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LEUKEMIA (A AGUAYO, SECTION EDITOR)

Chronic Myelomonocytic Leukemia: Insights into Biology, Prognostic Factors, and Treatment

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Abstract

Purpose of Review Chronic myelomonocytic leukemia (CMML) is a clonal hematological malignancy characterized by both dysplastic and proliferative features, with an inherent risk for leukemic transformation. With the help of this review, we aim to summarize key concepts with regards to CMML biology, diagnosis, risk stratification, and therapeutics.

Recent Findings Based on recent studies, CMML is hallmarked by a relatively low genetic complexity, which contrasts with a compelling phenotypical heterogeneity, largely driven by epigenetic mechanisms. Recent advances in the characterization of CMML biology has led to an improvement in risk-stratification, by means of incorporating prognostically relevant gene mutations. This, however, has not significantly impacted available therapies and outcomes continue to remain poor.

Summary Advances in CMML biology have better explained the phenotypic heterogeneity, while continuing to define the genetic and epigenetic landscape. In spite of recent advances, limited effective therapies exist and developing rationally derived therapeutic approaches is much needed.

Keywords Chronic myelomonocytic leukemia · Myelodysplastic syndromes · Myeloproliferative neoplasms · Clonal architecture · Prognostication · Target therapy

Abbreviations

ASXL1	Additional sex combs like 1
BAP1	BRCA1-associated protein 1
BCOR	BCL6 corepressor
CBL	Cbl proto-oncogene
CSF3R	Colony-stimulating factor 3 receptor
DNMT3A	DNA methyltransferase 3 alpha
EZH2	Enhancer of zeste 2 polycomb repressive complex 2 subunit
FLT3	Fms-related tyrosine kinase 3
IDH1/IDH2	Isocitrate dehydrogenase 1/2
JAK2	Janus kinase 2
NPM1	Nucleophosmin 1
NRAS	Neuroblastoma RAS viral oncogene homolog
PHF6	Plant homeodomain finger protein 6
PRC1/2	Polycomb repressive complex 1/2
PTPN11	Protein tyrosine phosphatase non-receptor type 11
RUNX1	Runt-related transcription factor 1
SETBP1	SET binding protein 1
SF3B1	Splicing factor 3b subunit 1
SRSF2	Serine and arginine rich splicing factor 2
TET2	Tet methylcytosine dioxygenase 2
TP53	Tumor protein P53
U2AF1	U2 small nuclear RNA auxiliary factor 1
SPRY2	Sprouty RTK signaling antagonist 2
US FDA	United States Food and Drug Administration
ZRSR2	Zinc finger CCCH-type RNA binding motif and serine/arginine rich 2

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Introduction

Chronic myelomonocytic leukemia (CMML) is a clonal hematopoietic stem cell-derived disorder characterized by abnormal bone marrow (BM) production of monocytes resulting

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in absolute ($\geq 1 \times 10^9$/L) and relative (> 10%) peripheral blood (PB) monocytosis, dysplasia in any or all hematopoietic cell lineages, and inherent risk of clonal evolution to acute leukemia. Historically, CMML had been long considered as a separate subtype among myelodysplastic syndromes (MDS) [1]. However, in 2001, the World Health Organization (WHO) proposed and further consolidated a new group of myeloid disorders with pathoclinical features of both MDS and myeloproliferative neoplasms (MPN), known as MDS/MPN overlap syndromes, within which CMML is the most frequent entity [2].

CMML is a relatively rare disease, with an approximated incidence of 0.3 to 0.7 per 100,000 person-years, a median age at diagnosis of 71–74 years, and a strong male predominance (M:F ratio, 1.5/3:1) [3–6]. It is a very heterogeneous disease with a unique biological diversity that is appreciable at several levels, ranging from morphologic features, clinical manifestations, natural history, and treatment responses. Clinical heterogeneity is broadly captured by the historical categorization into "proliferative" type (MPN-CMML) and "dysplastic" type (MDS-CMML) CMML, based on the presence of a white blood cell (WBC) count $\geq 13 \times 10^9$/L in the former [1].

CMML Biology

Over the last two decades, comprehensive mutational studies based mainly on next-generation sequencing technologies have scripted the mutational landscape of CMML and have identified recurrent mutated genes involved in epigenetic regulation (*TET2* 60%, *ASXL1* 40%), pre-messenger RNA splicing (*SRSF2* 40%), and cell signaling (oncogenic *RAS* pathway 30%) (Fig. 1b) [7, 8••, 9••]. Surprisingly, these studies show that the clinical heterogeneity of CMML contrasts with a relatively limited molecular diversity [7, 8••, 9••, 10•, 11]. In CMML, the prevalence of somatic mutations per exome (10–15 mutations/kilobase of coding region) is far lower than solid tumors and comparable to; if even lower than MDS and AML [7, 8••, 10].

Seminal work mapping clonal architecture in 28 CMML cases at a single cell level showed that early clonal dominance is a key feature of the disease, generally arising at a very early ($CD34^+/CD38^-$) stage of hematopoiesis, and is accompanied by granulomonocytic differentiation skewing [11]. Although the order of mutation acquisition is not stereotyped, aberrations in epigenetic and splicing regulators frequently precede mutations in signaling pathways. Accordingly, Tet methylcytosine dioxygenase 2 (*TET2*) mutations are the more common lesions involved in early clonal dominance and are frequently associated with splicing genes lesions, most commonly serine and arginine rich splicing factor 2 (*SRSF2*). The acquisition of additional genetic aberrations occurs mostly linearly with a low rate of branching, often resulting from loss of heterozygosity following mitotic recombination, conferring a selective growth advantage that is proportional to the number of mutations in subclones [11]. Finally, transformation of CMML to acute myeloid leukemia (AML) is still largely genetically determined and is probably driven by the acquisition of novel genetic lesions, such as additional sex combs like 1 (*ASXL1*) and oncogenic *RAS* pathway mutations, with high fitness and congruent massive expansion of newly mutated subclones (Fig. 1a). On this basis, CMML clinical heterogeneity, at least in part, is driven by different clonal evolution trajectories of the founding pre-leukemic clone.

