

Diagnosis and Management of Neutrophilic Myeloid Neoplasms

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Abstract: Chronic neutrophilia is commonly seen with persistent infections, inflammatory disorders, smoking, solid tumors, and specific medications. However, after reactive causes have been excluded, a workup for primary (clonal) neutrophilic disorders, such as myeloproliferative neoplasms (MPNs) and myelodysplastic/myeloproliferative overlap syndromes, should be pursued. Except for chronic myeloid leukemia, which is defined by the presence of the Philadelphia (Ph) chromosome, and the classic Ph chromosome–negative MPNs (polycythemia vera, essential thrombocythemia, and primary myelofibrosis), clonal neutrophilic neoplasms historically have been challenging to diagnose and classify. The 2016 revised World Health Organization classification of these disorders has been based mainly on clinicopathologic features. However, recent discoveries of the molecular alterations underlying these disorders have served to supplement our knowledge of their morphologic and clinical features, opening new therapeutic avenues. In this review, we discuss the diagnostic approach, prognostic features, and treatments of neutrophilic myeloid neoplasms, with a focus on chronic neutrophilic leukemia, atypical chronic myeloid leukemia, and chronic myelomonocytic leukemia.

Introduction

Chronic neutrophilia is a common reactive manifestation of various systemic disorders. After excluding secondary causes, workup for primary (clonal) neutrophilic disorders, such as myeloproliferative neoplasms (MPNs) and myelodysplastic/myeloproliferative overlap syndromes (MDS/MPN), should be pursued. These disorders include chronic myeloid leukemia (CML), the classic Philadelphia (Ph) chromosome–negative MPNs (polycythemia vera, essential thrombocythemia, and primary myelofibrosis), chronic neutrophilic leukemia (CNL), MPN-unclassifiable (MPN-U), chronic myelomonocytic leukemia (CMML), atypical (*BCR-ABL1*–negative) CML (aCML), MDS/MPN with ring sideroblasts and thrombocytosis

Keywords

Atypical chronic myeloid leukemia, chronic myelomonocytic leukemia, chronic neutrophilic leukemia, myeloid neoplasms, neutrophilia

(MDS/MPN-RS-T), juvenile myelomonocytic leukemia (JMML), and MDS/MPN-unclassifiable (MDS/MPN-U).¹

CML is defined by the presence of the Ph chromosome (or *BCR-ABL1* fusion on molecular testing). The 2016 revised World Health Organization (WHO) classification, which relies primarily on clinicopathologic features to diagnose the Ph chromosome–negative MPNs, has become increasingly reproducible across pathologists.²⁻⁴ However, other neutrophilic neoplasms can be more challenging to diagnose. In this regard, recent advances in our understanding of their molecular underpinnings⁵⁻⁷ have proved useful for adding diagnostic clarity. The identification of molecular abnormalities may also open new avenues of therapy for patients with these neoplasms, who have a poor prognosis and are commonly excluded from clinical trials.⁷⁻¹⁰ In this review, we discuss the diagnostic approach to some of the rare neutrophilic neoplasms, their molecular features, and the various therapies available, with a focus on CNL, aCML, and CMML.

Diagnosis

Secondary Causes of Chronic Neutrophilia

Neutrophilia is defined as an absolute neutrophil count (ANC) that is more than 2 standard deviations above the mean value for normal adults—that is, above approximately $7.5 \times 10^9/L$.¹¹ In the approach to a patient with persistent neutrophilia, the first step is to exclude secondary (reactive) causes (Figure 1). These include chronic infections, inflammatory disorders, solid tumors, asplenia, specific medications (eg, glucocorticoids, lithium), smoking, obesity, and pregnancy.¹²⁻¹⁷ Neutrophilia is generally mild (eg, white blood cell [WBC] count $<15 \times 10^9/L$, ANC $<10 \times 10^9/L$) in splenectomized patients, active smokers, obese persons, and pregnant women, and hematologic evaluation is warranted in those with higher and/or progressively increasing values.^{13,15-17} In contrast, an ANC above $50 \times 10^9/L$ can be associated with various leukemoid reactions and is not necessarily indicative of a hematologic neoplasm.¹⁸ Rarely, neutrophilia may be familial (hereditary), as in patients with germline mutations in the granulocyte colony–stimulating factor receptor gene (*CSF3R*).¹⁹

