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Chronic Neutrophilic Leukemia in the Context of 2016 WHO Classification

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Abstract

A particular mutation in the *CSF3R* may play a role in the development of CNL.SETBP1and JAK2 mutations have also recently found to be implicated in CNL. Presence of CSF3R T618I or other activating mutations is one of the diagnostic criteria in the current updated WHO 2016 classification of hematopoietic neoplasms.

Abbreviations: CNL: Chronic Neutrophilic leukemia; *CSF3R*: colony stimulating factor 3 receptor; G-CSF: Granulocyte colony-stimulating factor; SETBP1: Set binding protein 1; aCML atypical CML; MPN: Myeloproliferative neoplasm; PDGFRα_β: Platelet derived growth factor receptors alpha and beta; FGFR1: Fibroblast growth factor receptor 1.

Introduction

CNL is a clonal myeloid disorder that might orig¬inate from pluripotent hematopoietic stem cells or derive from the progenitor cells of neutrophils [1]. CNL is a rare but potentially aggressive subtype of MPN characterized by neutrophilia [2]. A major component of the diagnosis hinges on the exclusion of an underlying process (inflammatory, infectious, or malignant), capable of causing a reactive neutrophilia or a leukemoid reaction [3]. With the recent discovery of CSF3R mutations, CNL no longer remains a diagnosis of exclusion [4].

Diagnostic Criteria for CNL

i. PB WBC ≥25 X 10^9/L

Segmented neutrophils plus band forms ≥80% of WBCs, neutrophil precursors (promyelocytes, myelocytes and metamyelocytes) <10% of WBC, myeloblasts rarely observed, monocyte count <1 X 10^9/L and no dysgranulopoiesis.

ii. Hypercellular BM

Neutrophil granulocytes increased in percentage and number, neutrophil maturation appears normal and myeloblasts < 5% of nucleated cells.

iii. Not meeting WHO criteria for BCR-ABL1$^+$ CML, PV, ET, or PMF.

iv. No rearrangement of PDGFRA, PDGFRB, or FGFR1, or PCM1-JAK2

v. Presence of CSF3R T618I or other activating CSF3R mutation or In the absence of a CSFR3R mutation, persistent neutrophilia (at least 3 months), splenomegaly and no identifiable cause of reactive neutrophilia including absence of a plasma cell neoplasm or, if present, demonstration of clonality of myeloid cells by cytogenetic or molecular studies [2].

Gene mutations Implicated in CNL

CSF3R and CNL

The *CSF3R* gene is located on the short arm of chromosome 1. The gene encodes the trans-membrane receptor for G-CSF [4]. Two types of mutations were found; most were in the membrane proximal region which mediates proliferative and survival signals: CSF3R T618I (most common) and CSF3R T615A. These occurred alone or in association with nonsense mutations that truncate cytoplasmic tail (a region important in transduction of maturation and suppression of proliferation). Both types of mutations possess *in vitro* transforming capacity mediated via different downstream signaling pathways: the JAK-STAT (activated by membrane proximal mutations) and the SRC family–TNK2 kinase (activated by truncation mutations) [3].

Mutations that alter the receptor structurally and functionally disrupt its ability to regulate granulocytic differentiation and increase granulocytic proliferative capacity. The *CSF3R* mutations have proven potential to the diagnosis of CNL and the development of possible target therapies also. Germ line *CSF3R* mutations have been previously reported in more than 30% of patients with severe congenital neutropenia [4].

SETBP1 mutations in CNL

Heterozygous SETBP1 mutations have been identified in one of four cases of CNL in one series. SETBPI mutations

prevalence of 33% has been reported in WHO-defined CNL cases in other series. In that series, 38% of CSFR-mutated CNL patients co-expressed a SETBP1 mutation. An association with high leukocyte counts and a detrimental prognostic effect was confirmed in most but not all series. A more recent study indicated that these somatic SETBP1 mutations were acquired during leukemic evolution. SETBP1 mutations appear to be enriched in aCML and are a ubiquitous molecular abnormality in CMML [3].

JAK2 Mutations in CNL

Cytokine receptors for CSF3 lack phosphorylation activity. Upon their activation by their respective ligand binding, they induce phosphorylation of JAKs, which then phosphorylate further downstream targets regulating transcription such as the STAT pathway [3]. The mature neutrophils might be the major target of JAK2 V617F mutation in CNL, and the increased percentage of neutrophils was the eventual phenotype [1]. Several case reports of WHO defined CNL have been shown to carry JAK2V617F mutation which corroborates clonality. Recently fourteen WHO defined CNL carrying CSF3R mutations were all negative for JAK2V617F [3]. Patients with CNL concurrent with JAK2 V617F mutation usu¬ally had a long survival period with a good quality of life. Therefore, JAK2 V617F was regarded as a potential indicator for good prognosis [1].