CMML Diagnosis

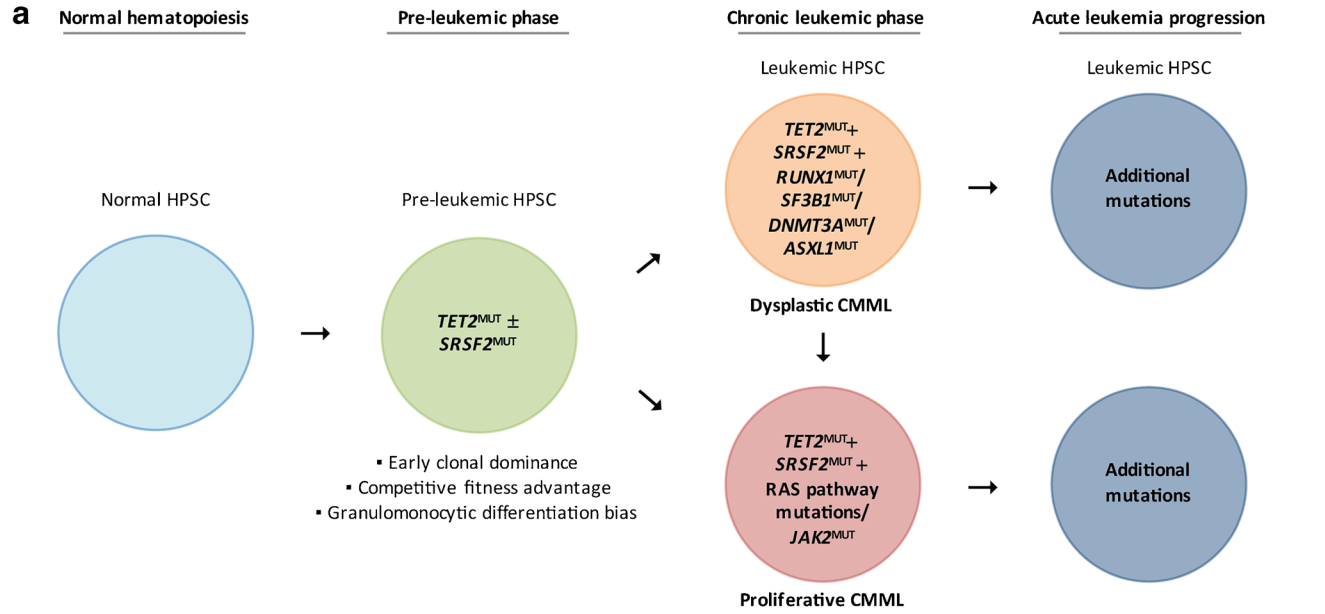
According to the WHO 2016 diagnostic criteria, PB monocytosis is the sine qua non in CMML diagnosis (Supplementary Table 1 and 2) [2]. However, monocytosis is not an infrequent finding, largely seen to be reactive in the context of infections, inflammation, and autoimmune diseases and can occur in other myeloid neoplasms such as MPN. Thus, it is mandatory that the diagnostic algorithm for CMML is based on the integration of morphologic, immunophenotypic, cytogenetic, and molecular assessments, in order to exclude reactive and other clonal causes of monocytosis.

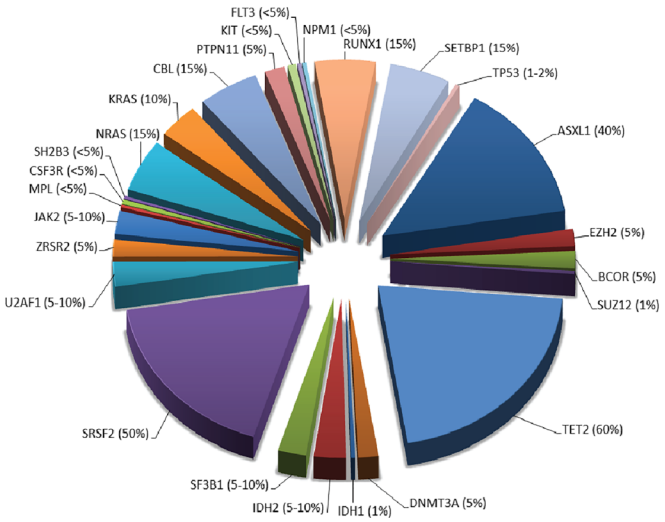
(a) Morphology

Despite recent advances, diagnosis of CMML remains largely based on morphologic evaluation of both PB and BM. At the PB smear examination, monocytes are increased in number and usually appear mature, but can display nuclear and cytoplasmic abnormalities and be accompanied by immature forms such as promonocytes (Fig. 1c). Neutrophilia along with dysgranulopoiesis can also be seen (Fig. 1c). Circulating immature myeloid cells (IMCs; metamyelocytes, myelocytes, and promyelocytes) may be present and usually constitute < 10% of WBC differential count. Despite the absence of single pathognomonic features, BM is usually hypercellular with prominent granulocytic hyperplasia and dysplasia in any or all hematopoietic lineages. The differentiation of normal and abnormal monocytes from their precursors requires high expertise and is formally indispensable for CMML diagnosis, since monoblasts and promonocytes are considered as blast equivalents and should be included in the blast count [2].

(b) Immunohistochemistry and cytochemical stains

In an attempt to distinguish monocytes from monoblasts, promonocytes, and other myeloid cells, morphologic assessment of BM is frequently supported by cytochemical and immunohistochemical studies. Monocytes are generally positive for lysozyme, alpha-naphthyl butyrate (nonspecific) esterase, and alpha-





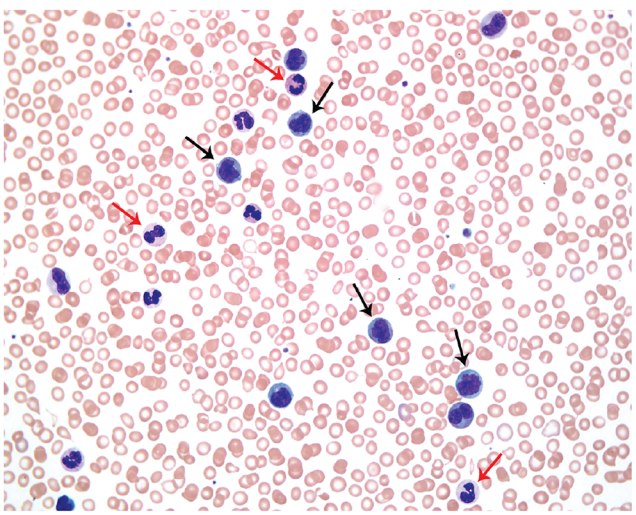


Fig. 1 **a** Schematic representation of clonal onset and evolution of chronic myelomonocytic leukemia (CMML). Mutations in *TET2* are thought to represent an early event that occurs at the hematopoietic stem cell level, with or without other lesions in epigenetic and splicing genes, most frequently *SRSF2*. *TET2* mutations confer a competitive fitness advantage to the mutated clone, thus resulting in early clonal dominance and granulomonocytic differentiation skewing. The acquisition of additional mutations at later stages of differentiation contributes to full-blown phenotypical expression and differentiation of the disease. For example, the acquisition of mutations in *RUNX1* or *SF3B1* leads typically to the development of dysplastic features, with the former frequently associated with thrombocytopenia and the latter with erythroid dysplasia and ring sideroblasts. Alternatively, but similarly, mutations in RAS pathway genes, such as *NRAS*, *KRAS*, and *CBL*, can be acquired at different later phases of clonal hematopoiesis and promotes the expansion of myelomonocytic compartment, resulting in the myeloproliferative phenotype of CMML. Finally, transformation to acute myeloid leukemia is still genetically determined and is driven by the acquisition of novel genetic lesions with high fitness and congruent massive expansion of newly mutated subclones. This model only aims to provide a general overview of clonal evolution in CMML and does not account for genetic and phenotypic heterogeneity of the disease. **b** Pie-chart illustrating spectrum and frequency of gene mutations in CMML. **c** Peripheral blood smear of a patient with CMML showing presence of abnormal monocytes and promonocytes (black arrows) and dysplastic neutrophils (red arrows) (Wright-Giemsa, × 100 magnification). Monocytes are usually increased in number and can appear mature or display nuclear and cytoplasmic abnormalities such as nuclear lobulation, hypergranulation, and increased cytoplasmatic basophilia. Neutrophilia is a frequent finding and may be accompanied by dysgranulopoiesis, including pseudo-Pelger-Huët anomaly and hypogranulation

naphthyl acetate esterase and stain negative with naphthol AS-D chloroacetate esterase. On immunohistochemistry, the most reliable markers include CD14, CD16, CD68R (PG-M1), CD11c, and CD123, while CD34 is useful to detect the increased number of blasts seen in aggressive cases of the disease [12].