Neutrophilic Myeloid Neoplasms

After secondary causes of persistent neutrophilia have been excluded, further evaluation for an underlying neutrophilic myeloid neoplasm should be pursued. The clinical symptoms (eg, night sweats, weight loss, splenomegaly) and morphologic features (eg, increased marrow cellularity, the variable presence of marrow reticulin fibrosis) of these disorders overlap substantially, with a

variable risk for progression to blast phase disease/acute leukemia. Evaluation starts with a consideration of the relatively common MPNs: CML, polycythemia vera, essential thrombocythemia, and primary myelofibrosis. CML is characterized by granulocytic immaturity and basophilia,^{20,21} and the diagnosis requires the presence of the *BCR-ABL1* fusion gene. This gene product results from a reciprocal translocation of the *BCR* region on chromosome 22 and regions of *ABL1* on chromosome 9, forming the Ph chromosome. The fusion gene can be the result of variant and cryptic translocations in approximately 5% of patients,^{22,23} which can be missed on routine cytogenetic analysis. Such cases can be detected by fluorescence in situ hybridization and/or reverse transcription polymerase chain reaction.²³ A neutrophilic variant of CML, in which the leukocytosis consists mostly of mature neutrophils without a “myelocyte bulge,” is rare and usually detected by routine cytogenetic analysis.²⁴ These cases have an uncommon rearrangement (e19/a2) that results in a fusion protein (p230) larger than the p210 fusion protein seen in classic CML.²⁴ The presence of erythrocytosis and/or thrombocytosis and positivity for a *JAK2*, *CALR*, or *MPL* mutation can help support the diagnosis of a classic Ph chromosome–negative MPN. Morphologic evaluation of the bone marrow, with close attention to megakaryocytic atypia and clustering, will further support the diagnosis in such cases, especially because mutations in the JAK/STAT pathway are not specific to polycythemia vera, essential thrombocythemia, or primary myelofibrosis and can be seen in other rare neutrophilic neoplasms, such as MDS/MPN-RS-T and MDS/MPN-U.^{6,7} The diagnosis of MDS/MPN-RS-T is strongly supported by the concomitant presence of *SF3B1* mutations with a *JAK2*, *CALR*, or *MPL* mutation.²⁵ Concomitant eosinophilia should prompt the exclusion of rearrangements in *PDGFRA*, *PDGFRB*, or *FGFR1*, or a *PCMI-JAK2* fusion, although eosinophilia is not invariably found in these myeloid/lymphoid neoplasms.²⁶ Persistent monocytosis ($\geq 10\%$ of the total number of WBCs and a monocyte cell count of $\geq 1 \times 10^9/L$), without a concurrent *JAK2*, *CALR*, or *MPL* mutation, favors the diagnosis of CMML or juvenile myelomonocytic leukemia. Juvenile myelomonocytic leukemia, a disorder of childhood involving the RAS signaling pathway, with mutations in *PTPN11*, *NRAS*, *KRAS*, *CBL*, or *NFI*, is discussed elsewhere.²⁷

Exclusion of the preceding diagnoses should prompt evaluation for the rare neutrophilic myeloid neoplasms CNL and aCML. Both entities have an age-adjusted incidence estimated at 0.1 per 1,000,000 person-years according to the Surveillance, Epidemiology, and End Results database, with a median age at diagnosis of 69 to 71 years.²⁸ The diagnostic criteria for aCML and CNL are