ASXL1 mutations and CNL

In a series of fourteen patients with CSF3R-mutated WHO-defined CNL [3], 57% harbored an ASXL1 mutation. The presence of ASXL1 mutations was independently predictive of shortened survival [5]. ASXL1and *SETBP1* mutations appear to be of prognostic significance and correlate with disease progression [4].

CALR Mutations and CNL

Only one of 13 WHO-defined CSFR-mutated CNL patients carried a novel CALR point mutation, the consequences of which are unknown [3].

Clinical Features at Diagnosis

Average age of onset was commonly 62.5 years, with no gender preference [1]. Most patients are often discovered as incidental leukocytosis during laboratory testing. The median duration before diagnosis was 12.5 months (range 5-84). Fatigue is a common presenting symptom. Other reported symptoms include weight loss, easy bruising, bone pain and night sweats. Palpable splenomegaly was present at diagnosis in 36% of CSF3-R mutated CNL cases [3].

Laboratory Features at Diagnosis

The median leukocyte count was 39 x 10^9/L (but as high as 126), primarily due to a neutrophilia. The majority of patients are mildly anemic (median hemoglobin ~11 g/dl), the platelet count is often normal or slightly decreased but tends to fall, in the later stages and with increasing splenomegaly [3]. In a series of CSF3R-mutated CNL, neutrophil percentage was 85% (78–94), immature cells (myelocytes and metamyelocytes) percentage 6% (0–11) and monocyte percentage 3% (0–10). Toxic granulation of the neutrophils and Dohle bodies was often noted. LDH was elevated in all patients. None of the patients had a serum monoclonal protein [5].

Bone Marrow Biopsy at Diagnosis

Classically, the BM biopsy reveals hypercellularity (>90% cellularity) due to marked granulocytic hyperplasia with an increased myeloid: erythroid ratio, which may reach ≥20:1. The majority of granulocytes are at the metamyelocyte to segmented stages of maturation with <5% myeloblasts. No dysplastic features or Auer rods are present. Erythroid precursors typically have normoblastic maturation and megakaryocytes are quantitatively normal or slightly increased with a normal morphologic appearance. Reticulin fibrosis is uncommon, but reticulin stain may show 1+ reticulin fibrosis (on a scale of 0–4). In view of the reported frequency of CNL and monoclonal gammopathy of undetermined significance and multiple myeloma, the WHO recommends BM examination in CNL for evidence of a plasma cell dyscrasia. If a plasma cell dyscrasia is present, clonality of the neutrophil lineage should be supported by cytogenetic or molecular techniques before making the diagnosis of CNL [3]. Molecular and cytogenetic analysis must be performed to confirm the absence of Philadelphia chromosome and/or the BCR–ABL1 fusion gene), and rearrangements in genes encoding PDGFRA/B and FGFR1 [4].

Cytogenetics and CNL

Cytogenetics is normal in the majority of CNL patients at diagnosis. Cytogenetic abnormalities were present in 23% of patients at diagnosis and clonal evolution developed during the course of the disease in 25% of those with normal cytogenetics at baseline. The most commonly reported recurrent abnormalities included Del 20q, +21, Del 11q, and Del 12p. These cytogenetic aberrations are nonrandom nonspecific findings in myeloid disorders in general [3].

Differential diagnosis of CNL

Reactive Leukocytosis

Presence of CSF3R and/or other recurrent mutations makes its distinction easier from reactive leukocytosis [4].

aCML

It has higher genetic complexity, including a high prevalence of SETBP1 mutations and/or ETNK1 mutations in up to a third of cases. The MPN-associated driver mutations (JAK2, CALR, and MPL) are typically absent [2]. CSF3R mutations, are very rare in aCML (<10%). Some cases of aCML exhibit hyperplastic bone marrows with myeloid hyperplasia and peripheral blood leukocytosis characterized by a prominent dysplastic granulopoiesis (e.g., acquired Pelger-Hu et anomaly; hyper segmentation, nuclear projections, and abnormally clumped nuclear chromatin; and hypo granularity). Multlineage dysplasia

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may be observed in some cases. The finding of ≥10% immature myeloid cells (promyelocytes, myelocytes, and metamyelocytes) in the peripheral blood and/or dysplasia is useful criteria in distinguishing aCML from CNL, which lacks these features. Identification of CSF3R T618I in the context of neutrophilic leukocytosis strongly favors a diagnosis of CNL where it is present in ~80% of patients [6].

Course

CNL is characterized by progressive neutrophilic leukocytosis, which is transiently controlled with current drugs, including ruxolitinib. However, complications associated with progressive treatment-refractory leukocytosis may occur. CNL can progress into blast phase disease or CMML [5]. The survival periods of patients ranged between 6 months and 20 years (with a median survival peri¬od of 30 months) with the 5-year survival rate of 28% [1]. A previous study suggests pathogenetic roles for SETBP1 and ASXL1 mutations in disease transformation into blast phase disease and CMML. ASXL1 mutations independently predict a shortened OS in CNL. Thrombocytopenia is also a risk factor for survival. The presence of mutated SETBP1 was not an independent predictor of overall survival [5].