(c) Flow cytometry

Multiparametric flow cytometry allows differentiating various stages of monocytic differentiation based on diverse expression of myelomonocytic markers (CD13 and CD33) and other antigens, such as CD14, CD64, and CD68. In addition, abnormal expression of myeloid antigens in terms of loss and/or altered antigen density (CD13, CD14, CD34, HLA-DR, CD36), and aberrant expression of non-myeloid antigens (CD2, CD15, CD56), are frequently seen in both monocytic and granulocytic population. In recent years, flow cytometry has emerged as a powerful tool able to address CMML diagnosis by distinguishing different monocyte subpopulation. Based on current nomenclature, human monocytes can be immunophenotypically classified into three subsets with distinctive gene expression profile and phagocytic activities that are independent of the mutational background [13–15]: $CD14^{+}/CD16^{-}$ classical monocytes (MO1), that represent about 85% on monocytic population in healthy conditions; $CD14^{+}/CD16^{+}$ intermediate monocytes (MO2); and $CD14^{low}/CD16^{+}$ non-classical monocytes (MO3). Compared with healthy donors and patients with reactive monocytosis and non-CMML myeloid malignancies, CMML patients are typically enriched in the MO1 fraction, with a cut off value of 94% providing a specificity and sensibility both > 90% [15]. Importantly, this repartitioning corrected in CMML patients that were treated with hypomethylating agents (HMA) and did have a response, thus potentially serving as a biomarker for response assessment [15]. Subsequent studies demonstrated that this flow cytometry-based assay effectively distinguishes between CMML and MPN with monocytosis [16], and can identify MDS patients without monocytosis who eventually develop CMML [17].

(d) Cytogenetic abnormalities

Cytogenetic abnormalities occur in ~ 20–30% of patients with CMML, with a higher prevalence in CMML-2; with frequent abnormalities being + 8, − Y, del(20q), + 21, −7 and del(7q) (Supplementary Table 3) [6, 18–20]. Unlike in MDS, sole del(5q) and monosomal karyotypes are uncommon in CMML [21–23]. The Spanish group identified three cytogenetic categories with independent prognostic value that were integrated into the CMML-specific cytogenetic risk stratification (CPSS) system [19]: low risk (normal karyotype or sole − Y), intermediate risk (all other abnormalities not included in the low and high risk categories), and high risk (+ 8, chromosome 7 abnormalities, or complex karyotype). The 5-yeasr OS was 35%, 26%, and 4%, respectively [19]. Recently, an international collaborative study investigated cytogenetic and molecular abnormalities in a Mayo Clinic-French consortium cohort of 409 CMML patients. Thirty percent displayed an abnormal karyotype, with the most common cytogenetic alterations including + 8 (23%), − Y (20%), − 7/7q-(14%), 20q- (8%), +21 (8%), and der(3q) (8%) [23]. Upon a stepwise survival analysis, the Mayo-French cytogenetic risk stratification system was developed which included three distinct cytogenetic risk categories: low risk [normal karyotype, sole − Y, or sole der (3q)], intermediate risk (all abnormalities not included in the high or low risk groups), and high risk (complex or monosomal karyotypes), with median OS of 3, 21, and 41 months, respectively [23].

(e) Genetic abnormalities

Genetic abnormalities can be broadly classified into the following categories (Supplementary Table 4):

i. Mutation in epigenetic regulators of methylation—*TET2*, DNA methyltransferase 3 alpha (*DNMT3A*), isocitrate dehydrogenase 1 (*IDH1*), and isocitrate dehydrogenase 2 (*IDH2*)

Disruption of epigenetic mechanisms, which mainly include post-translational modification of histone proteins and DNA methylation at cytosine bases, is a well-established hallmark of cancer. The *TET2* gene encodes the second member of TET protein family, involved in the stepwise oxidation of 5-methylcytosine (5mC) to 5-hydroxyymethylcytosine (5hmC). This gene is located on chromosome 4q24, a region prone to recurrent mutations as well as microdeletions, copy-neutral loss of heterozygosity, and rare translocations. In CMML, *TET2* mutations are seen in ~ 60% of patients and, as expected, are associated with abnormalities in global methylation patterns [24–26]. As iterated before, in CMML mutations in *TET2* represent early, driving genetic events establishing pre-leukemic clonal hematopoiesis, but need other mutations for the development of a leukemic phenotype [9••, 11, 27]. Data on the prognostic relevance of *TET2* mutations in CMML are discordant, with some studies supporting either favorable [28, 29], unfavorable [30], or no impact on OS [24, 31]. Recent studies have confirmed the negative prognostic impact of *ASXL1* mutations on OS and have highlighted a favorable prognostic impact imparted by $TET2^{MUT}$ in the absence of *ASXL1* mutations [8••, 32•].

DNMT3A belongs to a family of highly conserved DNA methyltransferases, which are involved in either de novo DNA methylation (DNMT3A and DNMT3B) or maintenance of pre-existing methylation patterns throughout cell division (DNMT1) [33]. Mutations in *DNMT3A* occur in diverse hematological malignancies and are seen in ~ 5% of CMML patients.

We recently demonstrated that *DNMT3A* mutations independently and adversely impact both OS and LFS in CMML patients [34].