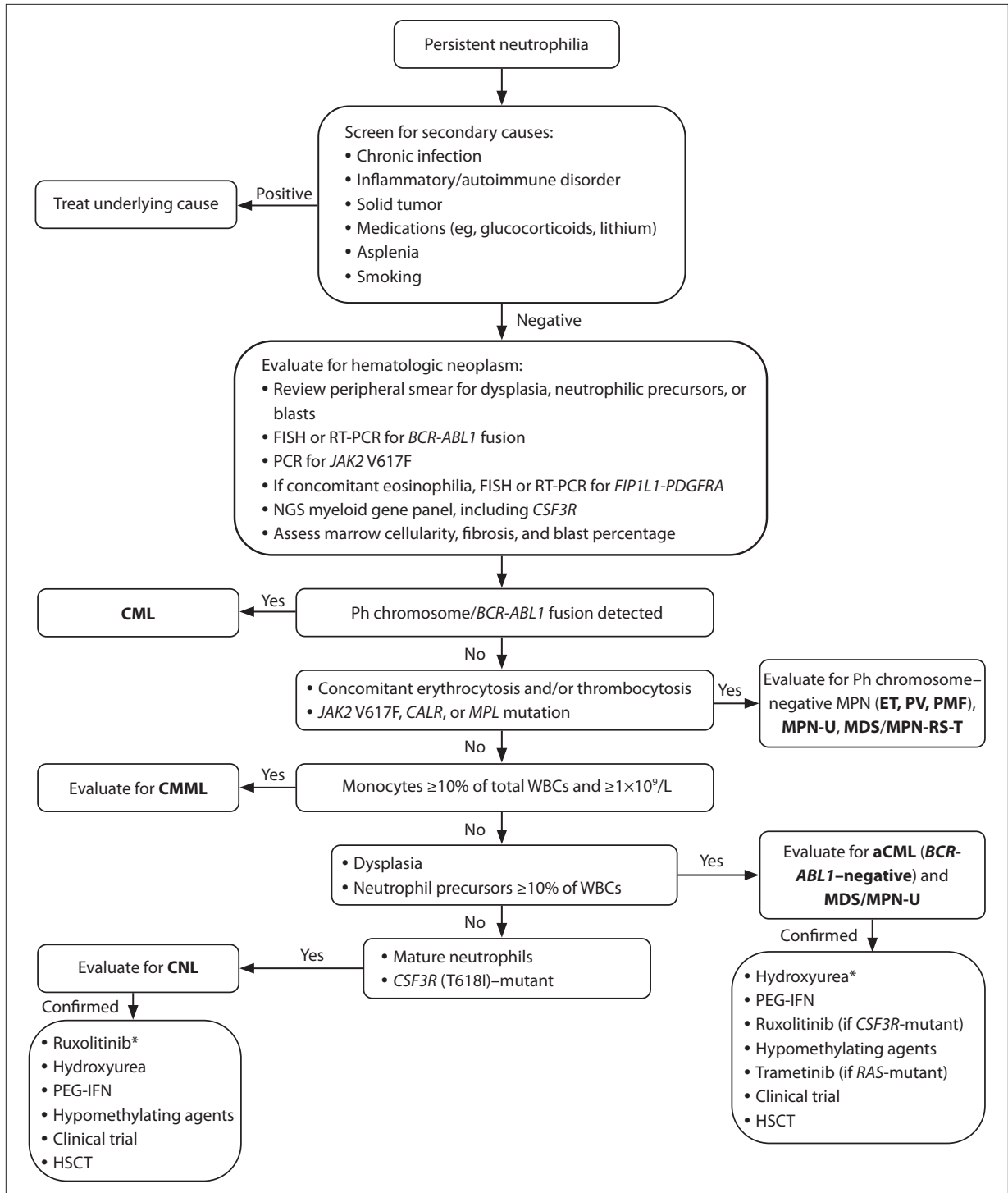


Figure 1. Diagnostic and therapeutic algorithm for neutrophilic myeloid neoplasms.

*Choice and sequence of treatment should be tailored to the individual patient.

aCML, atypical chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; CNL, chronic neutrophilic leukemia; ET, essential thrombocythemia; FISH, fluorescence in situ hybridization; HSCT, hematopoietic stem cell transplant; MDS/MPN-RS-T, myelodysplastic syndrome/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis; MPN-U, myeloproliferative neoplasm-unclassifiable; NGS, next-generation sequencing; PCR, polymerase chain reaction; PEG-IFN, pegylated interferon; Ph chromosome, Philadelphia chromosome; PMF, primary myelofibrosis; PV, polycythemia vera; RT-PCR, reverse transcription polymerase chain reaction; WBCs, white blood cells.

Table. World Health Organization Diagnostic Criteria for Chronic Neutrophilic Leukemia and Atypical Chronic Myeloid Leukemia

Criteria	Chronic Neutrophilic Leukemia	Atypical Chronic Myeloid Leukemia
In peripheral blood	<ul style="list-style-type: none"> • WBC count $\geq 25 \times 10^9/L^*$ • Segmented plus banded neutrophils $\geq 80\%$ of WBCs • Neutrophilic precursors $< 10\%$ of WBCs • Blasts rarely observed • Monocyte count $< 1 \times 10^9/L$ • No dysgranulopoiesis 	<ul style="list-style-type: none"> • WBC count $\geq 13 \times 10^9/L$ owing to increased neutrophils and their precursors • Neutrophil precursors $\geq 10\%$ of WBCs • No or minimal absolute monocytosis; monocytes $< 10\%$ of WBCs • Basophils $< 2\%$ of WBCs • Blasts $< 20\%$ • Dysgranulopoiesis
In bone marrow	<ul style="list-style-type: none"> • Neutrophil granulocytes increased in percentage and number • Neutrophil maturation normal in appearance • Blasts $< 5\%$ of nucleated cells 	<ul style="list-style-type: none"> • Granulocytic proliferation AND granulocytic dysplasia, with or without dysplasia in erythroid and megakaryocytic lineages • Blasts $< 20\%$
Other criteria	<ul style="list-style-type: none"> • <i>CSF3R</i> T618I or another activating <i>CSF3R</i> mutation OR • Persistent neutrophilia (≥ 3 mo), splenomegaly, and no identifiable cause of reactive neutrophilia, including absence of plasma cell neoplasm; if plasma cell neoplasm present, demonstration of clonality of myeloid cells by cytogenetic or molecular studies 	<ul style="list-style-type: none"> • <i>SETBP1</i> and/or <i>ETNK1</i> mutations support diagnosis of aCML • Prior history of MPN, MPN features in the marrow, and/or an MPN-associated mutation (<i>JAK2</i>, <i>CALR</i>, or <i>MPL</i>) tend to exclude aCML • <i>CSF3R</i> mutation should prompt consideration of CNL
Exclusions	<ul style="list-style-type: none"> • Not meeting WHO criteria for <i>BCR-ABL1</i>-positive CML, PV, ET, or PMF • No rearrangement of <i>PDGFRA</i>, <i>PDGFRB</i>, or <i>FGFR1</i>, and no <i>PCM1-JAK2</i> fusion 	

