progressed to acute myeloid leukemia.

No consensus standard frontline treatment exists for CEL, NOS. Most agents have been co-opted from their use in idiopathic HES, and have included corticosteroids, hydroxyurea, [PEG]-interferon-alpha (PEG-IFN), and imatinib. In selected patients, these agents can elicit improvements in leukocytosis and hypereosinophilia, but responses tend not to be durable. PEG-IFN can elicit hematologic and cytogenetic responses, as well as reversion of end-organ damage, including in patients who are relapsed/refractory to corticosteroids and hydroxyurea. In the absence of an established (or cryptic) tyrosine kinase target, hematologic improvement with imatinib may reflect non-specific myelosuppression, and responses tend to be short-lived. The role of the anti-CD52 antibody alemtuzumab remains undefined. Lack of response to the anti-IL5 antibody mepolizumab (currently approved for HES), and anti-IL5 receptor antibody benralizumab have been observed in CEL, NOS/myeloproliferative HES. Given the poor prognosis of CEL, NOS, allogeneic hematopoietic stem cell transplantation should be considered early for suitable patients in whom a donor is available.

Conclusion

CEL, NOS is a rare, genetically and clinically heterogeneous neoplasm with limited survival. NGS may be a useful diagnostic adjunct to identify oncogenic, druggable targets. A high priority is enrollment of CEL, NOS patients into clinical trials given the paucity of agents which can modify disease natural history. An unmet need remains the establishment of consensus response criteria to harmonize reporting of results from studies of novel agents.

References