Two other epigenetic regulators, with functions involved in both DNA methylation and histone modification, are encoded by *IDH1* and *IDH2* genes. IDH1/2 enzymes participate in the tricarboxylic acid cycle and catalyze the formation of alpha-ketoglutaric acid (α-KG) from isocitrate. *IDH1/2* mutations mostly occur at substrate-binding specific amino acid residues (*IDH1* Arginine140, *IDH2* Arginine142, and Arginine170) and are neomorphic, leading to production and accumulation of the oncometabolite D-2-hydroxyglutarate (D-2HG) [35]. D-2HG, in turn, disrupts cellular metabolism and epigenetic regulation interfering the activity of numerous α-KG-dependent enzymes, such as TET2 and diverse histone lysine demethylases, eventually contributing to leukemogenesis [36]. Mutations involving *IDH1* and *IDH2* are uncommon in CMML (1% and 5–10%, respectively), are considered mutually exclusive with *TET2* mutations, and have thus far lacked an independent prognostic impact [24, 37], but present therapeutic options with IDH1/2 inhibitors.

ii. Mutations in chromatin regulating genes—*ASXL1*, enhancer of zeste 2 polycomb repressive complex 2 subunit (*EZH2*), BCL6 corepressor (*BCOR*), and *SUZ12*

The *ASXL1* gene encodes a chromatin-binding protein of the polycomb family involved in the epigenetic regulation of gene expression through the interaction with polycomb repressive complex 1 (PRC1), polycomb repressive complex 2 (PRC2), and other transcription activators and repressors [38, 39]. Canonical PRC1 and PRC2 catalyze the monoubiquitination of histone H2A at lysine 119 (H2AK119ub1) and the mono-, di-, and trimethylation of histone H3 at lysine 27 (H3K27me1/2/3), respectively, which eventually play an important role in maintaining transcriptional repression. In a seminal paper, Abdel-Wahab et al. demonstrated that loss of ASXL1 resulted in global reduction of PCR2-mediated H3K27me3 levels [40]. In addition, ASXL1 interacts with BRCA1-associated protein 1 (BAP1) in a repressive deubquitylase complex, and pathogenic mutations of *ASXL1* encodes truncated protein products that increase the deubiquitination activity of BAP1, resulting in global erasure of H2AK119ub1 and depletion of H3K27me3 [41, 42]. About 40% of CMML patients display *ASXL1* mutations [23, 24]. Several studies identified nonsense and frameshift mutations, but not missense variants, of *ASXL1* as having an independently adverse impact on overall survival (OS) [7, 24, 43–46]. These findings led to their incorporation into recent prognostic models. The *EZH2* gene encodes a histone lysine *N*-methyltransferase and represents the enzymatic component of the PRC2. Loss-of-function mutations in *EZH2* are found in around 5% of CMML patients, where they are frequently associated with a proliferative phenotype and almost invariably co-occur with *ASXL1* mutations [47]. Mutations involving *BCOR* and *SUZ12* are uncommon (< 5%) and have an indeterminate prognostic impact.

iii. Pre-mRNA splicing mutations—splicing factor 3b subunit 1 (*SF3B1*), *SRSF2*, U2 small nuclear RNA auxiliary factor 1 (*U2AF1*), zinc finger CCCH-type RNA binding motif and serine/arginine rich 2 (*ZRSR2*)

Mutations in genes encoding regulators of spliceosome machinery can be observed in more than 60% of CMML patients and are in general mutually exclusive. Among these genes, *SRSF2* is the most frequently mutated (~ 50% of patients), with mutations almost exclusively occurring at the Proline95 residue [48]. Mutations involving *SF3B1* are less common (< 10%), and are frequently seen in CMML patients with BM RS [6]. Thus far, spliceosome component mutations have not been shown to independently impact prognosis in CMML [6, 24, 48].

iv. Cell signaling pathway mutations

Mutations in oncogenic *RAS* pathway genes (*NRAS*, *KRAS*, *NF1*, *CBL*, *PTPN11*) are documented in 30–40% of CMML patients and are typically associated with MPN features and high spontaneous myeloid colony growth [49–51]. The prognostic impact of *RAS* mutations remains unclear, with some studies, but not all, demonstrating inferior outcomes [18, 24, 46]. $JAK2^{V617F}$ is the predominant MPN associated-driver mutation in CMML (~ 9%) and is associated with MPN phenotype, higher hemoglobin/hematocrit, WBC and platelet counts, normal karyotype, and co-occurring *TET2* mutations, without any impact of survival [52].

v. Mutations in transcription factors and nucleosome assembly—Runt-related transcription factor 1 (*RUNX1*), SET binding protein 1 (*SETBP1*)

Mutations in *RUNX1* gene, encoding the DNA-binding subunit of the core binding factor involved in regulation of normal hematopoiesis, are found in ~ 15% of CMML patients [24, 53]. *RUNX1* mutations may be associated with a higher risk of leukemic progression, especially for lesions located in the C-terminal region [53]. Furthermore, one recent study

found *RUNX1* mutations being independently associated with shortened OS [46]. *SETBP1* gene encodes a nuclear protein that binds the multifunctional SET oncoprotein, and mutations in *SETBP1* are seen in ~ 10–15% of CMML cases. The prognostic significance of *SETBP1* mutations is controversial, with some, but not all studies demonstrating inferior outcomes [7, 33, 46, 54, 55].

vi. Mutations involving DNA damage response genes—tumor protein P53 (*TP53*), plant homeodomain finger protein 6 (*PHF6*)

TP53 mutations are extremely rare in CMML (< 1%), with most cases occurring in the context of therapy related neoplasms [56]. *PHF6* has been suggested to act as a tumor suppressor gene involved in rRNA synthesis and mutations are rare in CMML (< 5%) [57].

CMML Prognostication

CMML is a heterogeneous disease with median OS ranging from less than 1 year to over 50 months and an estimated 15–30% risk of leukemic transformation [5, 7, 58]. Initially, prognostication was based on models primarily developed for MDS patients, such as the international prognostic scoring system (IPSS) and its subsequent revision (IPSS-R) [59, 60]. These models excluded patients with MPN-CMML.

In 2002, Onida et al. developed the first CMML-specific prognostic system, called M.D. Anderson prognostic score (MDAPS), which included hemoglobin (Hb) level < 12 g/dL, presence of circulating IMCs, absolute lymphocyte count > 2.5×10^9/L, and BM blasts ≥ 10% as independent predictors for inferior OS (Table 1) [18]. Subsequently, the MDAPS was applied on the Düsseldorf CMML cohort: the prognostic impact of circulating IMCs was not confirmed in univariate analysis, while male gender, elevated lactate dehydrogenase (LDH), Hb < 12 g/dL, ALC > 2.5×10^9/L, and BM blast count > 10% were found as independent predictors of inferior OS. In 2008, the global MDAPS was developed for patients with de novo MDS, secondary MDS, therapy-related MDS and CMML. The model included age ≥ 65 years, poor performance status, thrombocytopenia, anemia, increased BM blasts, leukocytosis, chromosome 7 abnormalities or complex karyotype, and a prior history of red blood cell (RBC) transfusions as independent predictor of inferior OS [61].

The CPSS model was developed in 2013 based on the analysis of a Spanish cohort of 558 patients, and validated using an independent cohort of 274 patients [5]. The model included four variables being prognostic for both OS and leukemia-free survival (LFS): WHO CMML-2 subtype, FAB MPN-CMML subtype, intermediate and high cytogenetic risk per the Spanish cytogenetic risk stratification system, and RBC transfusion dependency [5]. Based on these variables, the CPSS was able to identify four risk categories: low, intermediate-1, intermediate-2, and high risk, with median OS of 72, 31, 13, and 5 months, respectively [5].