*This threshold is arbitrary. A diagnosis of CNL should also be considered in patients with a WBC count lower than $25 \times 10^9/L$ who harbor a *CSF3R* T618I mutation or another activating *CSF3R* mutation.

aCML, atypical chronic myeloid leukemia; CNL, chronic neutrophilic leukemia; ET, essential thrombocythemia; mo, month; MPN, myeloproliferative neoplasm; PMF, primary myelofibrosis; PV, polycythemia vera; WBC, white blood cell; WHO, World Health Organization.

Sources: Orazi A, et al. In: Swerdlow SH, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: IARC Publications; 2017:87-89.²⁹ and Bain BJ, et al. In: Swerdlow SH, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: IARC Publications; 2017:37-38.³⁰

summarized in the Table. The differentiation of aCML from proliferative CMML can be challenging, as the 2 disorders share many features (eg, WBC count $\geq 13 \times 10^9$, neutrophilic immaturity, dyspoiesis, absolute monocytosis), in addition to genetic and epigenetic aberrations. In contrast to the diagnosis of aCML, that of CMML requires the presence of both absolute ($\geq 1 \times 10^9/L$) and relative ($\geq 10\%$) monocytosis.¹ Dysplasia in CMML can be subtle or absent, and therefore the presence of 1 or more mutations on a multigene next-generation sequencing (NGS) panel (discussed below) can help distinguish CMML from reactive monocytosis.¹ Neutrophilic precursors in the peripheral blood, dysgranulopoiesis (ie, pseudo-Pelger-Huët anomaly, hypogranular neutrophils, nuclear hypersegmentation, abnormally clumped chromatin), and the mutational profile (discussed below) on NGS help differentiate aCML from CNL.²⁹ In contrast, patients with CNL typically have a WBC count of at least $25 \times 10^9/L$, consisting of mostly mature neutrophils ($\geq 80\%$ segmented or band neutrophils), with a minimal presence

of neutrophilic precursors ($< 10\%$) and the absence of dysplastic features (Figure 2).³⁰ CNL is strongly associated with activating mutations in *CSF3R*,⁵ and the presence of those mutations has recently become part of the WHO diagnostic criteria for this disease.³⁰ The *CSF3R* gene is not routinely included in several commercially available NGS panels, and knowledge of the genes tested in these panels is important because the detection of *CSF3R*-activating mutations is of both diagnostic and therapeutic significance (discussed below). Uncommonly, plasma cell neoplasms can mimic CNL, which is thought to result from the plasma cell production of granulocyte colony-stimulating factor, and this association should be considered during patient evaluation.^{31,32}

When a neutrophilic myeloid neoplasm fails to meet the diagnostic criteria for one of the preceding WHO entities or has overlapping features, a diagnosis of either MPN-U or MDS/MPN-U is entertained, with the latter requiring the presence of dysplastic morphologic features. In comparison with patients who have aCML, those who