Management

Optimal therapy of CNL has yet to be defined. In the earliest reported cases, splenic irradiation and splenectomy were used to reduce tumor bulk and relieve abdominal discomfort. Splenectomy cannot be recommended since it resulted in worsening of neutrophilic leukocytosis. Cytoreductive agents, oral hydroxyurea and to a much lesser extent, parenteral alpha interferon control myeloproliferation and have demonstrated efficacy in maintaining a stable chronic phase, at least initially [3].

Hydroxy Urea

It is the most commonly used drug and is effective in controlling leukocytosis and splenomegaly until there is evidence of disease acceleration or blast transformation [3]. Subsequent therapies for hydroxyurea resistance or refractoriness include interferon or its pegylated form, hypomethylating agents, ruxolitinib, thalidomide, cladribine, and Imatinib. All provided transient benefit, including ruxolitinib, which produced an initial reduction in leukocytosis with the addition of hydroxyureain a previous study [5].

Alpha-interferon

Successful use of alpha-interferon has been published in case reports, with one clinical remission of 41 months and two patients achieving disease control with intermittent interferon for progressive disease [3].

Induction Chemotherapy

No hematologic complete remission has been reported following standard induction therapy (anthracycline and cytarabine) for accelerated or blast phase CNL. For blast phase, standard induction chemotherapy was successful at attaining a second chronic phase in one patient only in a published study. In the remaining patients the leukemia was either refractory, the marrow remained hypoplastic following induction chemotherapy or death occurred during attempts at remission induction [3].

Hematopoietic Stem Cell Transplantation

The allogeneic HSC transplanta¬tion was considered as a cure for CNL. However, the incidence of transplantation-related death and complications was high [1]. All patients received myeloablative conditioning (cyclophosphamide and total body irradiation). Most had sibling donors, although matched unrelated transplants were done. SCT was performed in stable chronic phase, in accelerated phase, or following treated blast transformation, respectively. Relatively few cases have been reported in the literature, reflecting the rarity of this disease and the older age of many affected [3]. However, two patients who received transplants following blast transformation or in accelerated phase, died shortly after the procedure due to regimen related toxicity and relapse, respectively. At the present time there is no information on the use of nonmyeloablative, cord blood, or autologous stem cell transplantation for CNL [3].

Novel Therapeutic Approaches

Ruxolitinib, JAK1/2 inhibitor, is not FDA-approved for CNL. A dose-dependent clinical response to ruxolitinib has been reported in one patient carrying a CSF3R T618I. The patient achieved marked reduction in neutrophil count and resolution of thrombocytopenia with ruxolitinib [6]. However, other studies described cases of CNL co-expressing CSF3R T618I and SETBP1 mutations with normal cytogenetics refractory to ruxolitinib treatment. These cases were treated with ruxolitinib after hydroxyurea failure to control progressive neutrophilic leukocytosis [3]. It is currently unknown if co-expression of SETBP1 in CSFR3T618I-mutated CNL patient contributed to JAK inhibitor therapy ineffectiveness [3].

Type of CSF3R Mutation and *in Vitro* drug Sensitivity

In vitro drug sensitivity assays showed clinical improvement in CNL patients that had CSF3R T681I with ruxolitinib treatment, whereas those who had truncated mutations responded selectively to a SRC kinase inhibitor, dasatinib. This observation supported the theory that CNL patients may show differences in sensitivity to different pathway inhibitors based on the type of CSF3R mutation they harbored [4]. Currently, a multicenter study (#NCT02092324) is evaluating the safety and efficacy of ruxolitinib in CNL patients, regardl

Reference

1. Hu J, Xu Y, Li Z, Hong X, Lu Q (2016) Chronic neutrophilic leukemia with JAK2 V617F mutation: a case report. Int J Clin Exp Pathol 9(7): 7482-7487.

2. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, et al. (2016). The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 127(20): 2391-2405.

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3. Elliott MA, Tefferi A (2016) Chronic neutrophilicleukemia 2016: Update on diagnosis, molecular genetics, prognosis and management. Am J Hematol 91(6): 342-349.

4. Villatoro TM, Uppal GK (2017) Implications of CSF3R and other novel mutations in chronic neutrophilic leukemia. Austin J ClinPathol 4(1): 1047.

5. Elliott MA, Pardanani A, Hanson CA, Lasho TL, Finke CM, et al. (2015) ASXL1 mutations are frequent and prognostically detrimental in CSF3R-mutated chronic neutrophilic leukemia. Am J Hematol 90(7): 653-656.

6. Gotlib J (2017) How I treat atypical chronic myeloid leukemia. Blood 129(7): 838-845.

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