The increasing knowledge of genetic landscape of CMML and its prognostic relevance led to incorporation of molecular aberrations into prognostic model. In 2013, a Mayo Clinic study was conducted on 226 CMML patients and identified hemoglobin level < 10 g/dL, absolute monocyte count (AMC) > 10×10^9/L, platelet count < 100×10^9/L, and presence of circulating IMCs as risk factors with independent prognostic impact on OS [62]. Genetic analysis involved *ASXL1* (missense, nonsense, and frameshift mutations), *SF3B1*, *SRSF2*, and *U2AF35*; pathogenic mutations in neither of the four genes did not impact either OS or LFS [62]. The Mayo prognostic model was developed and was able to stratify patients into three risk categories: low, intermediate, and high risk, with median OS of 32, 18.5, and 10 months, respectively [62].

Subsequently in 2013, the Groupe Francophone des Myelodysplasies (GFM) model was published by the French group after analyzing a cohort of 312 CMML patients [24]. Nonsense and frameshift *ASXL1* mutations, in addition to age ≥ 65 years, WBC count ≥ 15×10^9/L, platelet count < 100×10^9/L, and Hb < 10 g/dL in females and < 11 g/dL in males, were identified as risk factor with an independent prognostic impact [24]. The model defined three risk categories: low, intermediate, and high risk; respective median OS were not reached, 38.5, and 14.4 months [24].

Lack of an association between *ASXL1* mutations and shorter survival times in the Mayo prognostic model could be explained considering that in the Mayo study all missense, nonsense, and frameshift mutations were included, while the French analysis considered only nonsense and frameshift variants. Accordingly, an international collaborative study conducted in 2014 on a combined Mayo-French cohort demonstrated that nonsense and frameshift mutations of *ASXL1* retained an independent prognostic impact in a multivariable model [7]. Additional risk factor included AMC > 10×10^9/L, platelet count < 100×10^9/L, Hb < 10 g/dL, and presence of circulating IMCs [7]. The Mayo molecular model was developed providing a four-tiered risk categorization: low, intermediate-1, intermediate-2, and high risk. Median OS was 97, 59, 31, and 16 months, respectively [7].

Recently, the Spanish group updated the CPSS model into the clinical/molecular CMML-specific prognostic scoring system (CPSS-Mol), which includes a combination of clinical and molecular variables [46]. Cytogenetic abnormalities and mutations in *ASXL1* (nonsense/frameshift variants), *RUNX1*, neuroblastoma RAS viral oncogene homolog (*NRAS*) and *SETBP1* were found to be associated to a shortened OS. These four mutations and the prior Spanish cytogenetic risk stratification system were integrated to define the CMML-specific genetic score [46]. One point each was assigned to

Table 1 Main prognostic scoring models for risk assessment of CMML

Prognostic model	Year	Number of patients	Variables included	Risk categories (points/risk factors)	Median OS	Risk of leukemic transformation
MDAPS Onida et al. [18]	2002	213	• ALC > 2.5×10^9/L • Presence of circulating IMCs • Hb < 12 g/dL • BM blasts > 10%	Low (0–1) Intermediate-1 (2) Intermediate-2 (3) High (4)	24 months 15 months 8 months 5 months	Not reported
Global MDAPS Kantarjian et al. [61]	2008	958 (84% MDS, 16% CMML)	• Performance status ≥ 2 (2 points) • Age 60–64 years (1 point)/≥ 65 years (2 points) • WBC > 20×10^9/L (2 points) • Platelet count 50-199 × 10^9/L (1 point)/ 30–49 × 10^9/L (2 points)/< 30×10^9/L (3 points) × 10^9/L • Hb < 12 g/dL (2 points) • BM blasts 5–10% (1 point)/11–29% (2 points) • Chr7 abnormalities or complex karyotype (3 points) • RBC transfusion dependence (1 point)	Low (0–4) Intermediate-1 (5–6) Intermediate-2 (7–8) High (9–15)	54 months 25 months 14 months 6 months	Not reported
CPSS Such et al. [5]	2013	558	• FAB MPN-CMML subtype (1 point) • WHO CMML-2 subtype (1 point) • Intermediate (1 point) or high (2 points) • cytogenetic risk[a] • d. RBC transfusion dependence[c] (1 point)	Low (0) Intermediate-1 (1) Intermediate-2 (2–3) High (4–5)	72 months 31 months 13 months 5 months	AML risk at 5 years: 13% AML risk at 5 years: 29% AML risk at 5 years: 60% AML risk at 5 years: 73%
Mayo prognostic model Patnaik et al. [62]	2013	226	• AMC > 10×10^9/L • Presence of circulating IMCs • Hb < 10 g/dL • d. Platelet count < 100×10^9/L	Low (0) Intermediate (1) High (2–4)	32.0 months 18.5 months 10.0 months	Not reported
GFM model Itzykson et al. [24]	2013	312	• Age > 65 years (2 point) • WBC count > 15×10^9/L (3 points) • Hb < 10 g/dL (♀)/< 11 g/dL (♂) (2 points) • Platelets < 100×10^9/L (2 points) • *ASXL1* mutations (nonsense or • frameshift) (2 points)	Low (0–4) Intermediate (5–7) High (8–12)	Not reached 38.5 months 14.4 months	Median LFS: 56.0 months Median LFS: 27.4 months Median LFS: 9.2 months
Mayo molecular model Patnaik et al. [7]	2014	466	• AMC > 10×10^9/L (2 points) • Presence of circulating IMCs (2 points) • Platelet count < 100×10^9/L (1.5 points) • *ASXL1* mutations (nonsense or • frameshift) (1.5 points)	Low (0/0) Intermediate-1 (1–2/1) Intermediate-2 (2.5–4.5/2) High (5–9/3–5)	97 months 59 months 31 months 16 months	Not reported
CPSS-Mol Elena et al. [46]	2016	214	• WBC count ≥ 13×10^9/L (1 points) • BM blasts ≥ 5% (1 points) • RBC transfusion dependence[c] (1 point) • Intermediate (1 point), intermediate-2 (2 • points) or high (3 points) genetic risk[b]	Low (0) Intermediate-1 (1) Intermediate-2 (2–3) High (4–6)	Not reached 64 months 37 months 18 months	AML risk at 4 years: 0% AML risk at 4 years: 3% AML risk at 4 years: 21% AML risk at 4 years: 48%

ALC absolute lymphocyte count, *AMC* absolute monocyte count, *AML* acute myeloid leukemia, *ASXL1* additional sex combs like 1, *BM* bone marrow, *CMML* chronic myelomonocytic leukemia, *CPSS* CMML-specific prognostic scoring system, *CPSS-Mol* clinical/molecular CMML-specific prognostic scoring system, *FAB* French-American-British, *GFM* Groupe Francophone des Myelodysplasies, *Hb* hemoglobin, *IMCs* immature myeloid cells, *LFS* leukemia-free survival, *MDAPS* M.D. Anderson prognostic score, *MDS* myelodysplastic syndrome, *NRAS* neuroblastoma RAS viral oncogene homolog, *OS* overall survival, *RBC* red blood cell, *RUNX1* Runt-related transcription factor 1, *SETBP1* SET binding protein 1, *WBC* white blood cell