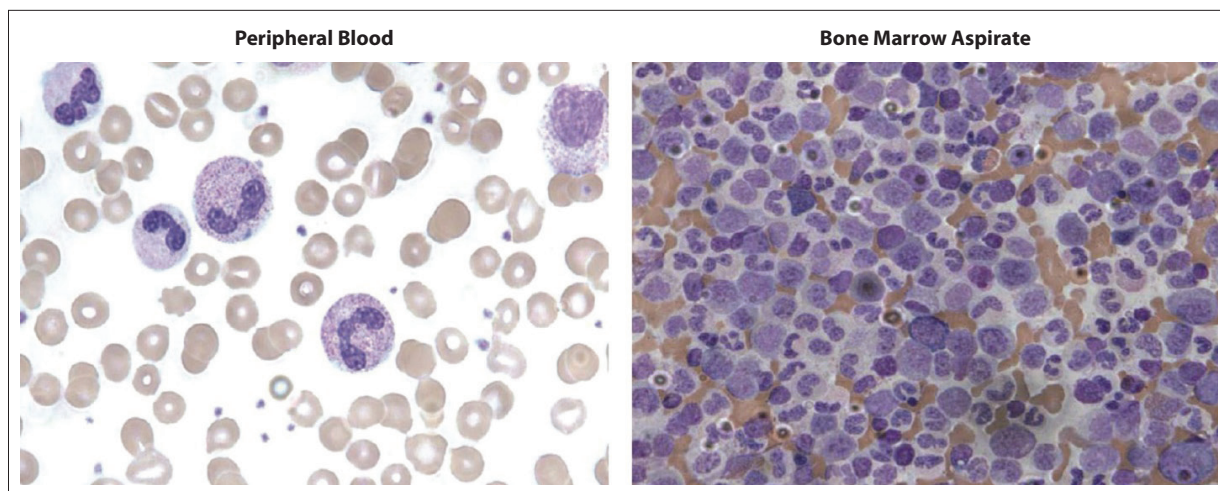


Figure 2. Peripheral blood (left) and bone marrow aspirate (right) from a patient with chronic neutrophilic leukemia. The peripheral blood smear shows segmented and band neutrophils, with toxic granulation and Döhle bodies. The bone marrow aspirate shows marked hypercellularity from myeloid hyperplasia, with full-spectrum maturation.

From Maxson JE, et al. *N Engl J Med.* 2013;368(19):1781-1790.⁵ Reprinted with permission from the Massachusetts Medical Society.

have MDS/MPN-U tend to have a lower WBC count and longer survival, as discussed below.^{7,9} Patients with MDS or MPN in whom features of neutrophilic MDS/MPN overlap syndromes develop are considered to have progressive disease, and the natural history of their disease may be different from that of patients with de novo MDS/MPN.²⁹

NGS myeloid gene panels are key in the evaluation of neutrophilic myeloid neoplasms because at least one somatic mutation will be detected in more than 90% of cases,^{6,33} whereas leukemoid reactions should not exhibit such mutations, although similar morphology can be detected in peripheral blood, including toxic granulations, Döhle bodies, and early neutrophilic precursors.³² Nevertheless, the possibility of clonal hematopoiesis of indeterminate potential (CHIP) should be considered when NGS panels are interpreted in the setting of reactive states, including leukemoid reactions, because CHIP can create diagnostic confusion if not interpreted correctly. Figure 1 summarizes the diagnostic and therapeutic algorithm for patients with a neutrophilic myeloid neoplasm.

Molecular and Chromosomal Features

Genomic Landscape

Although the clinical features of the neutrophilic neoplasms overlap to a considerable degree, recent advances in deciphering their molecular landscape have improved our ability to understand and classify them. Perhaps the most prominent recent development was the discovery of *CSF3R* mutations in 64% to 89% of patients with

CNL,^{5,6,34} identifying a biomarker for this rare disease. The *CSF3R* mutations include the extracellular domain (membrane-proximal) mutations T618I (the most common one, found in approximately 80% of patients with CNL) and T615A, in addition to the transmembrane domain mutation T640N.^{5,34,35} These mutations result in ligand-independent activation of *CSF3R* and constitutive activation of the JAK/STAT signaling pathway.³⁶ Cytoplasmic truncation mutations in *CSF3R*, which are seen in individuals with severe congenital neutropenia, are uncommon in CNL and usually co-occur with membrane-proximal mutations.⁵ Additionally, *CSF3R* T618I or truncation mutations are detected in 1% to 2% of cases of acute myeloid leukemia,^{5,37} the majority of which have *CEBPA* mutations or core binding factor translocations.^{37,38}

CSF3R mutations appear to be unique to CNL, with several studies noting that they were either absent in other neutrophilic neoplasms or present in a minority of patients with aCML (up to 10%-20%).^{6,7,9,34,39} Co-occurrence of *SETBP1* and *CSF3R* mutations is also frequently seen in patients with CNL. Nevertheless, CNL shows multiple pathway mutation co-occurring patterns that closely resemble those of aCML, CMML, and MDS/MPN-U, challenging its classification as a separate MPN.⁶ In one series, other mutations detected in at least 20% of patients with CNL included *ASXL1*, *SRSF2*, *EZH2*, and *TET2*.⁶

Significant mutational overlap also exists among aCML, CMML, and MDS/MPN-U, implying that they may represent a continuum of related disorders.

