Pathogenesis CSF3 is the main growth factor for granulocyte proliferation and differentiation. Accordingly, recombinant CSF3 is used for the treatment of severe neutropenia, including severe congenital neutropenia (SCN). Some patients with SCN acquire *CSF3R* mutations, and the frequency of such mutations is significantly higher (~80%) in patients who experience leukemic transformation. SCN-associated *CSF3R* mutations occur in the region of the gene coding for the cytoplasmic domain of CSF3R and result in truncation of the C-terminal-negative regulatory domain. A different class of *CSF3R* mutations is noted in ~90% of patients with CNL; these are mostly membrane proximal, with the most frequent being a C-to-T substitution at nucleotide 1853 (T618I). About 40% of the T618I-mutated cases also harbored *SETBP1* mutations. *CSF3R* T618I induces a lethal myeloproliferative disorder in a mouse model and is associated with in vitro sensitivity to JAK inhibition.

Diagnosis Diagnosis of CNL requires exclusion of the more common causes of neutrophilia including infections and inflammatory processes. In addition, one should be mindful of the association between some forms of metastatic cancer or plasma cell neoplasms with secondary neutrophilia. Neoplastic neutrophilia also occurs in other myeloid malignancies including atypical chronic myeloid leukemia and chronic myelomonocytic leukemia. Accordingly, the WHO diagnostic criteria for CNL are designed to exclude the possibilities of both secondary/reactive neutrophilia and leukocytosis associated with myeloid malignancies other than CNL (Table 135e-5): leukocytosis ($\geq 25 \times 10^9$/L), >80% segmented/band neutrophils, <10% immature myeloid cells, <1% circulating blasts, and absence of dysgranulopoiesis or monocytosis. Bone marrow in CNL is hypercellular and displays increased number and percentage of neutrophils with a very high myeloid-to-erythroid ratio and minimal left shift, myeloid dysplasia, or reticulin fibrosis.

Treatment Current treatment in CNL is largely palliative and suboptimal in its efficacy. Several drugs alone or in combination have been tried, and none have shown remarkable efficacy. As such, allogeneic stem cell transplantation (ASCT) is reasonable to consider in the presence of symptomatic disease, especially in younger patients. Otherwise, cytoreductive therapy with hydroxyurea is probably as good as any treatment, and a more intensive combination chemotherapy may not have additional value. However, response to hydroxyurea therapy is often transient, and some have successfully used interferon α as an alternative drug. Response to treatment with ruxolitinib (a JAK1 and JAK2 inhibitor) has been reported but has not been confirmed.

ATYPICAL CHRONIC MYELOID LEUKEMIA

Atypical chronic myeloid leukemia, *BCR-ABL1* negative (aCML) is formally classified under the MDS/MPN category of myeloid malignancies and is characterized by left shifted granulocytosis and dysgranulopoiesis. The differential diagnosis of aCML includes chronic myeloid leukemia (CML), which is distinguished by the presence of *BCR-ABL1*; CNL, which is distinguished by the absence of dysgranulopoiesis and presence of *CSF3R* mutations; and chronic myelomonocytic leukemia, which is distinguished by the presence of monocytosis (absolute monocyte count $>1 \times 10^9$/L). The WHO diagnostic criteria for aCML are listed in Table 135e-5 and include granulocytosis (WBC $\geq 13 \times 10^9$/L), neutrophilia with dysgranulopoiesis, ≥10% immature granulocytes, <20% peripheral blood myeloblasts, <10% peripheral blood monocytes, <2% basophils, and absence of otherwise specific mutations such as *BCR-ABL1*. The bone marrow is hypercellular with granulocyte proliferation and dysplasia with or without erythroid or megakaryocytic dysplasia.

The molecular pathogenesis of aCML is incompletely understood; about one-fourth of the patients express *SETBP1* mutations, which are, however, also found in several other myeloid malignancies, including CNL and chronic myelomonocytic leukemia. *SETBP1* mutations in aCML were prognostically detrimental and mostly located between codons 858 and 871; similar mutations are seen with Schinzel-Giedion syndrome (a congenital disease with severe developmental delay and various physical stigmata including midface retraction, large forehead, and macroglossia).

In a series of 55 patients with WHO-defined aCML, median age at diagnosis was 62 years with female preponderance (57%); splenomegaly was reported in 54% of the patients, red cell transfusion requirement in 65%, abnormal karyotype in 20% (20q– and trisomy 8 being the most frequent), and leukemic transformation in 40%. Median survival was 25 months. Outcome was worse in patients with marked

TABLE 135e-5 WORLD HEALTH ORGANIZATION DIAGNOSTIC CRITERIA FOR CHRONIC NEUTROPHILIC LEUKEMIA (CNL); ATYPICAL CHRONIC MYELOID LEUKEMIA, *BCR-ABL1* NEGATIVE (ACML); AND CHRONIC MYELOMONOCYTIC LEUKEMIA (CMML)

Variables	CNL	aCML	CMML
PB leukocyte count	$\geq 25 \times 10^9$/L	$\geq 13 \times 10^9$/L	
PB segmented neutrophils/bands	>80%		
PB immature granulocytes[a]	<10%	≥10%	
PB blast count	<1%		
PB monocyte count	$<1 \times 10^9$/L	$<1 \times 10^9$/L	$>1 \times 10^9$/L
PB increased neutrophils or precursors with dysgranulopoiesis	No	Yes	
PB basophil percentage		<2%	
PB monocyte percentage		<10%	
Bone marrow	↑Neutrophils, number and % <5% blasts Normal neutrophilic maturation Megakaryocytes normal or left shifted	↑Granulocyte proliferation Granulocytic dysplasia ± erythroid/megakaryocyte dysplasia	Dysplasia in ≥1 myeloid lineages *or* Clonal cytogenetic/molecular abnormality
BCR-ABL1	No	No	No
PDGFRA, *PDGFRB*, or *FGFR1* mutation	No	No	No
PB and BM blasts/promonocytes	<20%	<20%	<20%
Hepatosplenomegaly	±	±	±
Evidence for other MDS/MPN	No	No	No
Evidence for other MPN	No	No	No
Evidence for reactive leukocytosis[b] or monocytosis	No	No	No

[a]Immature granulocytes include myeloblasts, promyelocytes, myelocytes, and metamyelocytes. [b]Causes of reactive neutrophilia include plasma cell neoplasms, solid tumor, infections, and inflammatory processes.

Abbreviations: BM, bone marrow; MDS, myelodysplastic syndromes; MPN, myeloproliferative neoplasms; PB, peripheral blood.