[a] As defined by the Spanish cytogenetic risk stratification system

[b] As defined by the CMML-specific genetic score: intermediate (1 point) or high (2 points) cytogenetic risk per the Spanish cytogenetic risk stratification system, ASXL1 (nonsense and frameshift), RUNX1, NRAS, and SETBP1 mutations (1 point each); low genetic risk (0 points), intermediate-1 genetic risk (1 points), intermediate-2 genetic risk (2 points), high genetic risk (3–6 points)

[c] RBC transfusion dependency was defined as having at least 1 RBC transfusion every 8 weeks over a period of 4 months

WBC count ≥ 13 × 109/L, BM blasts ≥ 5%, RBC transfusion dependency, and intermediate-1 genetic risk group; two points to intermediate-2 genetic risk group; and three points to high risk genetic risk group. In the resulting four-tiered model, patients were stratified in low, intermediate-1, intermediate-2, and high risk, with median OS of not reached, 64, 37, and 18 months. The respective 4-year leukemic transformation rates were 0%, 3%, 21%, and 48% [46].

Overall, risk assessment of CMML patients can be very challenging. Physicians have access to a large number of prognostic models and the international working group (IWG) for CMML is currently working on integrating clinical and molecular parameters, so as to develop a uniform prognostication system.

Therapy

CMML is primarily a disease of the elderly and remains incurable for patients who are not successful recipients of allogenic stem cell transplantation (alloHCT). Given the lack of disease-modifying therapies and the heterogeneous, ever-changing clinical features of CMML, therapy is mainly guided by risk stratification and specific patient's clinical needs. Overall, there are no CMML-specific recommendations and treatment is substantially based on existing guidelines that have been extrapolated from MDS and MPN. Recently, the IWG has proposed MDS/MPN response criteria, which take into account both dysplastic and proliferative features and have been validated retrospectively [63, 64]. Our approach to CMML patients is addressed as follows:

Symptom Management

Erythropoiesis-stimulating agents (ESA) are commonly used for treatment-requiring anemia. In the only published series on CMML cases treated with ESA [65], 64% of patients achieved erythroid response (ER) and 31% RBC transfusion independence, with low/intermediate-1 risk according to CPSS and a low endogenous serum EPO level being independent predictors of ER. However, we recommend a careful use of ESA in patients with MPN-CMML because of the inherent risk of splenic rupture [66]. Management of RBC transfusional support is generally based on similar recommendations for MDS. We routinely do not use iron chelation therapy, given the side effect profile of the drugs and lack of prospective evidence-based data in CMML. Exceptions to this being lower risk CMML patients, with prolonged survival, who are transfusion dependent and have an adequate renal function. Sotatercept and luspatercept, two first-in-class novel agents targeting late-stage erythropoiesis through inhibition of transforming growth factor β signaling, are currently in development for MDS and MDS-CMML (Table 2) and are anticipated to be promising agents for management of anemia.

Thrombocytopenia is generally disease-related, although rare cases of CMML-associated immune thrombocytopenia have been described [75]. Platelet transfusion guidelines are similar to those used for MDS and MPN. Eltrombopag, a thrombopoietin receptor agonist, has proven to be effective and safe in patients with MDS and is currently under investigation in CMML (Table 2) [76]. Off-label use of this agent in patients with CMML-associated ITP resulted in durable platelet increase [77]. However, given the inherent stimulatory effect on hematopoiesis, we strongly recommend the use of thrombopoietin receptors agonists only in clinical trials, since they have been associated with an augmentation of proliferative features in MPN-CMML [78].

Cytoreductive therapy using hydroxyurea (HU) has long been the main treatment for CMML patients with MPN features and is used to counter progressive leukocytosis, MPN-like constitutional symptoms, symptomatic splenomegaly, and other EMH-related manifestations. Standard AML-like induction therapy has very limited disease-modifying activity, even with intensified regimens, and should be considered in cases transforming to AML. In addition to being an emergent, life-saving procedure in the event of splenic rupture, splenectomy still has a therapeutic role in the palliative treatment of spleen-related symptoms and refractory cytopenias (especially in the case of immune mediated thrombocytopenia), with significant and durable responses [79].

CMML-Directed Therapies

Azanucleotides are nucleoside analogues which can be incorporated into DNA in place of cytosine and act as fraudulent bases, resulting in depletion of active DNMT activity and disruption of DNA methylation patterns. 5-Azacytidine (AZA) and 5-aza-2-deoxycytidine (decitabine, DAC) are the only two drugs approved in CMML by the United States Food and Drug Administration (US FDA) on the basis of two pivotal phase 3 randomized studies that included 361 patients with MDS and only 28 with CMML (mostly MDS-CMML) [67, 70]. In Europe, only AZA is approved for treatment of patients with CMML-2 without MPN features based on a randomized phase 3 that included only 11 CMML patients [68].

Following these pivotal studies, several retrospective series and a number of phase 1/2 prospective studies investigated the efficacy and safety of HMA in CMML patients (for details, refer to ref. [80], Table 4). Overall, these studies reported a median OS ranging from 12 to 37%, and an overall and complete response rate of 17–70% and 7–58%, respectively. Responses are usually non-sustained, but nonetheless treatment is recommended until progression. Recently, two retrospective studies deeply explored the mutational landscape and dynamics in patients treated with HMA [9••, 32•]. Duchmann et al. analyzed 174 CMML patients treated with HMA and