They share mutations in genes involved in epigenetic regulation (*ASXL1*, *TET2*, *EZH2*, *DNMT3A*); signal transduction (*JAK2*, *KRAS*, *NRAS*, *CBL*, *ETNK1*); the spliceosome complex (*SF3B1*, *SRSF2*, *U2AF1*); and transcription factors (*RUNX1*, *GATA2*).^{6,7} Nonetheless, specific gene combinations were shown to be associated with distinct subtypes: *ASXL1/SETBP1* and *SETBP1/SRSF2* in aCML; biallelic *TET2*, *TET2/SRSF2*, and *RUNX1/SRSF2* in CMML; and *SF3B1/JAK2* and *SF3B1/DNMT3A* in MDS/MPN-RS-T.⁷ *ASXL1* is potentially the founder mutation for aCML, and *SETBP1*, which is present in 30% to 40% of patients, is either co-dominant with or secondary to *ASXL1*.⁷ In contrast, *TET2* is the founder mutation in CMML, a finding corroborated by other studies showing that early *TET2* mutations skew differentiation toward a granulomonocytic lineage.^{7,40} The mutations most commonly detected in aCML ($\geq 20\%$ of patients) are *ASXL1* (present in 80%-90%), *SRSF2*, *SETBP1*, *TET2*, *EZH2*, *NRAS*, and *CSF3R*.^{6,7}

Chromosomal Abnormalities

Unlike CML, which is defined by the presence of the Ph chromosome, none of the other neutrophilic neoplasms discussed in this review have such a unique cytogenetic abnormality. If a translocation involving 4q12, 5q31-33, 8p11-12, or 9p24 is found on standard cytogenetic analysis, then fluorescence in situ hybridization testing for involvement of the suspected gene (*PDGFRA*, *PDGFRB*, *FGFR1*, or *JAK2*, respectively) should be performed to confirm gene rearrangement.²⁶ If any of these rearrangements is detected, then the disease is reclassified as belonging to the WHO category of "myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1* or with *PCMI-JAK2*," a subgroup in which hyper-eosinophilia is characteristic but not universal.⁴¹

Cytogenetic abnormalities tend to be more frequent in aCML and MDS/MPN-U than in CMML, and they are usually absent in CNL.^{6,8} They are detected in 20% to 50% of cases across these conditions^{7,8,33,42,43} and can include trisomy 8, trisomy 14, trisomy 21, del(20q), isochromosome 17q, -7/7q-, and complex cytogenetic abnormalities.^{6-9,42,44} Cytogenetic abnormalities can also be acquired (evolve) over time, as observed in CNL.⁸

Prognosis

The median overall survival (OS) of patients with neutrophilic myeloid neoplasms is variable. Patients with aCML or CNL have the worst median OS, at 1 to 2 years, whereas patients with MDS/MPN-U have a longer OS, ranging from 2 to 6.5 years in different cohorts.^{6,7,9} aCML is historically associated with the highest rate of transformation to acute myeloid leukemia (AML; 37%

in aCML, 23% in MDS/MPN-U,⁹ 20% in CNL⁸), with a recent cohort reporting a lower risk for leukemic transformation in aCML and MDS/MPN-U of approximately 10%.⁷ Bone marrow failure, hemorrhage, and transformation to AML are the common causes of death in those disorders.

Clinical prognostic factors in MDS and CMML, such as advanced age, degree of cytopenias, transfusion dependence, and increase in blood and/or marrow blasts are likely negative prognostic factors across those disorders, but those need validation in large cohorts. Recently, a higher WBC count (as a continuous variable or at a cutoff of $50 \times 10^9/L$) and an increased percentage of myeloid precursors in blood, in addition to advanced age (>67 years) and anemia (<10 mg/dL), were significant risk factors for inferior survival in aCML,^{9,33} whereas leukocytosis ($>60 \times 10^9/L$) and a platelet count below $160,000/\mu L$ were associated with inferior OS in CNL.⁴⁵

Several genetic mutations have been found to be independently prognostic in these complex disorders, and a higher number of mutations (≥ 4) is associated with leukemic transformation and worse survival.⁶ *ASXL1* mutations have collectively been associated with a worse prognosis across these conditions,^{6,7} and they are included in different prognostic models for CMML.^{10,46} In addition to mutations in *ASXL1*,^{10,43,47} mutations in *RUNX1*, *NRAS*, and *SETBP1* were independently associated with OS in CPSS-Mol, a clinical/molecular CMML-specific prognostic scoring system.⁴³ In aCML, mutations in *RUNX1*, *NRAS*, and *CUX1* are associated with worse survival, whereas the prognostic significance of *SETBP1* and *TET2* mutations is variable in different cohorts.^{7,33,48,49} In CNL, the presence of *SETBP1* mutations has been shown to have no effect on OS in a meta-analysis.⁴⁸ In patients with MDS/MPN-U, besides *ASXL1*,⁷ the presence of mutations in *TP53* carries an unfavorable prognosis.⁴² In addition to the molecular abnormalities previously discussed, complex cytogenetics and -7/7q independently predict a poor prognosis in MDS/MPN-U, CMML, and aCML.^{7,9,44}