Table 2 Contemporary therapeutic strategies and novel agents for CMML treatment

Treatment	Major clinical trial	Study population	Treatment regimens	Response rate	Median OS (months, range)	Median LFS (months, range)	Grade ≥ 3 toxicity
Hypomethylating agents							
Azacitidine	Phase 3 (completed) (2002) [67]	MDS: 157 AML: 20 CMML: 14	• I) AZA 75 mg/m^2/day sc for 7 days every 28 days • II) Best supportive care	ORR/CR: 60%/7%[a] ORR/CR: 5%/0%[a]	20 (16–26)[a] 14 (12–14)	21 (16–27) 12 (8–15)	Leukopenia (59%), granulocytopenia (81%), thrombocytopenia (70%)
Azacitidine	Phase 3 (completed) (2009) [68]	Total: 229 AML: 113 CMML: 16	• I) AZA 75 mg/m^2/day sc for 7 days every 28 days • II) Conventional therapy[b]	ORR/CR: 51%/30%[a] ORR/CR: 21%/14%[a]	24.5 (9.9-NR)[a] 15.0 (5.6–24.1)[a]	17.8 (13.6–23.6)[a] 11.5 (4.9-NR)[a]	Neutropenia (91%), anemia (57%), thrombocytopenia (85%)
Azacitidine + lenalidomide or vorinostat	Phase 2 (active, not recruiting) NCT01522976 [69]	Total: 277 CMML: 53	• I) AZA 75 mg/m^2/day sc/iv for 7 days every 28 days • II) AZA (s.a.b.) + lenalidomide 10 mg/day po days 1–21 • III) AZA (s.a.b.) + vorinostat 300 mg bid po days 3–9	ORR: 28% ORR: 68% ORR: 12%	Not reached in all groups	NA	Hematologic toxicity similar across arms (12%, 16%, 14%, respectively). Skin rashes more frequent in AZA + lenalidomide. Gastrointestinal toxicities more frequent in AZA + vorinostat
Decitabine	Phase 3 (completed) (2006) [70]	MDS: 156 CMML: 14	• I) DAC 15 mg/m^2/day iv tid for 3 days every 6 weeks • II) Best supportive care	ORR: 17%/9%[a] ORR: 0%/0%[a]	14.0[a] 14.9[a]	12.1[a] 7.8[a]	Leukopenia (17%), neutropenia (93%), anemia (15%), thrombocytopenia (17%)
Decitabine	Phase 3 (active, recruiting) NCT02214407	NA	• I) DAC 20 mg/m^2/day iv for 5 days every 28 days • II) HU 1 g/d po qd with dose adjustments up to 4 g/d	NA	NA	NA	NA
ASTX727 (decitabine + cedazuridine)	Phase 3 (active, not recruiting) NCT03306264	MDS CMML	• I) DAC 20 mg/m^2/day iv for 5 days every 28 days • II) ASTX727 100/35 mg/day po qd for 5 days every 28 days	NA	NA	NA	NA
Guadecitabine (SGI-110)	Phase 3 (active, recruiting) NCT02907359	NA	• I) SGI-110 60 mg/m^2/day sc for 5 days every 4 weeks • II) Best supportive care	NA	NA	NA	NA
Guadecitabine (SGI-110) + atezolizumab	Phase 1/2 (active, recruiting) NCT02935361	NA	• I) SGI-110 sc for 5 days + atezolizumab iv day 8 and 22 every 4 weeks	NA	NA	NA	NA
JAK inhibitors							
Ruxolitinib	Phase 2 (active, not recruiting) NCT01776723 [71]	CMML: 48	• Ruxolitinib po bid according to platelet count	ORR: 46%	28 (18–38)	NA	No grade 3–4 treatment-related hematologic toxicities
Ruxolitinib + azacitidine	Phase 1/2 (active, recruiting) NCT02935361 [72]	CMML: 17 aCML: 4 MDS/MPN-U: 14	• Ruxolitinib po bid according to platelet count + AZA 25–75 mg/m^2/d sc/iv days 1–5 every 28 days starting from cycle 4	ORR: 57% (26% after addition of AZA)	All: 17 (1–41) CMML: 15	14 (6–35)	Neutropenia (29%), anemia (51%), thrombocytopenia (54%), UTI (9%), pneumonia (9%), skin/soft tissue infections (9%)
Anti-GM-CSF antibodies							
Lenzilumab (KB-003)	Phase 1 (active, recruiting) NCT02546284	NA	• Lenzilumab iv day 1 and 15 every 4 weeks	NA	NA	NA	NA

Table 2 (continued)

Treatment	Major clinical trial	Study population	Treatment regimens	Response rate	Median OS (months, range)	Median LFS (months, range)	Grade ≥ 3 toxicity
Farnesyltransferase inhibitor							
Tifiparnib	Phase 2 (active, recruiting) NCT02807272	CMML	• Tifiparnib 900–1200 mg po bid days 1–7 and 15–21 every 4 weeks	NA	NA	NA	NA
Anti-CD123 diphtheria toxin-conjugated antibodies							
Tagraxofusp (SL-401)	Phase 1–2 (active, recruiting) NCT02268253 [73•]	SM PED MF CMML: 18	• Tagraxofusp 7/9/12 mcg/kg/day days 1–3 every 21 days (cycles 1–4), every 28 d (cycle 5–7), and every 42 days (cycle 8+)	SpleenR: 100% BM CR: 11%	NA	NA	Thrombocytopenia (13%) and nausea (6%). Capillary leak syndrome in 19% (all grade 2)
Histone deacetylase inhibitors							
Tefinostat (CHR-2845)	Phase 2 (active, recruiting) EudraCT 2015–002281-23	CMML	NA	NA	NA	NA	NA
Spliceosome inhibitors							
H3B-8800	Phase 1 (active, recruiting) NCT02841540	AML MDS CMML	NA	NA	NA	NA	NA
Sonic hedgehog pathway inhibitors							
Glasdegib (PF-04449913)	Phase 1b (active, recruiting) NCT02367456	AML MDS CMML	• Glasdegib 100 mg/day po + AZA 75 mg/m^2/day days 1–7 every 28 days	NA	NA	NA	NA
Thrombopoietin receptors agonists							
Eltrombopag	Phase 1/2 (active, not recruiting) NCT02323178	CMML	• Eltrombopag 50–300 mg/day po	NA	NA	NA	NA
Transforming growth factor-β ligand traps							
Sotatercept	Phase 2 (completed) NCT01736683	MDS MDS-CMML	• Sotatercept 0.1–2.0 mg/kg sc once every 3 weeks for 5 cycles	NA	NA	NA	NA
Luspatercept	Phase 3 (active, not recruiting) NCT02631070 [74]	MDS with RS	• Luspatercept 1.0–1.75 mg/kg sc once every 3 weeks for ≥ 24 weeks	RBC-TI^8: 38% RBC-TI^{12}: 28% mHI-E:53%	NA	NA	NA

aCML atypical chronic myeloid leukemia, *AML* acute myeloid leukemia, *AZA* azacytidine, *BM* bone marrow, *CMML* chronic myelomonocytic leukemia, *CR* complete remission, *DAC* decitabine, *GM-CSF* granulocyte-macrophage colony-stimulating factor, *JAK2* janus kinase 2, *LFS* leukemia-free survival, *MDS* myelodysplastic syndrome, *MDS/MPN-U* myelodysplastic/myeloproliferative neoplasm, unclassified, *MF* myelofibrosis, *mHI-E* modified hematologic improvement-erythroid, *MPN* myeloproliferative neoplasms, *NA* not available, *NR* not reached, *OS* overall survival, *ORR* overall response rate, *PED* primary eosinophilic disorder, *RBC-TI^8* red blood cell transfusion independence for ≥ 12 weeks, *RBC-TI^{12}* red blood cell transfusion independence for ≥ 12 weeks, *RS* ring sideroblasts, *SM* systemic mastocytosis, *SpleenR* spleen response, *UTI* urinary tract infection

[a] CMML-specific response rate not reported

[b] Conventional care regimens included best supportive care only, low-dose cytarabine, and intensive chemotherapy

found that presence of *RUNX1* and Cbl proto-oncogene (*CBL*) mutations independently predicted worse OS, while *TET2*^{mut}/*ASXL1*^{wt} genotype was associated with higher overall and complete response rate and prolonged survival [32•]. Combining whole-exome and whole-genome sequencing on sequential samples from HMA-treated CMML patients, Merlevede and colleagues demonstrated that the hematologic response is associated with significant changes in DNA methylation and gene expression, without any decrease in the mutational allele burdens, even in complete responders [9••]. These findings suggest that HMA restore balanced hematopoiesis through epigenetic mechanisms, without significantly modifying disease biology and the potential for disease progression.