Treatment

Despite our improved understanding of CNL, aCML, and MDS/MPN-U, treatment options are currently limited, and allogeneic hematopoietic stem cell transplant (HSCT) remains the only potentially curative option. Randomized prospective trials are lacking, especially given the rarity of these disorders and the diagnostic challenges they present. Until recently, treatment recommendations were based on anecdotal case reports and small case series, which are usually biased toward positive outcomes. In the recent cohort of Palomo and colleagues, more than one-third of patients with aCML or MDS/

MPN-U did not receive active therapy other than supportive care.⁷ Most recently, 2 prospective, open label, phase 2 trials have been published. The first, a trial of the JAK1/2 inhibitor ruxolitinib (Jakafi, Incyte) as a single agent, included 21 patients with CNL and 23 patients with aCML; the second, a trial of ruxolitinib in combination with azacitidine, included 4 patients with aCML and 14 with MDS/MPN-U. Different primary response criteria were used in the 2 studies.^{50,51} The treatment of CNL, aCML, and MDS/MPN-U is discussed below; the treatment of other neutrophilic neoplasms, including classic Ph chromosome–negative MPNs, CMML, and CML, has been extensively reviewed elsewhere.

Treatment initiation is recommended in symptomatic patients (eg, night sweats, weight loss, symptomatic splenomegaly), those with progressive cytopenias and/or leukocytosis, and those who have increased bone marrow and/or peripheral blood blasts (Figure 1).

Chronic Neutrophilic Leukemia

In patients with CNL, cytoreduction with hydroxyurea leads to a decrease in leukocytosis and splenomegaly in most cases, with a median duration of response of 12 months reported in a small series of 12 patients.⁸ The efficacy of ruxolitinib in patients with CNL and a *CSF3R* T618I mutation was initially demonstrated in case reports.^{5,52,53} This was recently confirmed in a phase 2 study that showed an overall response rate of 65% (13/20), including a complete response in 4 patients with CNL, with 76% of those patients harboring a *CSF3R* membrane-proximal or transmembrane mutation.⁵⁰ A total of 81.5% of patients had previously been treated with hydroxyurea. One patient with CNL in this trial had a complete response in the absence of a *CSF3R* mutation. In addition to decreases in leukocytosis and splenomegaly, hematologic improvement (decreases in anemia and/or thrombocytopenia) was noted in 10 patients in this trial. Median OS for all patients in the study (including those with aCML) was 18.8 months, and in the responders, median OS was 23.2 months. No difference in survival was noted according to the diagnosis (CNL vs aCML) or *CSF3R* mutational status. Expansion of *STAT3*-mutant clones was noted in 2 patients at the time of disease progression, which shed some light on a potential mechanism of resistance to ruxolitinib. Although prior studies had suggested that concomitant *SETBP1* mutations may confer resistance to ruxolitinib,^{54,55} this was not confirmed in the study.⁵⁰

Other agents that have been successfully used in small numbers of patients include interferon alfa and imatinib.^{8,56} Hypomethylating agents, either azacitidine or decitabine, can be considered in patients with resistant/progressive disease and those with increasing bone

marrow or peripheral blood blasts.⁵⁷ The use of induction-type chemotherapy in CNL is limited by its toxicity and modest activity.⁸

Atypical CML and MDS/MPN-U

We commonly initiate cytoreduction with hydroxyurea in patients who have aCML or MDS/MPN-U and whose disease is proliferative (ie, progressive leukocytosis, symptomatic splenomegaly), including those with minimally increased bone marrow/peripheral blood blasts.⁵⁸ Responses to hydroxyurea, including significant reductions in leukocytosis and splenomegaly, have been reported in small series of patients with aCML, although the responses are usually short-lived.⁵⁹ As in patients with MDS and MPNs, erythropoietin-stimulating agents can be considered in those with symptomatic anemia and a suboptimal response to endogenous erythropoietin (eg, serum erythropoietin <500 mU/mL).⁵⁸ In patients with *CSF3R* mutations, the use of ruxolitinib can be considered in the absence of increased bone marrow/peripheral blood blasts or severe thrombocytopenia (eg, platelet count <25×10⁹/L). In the trial by Dao and colleagues, previously discussed, 1 of 6 patients with aCML and a concomitant *CSF3R* mutation responded to ruxolitinib (partial response).⁵⁰ IFN alfa can be also considered. In a phase 2 study of pegylated IFN alfa-2b, 2 of the 5 patients with aCML achieved a complete response after a median of 3 months, with the responses lasting for a median of 37 months.⁶⁰