Recently, we retrospectively assessed HMA response rates in 121 CMML patients according to both IWG-MDS and MDS/MPN response criteria [81••]. Although HMA-treated patients had longer median OS compared to those treated with conventional care regimens (31 vs. 18 months), the response rates were overall low with true complete remission (CR) rate of < 20%, with five (29%) patients progressing to AML while in a CR, and with dismal outcomes associated with primary and secondary resistance (median OS of < 6 months and 4 months, respectively). Overall, these findings clearly highlight the suboptimal response rates to HMA in CMML and underscore the unmet need for newer, CMML-specific therapies.

Allogenic Stem Cell Transplantation

After risk assessment, CMML patients should be first evaluated for alloHCT, which remains the only potentially curative treatment. Moreover, the introduction of reduced intensity conditioning (RIC) and alternate donor sources (i.e., double umbilical cord blood units and haploidentical donors) has allowed more patients to have access to alloHCT. However, alloHCT is still fraught with substantial treatment-related morbidity and mortality, due to complications such as acute and chronic graft versus host disease (GVHD). The main issues in alloHCT for CMML patients include patient selection, optimal timing, and transplant modalities. These are difficult questions to address given that there have been no prospective studies as of yet assessing the impact of alloHCT in CMML. Analysis of large published retrospective series indicate a comparable response rates ranging from 17 to 50%, with corresponding relapse rate and treatment-related mortality of 17–52% and 7–52%, respectively [82–88, 89•, 90–93, 94•]. A recent retrospective study on 209 patients who underwent alloHCT for CMML validated the CPSS score and identified BM graft source, lower Karnofsky performance status, and higher transplantation-specific CPSS scores as significant predictors of inferior outcomes [94•]. Although the achievement of CR prior to alloHCT has been correlated with better outcomes in CMML patients [93], the role of prior induction therapy is still debated, due to the lack of prospective data. Two recent retrospective studies have demonstrated that treatment with HMA followed by alloHCT was associated with lower relapse rates and a lower transplant-related mortality [95, 96]. Overall, no evidence-based recommendation can be provided and current guidelines for alloHCT in CMML patients are largely derived from expert opinions and consensus statements [97].

In our institution, we reserve upfront alloHCT for younger patients (< 65 years) who have been diagnosed with intermediate- or high risk disease according to available clinical- and molecular-based prognostic models and have no major contraindication to transplant in terms of performance status, donor source, and comorbidities. Transplant can be considered also in selected patients with low risk CMML and adverse prognostic predictors, such as severe, refractory cytopenias, adverse cytogenetics, or high risk mutations. In addition, we recommend cytoreductive therapy prior to alloHCT in most patients with high disease burden (BM blasts ≥ 10%) and/or in those undergoing RIC alloHCT with > 5% blasts.

Novel Agents and Future Directions

Among currently explored new agents (Table 2), the oral selective JAK1/2 inhibitor ruxolitinib proved safe and potentially effective in a recent phase 1/2 clinical trial including 49 CMML patients, with an overall response rate of 46% and a median OS of 28 months (32 and 28 months for MDS- and MPN-CMML, respectively) [71]. Compared to a historical cohort of 1800 CMML patients, the median OS from disease diagnosis was significantly improved in patients treated with ruxolitinib (9 vs. 31 months, $p = 0.03$); however, the inherent limitations of such an analysis impose caution on interpretation of these results that need further confirmation. Recently, the preliminary results of a phase 2 trial investigating the combination of ruxolitinib and AZA in 35 MDS/MPN patients including 17 CMML cases were published (NCT01787487) [72]. The combination proved safe and was associated with an overall response rate of 57% and a median OS of 15 months in CMML patients. Other JAK inhibitors, such as momelotinib and pacritinib, may have a role in CMML treatment, particularly in patients with proliferative features. Pacritinib was effective in reducing the leukemic compartment in a CMML preclinical model [98], and showed synergy with AZA [99].

Second-generation HMA include guadecitabine (SGI-110), a decitabine-deoxyguanosine dinucleotide designed to be resistant to degradation by cytidine deaminase and prolong the exposure to the active metabolite. Guadecitabine is currently being tested in a phase 3, randomized trial recruiting patients with MDS and CMML previously treated with HMA (NCT02907359). Based on evidence suggesting a role of

HMA exposure in increasing the expression of surface immune checkpoint proteins [100], a phase I/II trial study is evaluating the association of guadecitabine and atezolizumab, an immune checkpoint inhibitor targeting PD-L1, in patients with resistant/refractory MDS or CMML (NCT02935361). Given the inherent GM-CSF hypersensitivity of CMML myeloid progenitors [50], a phase 1 trial designed for CMML patients (NCT02546284) is currently investigating lenzilumab, a novel, first-in-class monoclonal antibody structured to bind and neutralize circulating GM-CSF. Based on the same rationale, the farnesyltransferase inhibitor tipifarnib is being evaluated in a phase 2 study in CMML patients (NCT02807272). Interleukin-3 receptor (CD123) has been shown to be expressed in many hematological malignancies, including CMML. Tagraxofusp (SL-401), a diphtheria toxin-CD123 fusion protein, has being explored in a phase 1–2 trial including patients with advanced myeloid neoplasms (NCT02268253), and preliminary results on a limited cohort of 18 relapsed/refractory CMML patients demonstrated efficacy in reducing the spleen size and in obtaining BM morphological responses, with a manageable safety profile [73•]. Other drug classes under clinical investigation in myeloid neoplasms, including CMML, are spliceosome inhibitors (H3B-8800, NCT02841540) and sonic hedgehog pathway inhibitors (glasdegib, NCT02367456).

Conclusions

Among chronic myeloid neoplasms, CMML represent an extraordinary biological model where clinical heterogeneity embraces a constellation of both dysplastic and proliferative features and contrasts with a relatively low molecular complexity. Clonal germination and evolution of CMML follows a preferential order with specific aberrations disrupting cellular functions at several levels, and deeper understanding of these mechanisms may represent an important achievement with diagnostic, prognostic, and therapeutic implications. Despite recent advances in the molecular biology, CMML still remains a difficult to treat disease and our capacity to affect patient outcomes and quality of life is far from being satisfactory. Allogenic HCT, a procedure fraught with complications, including mortality, remains the only potential cure for a small number of eligible patients. The development of rationally derived therapies for impacted patients remains a top priority.

Compliance with Ethical Standards

Conflict of Interest Giacomo Coltro declares that he has no conflict of interest.

Mrinal M. Patnaik served on an advisory board for Stem Line Pharmaceuticals. The honorarium was issued directly to Mayo Clinic.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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