In patients not responding to cytoreduction, as previously discussed, or in those with a significant increase in blasts, hypomethylating therapy with either azacitidine or decitabine can be considered. This recommendation is based on case reports and retrospective experience.^{42,61-64} In the largest study of MDS/MPN-U, hypomethylating agents were given to 59 patients, and of the 27 patients who received at least 6 cycles, 7 (26%) achieved either a complete remission (n=1), partial remission (n=2), marrow response (n=3), or complete cytogenetic remission (n=1) according to the MDS/MPN International Working Group response criteria.^{42,65}

The combination of ruxolitinib and azacitidine was explored in a phase 2 study of CMML (n=17), aCML (n=4), and MDS/MPN-U (n=14), with objective responses seen in 57% according to the International Working Group criteria.⁵¹ These included spleen responses in 9 of 14, symptom reduction in 14 of 18, transfusion independence in 1 of 11, partial marrow response in 9 of 22, optimal marrow response in 1 of 22, and reduction in marrow blasts to less than 5% in 7 of 10 patients. The median duration of response was 8 months. The median OS for the study population was 16.6 months, and OS was significantly better in the patients with MDS/MPN-U

than in those with CMML or aCML (26.5, 15.1, and 8 months, respectively).

If the NGS panel results uncover a druggable acquired somatic variant or variants, targeted therapy approaches may be considered. For example, the use of MEK inhibition with trametinib (Mekinist, Novartis) resulted in a sustained remission in a patient with aCML harboring a *KRAS* G12D mutation.⁶⁶ Other currently targetable mutations, such as *FLT3* and *IDH1/2* mutations, are uncommon in these disorders.^{6,7} As in CNL, the role of induction-type chemotherapy is limited in aCML and MDS/MPN-U but can be considered in young, fit patients with accelerated or blast-phase disease as a bridge to HSCT.

Hematopoietic Stem Cell Transplant

Allogeneic HSCT is the only potentially curative therapeutic option for patients with these neoplasms; however, a limited number of patients are eligible for this treatment modality. In CNL, experience with HSCT is limited to case reports and small case series.⁶⁷⁻⁷⁰ In a retrospective nationwide study in Japan that included 5 patients with CNL, 2 received unrelated bone marrow, 2 received unrelated cord blood, and 1 received a transplant from an HLA-haploidentical sibling donor; all but 1 patient achieved complete remission after transplant, and 2 remained in remission at 362 and 441 days after HSCT.⁶⁸ The 1-year probability of survival after HSCT was 40%. The *CSF3R* mutation⁷¹ and other mutations⁷² may serve as useful biomarkers to predict post-transplant relapse in these disorders.

In the largest retrospective study of transplant outcomes in patients with aCML reported to the European Society for Blood and Marrow Transplantation registry, 42 patients were analyzed; the median age was 46 years, and 69% were in chronic phase.⁷³ Donors were HLA-identical siblings in 64% of cases, and myeloablative conditioning was used in 76% of patients. The median OS after HSCT was 70 months, and 87% of patients achieved a complete remission. At 5 years, the relapse-free survival rate was 36%, the non-relapse mortality rate was 24%, and relapse had occurred in 40%.⁷³ In a retrospective study of 86 patients with MDS/MPN-U from the Japan Society for Hematopoietic Stem Cell Transplantation, 72% had unrelated donors and 63% underwent myeloablative conditioning. The 3-year OS rate was 48.5%, with a non-relapse mortality rate of 26.3% and a cumulative incidence of relapse of 23.7%.⁷⁴

Conclusion

Neutrophilic myeloid neoplasms are rare disorders with overlapping clinical and morphologic features. Except for

CML and the classic Ph chromosome–negative MPNs, they carry a poor prognosis, and treatment options are limited. Allogeneic HSCT remains the only therapeutic modality with the potential to achieve prolonged survival, and it should be considered for suitable patients with CNL, aCML, or MDS/MPN-U. Recent advances in the molecular annotation of these diseases have afforded new therapeutic avenues, such as JAK/STAT pathway inhibition with ruxolitinib in CNL. Deciphering molecular evolution at the time of leukemic transformation and mechanisms of resistance to targeted therapies will further guide the development of rational approaches to treatment.

Disclosures

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