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CMML: Clinical and molecular aspects

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Abstract Chronic Myelomonocytic Leukemia is a chronic myeloid neoplasm occurring mostly in the elderly with overlapping features of myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN) characterized by chronic monocytosis. Recent progresses in the molecular and cellular pathogenesis of CMML have stirred a renewed interest in this clinically heterogeneous disorder. Here, we review the recent progresses in the biology of CMML and how it affects its current and future clinical management.

Keywords Chronic myelomonocytic leukemia · Myelodysplastic · Myeloproliferative

Introduction

Chronic Myelomonocytic Leukemia (CMML) is a chronic myeloid neoplasm of the elderly with a variable but overall poor prognosis. CMML arises from the clonal outgrowth of a hematopoietic stem cell resulting in expansion of the granulomonocytic compartment in the bone marrow,

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peripheral blood and spleen, contrasting with anemia and thrombocytopenia.

Chronic Myelomonocytic Leukemia (CMML), once classified as a myelodysplastic syndrome by the FAB classification, is now recognized by World Health Organization (WHO) classifications as an overlap Myelodysplastic/myeloproliverative (MDS/MPN) neoplasm, and represents as such the most frequent amongst MDS/MPN entities [1]. Recommendations for clinical management of CMML are mostly based on retrospective studies. For instance, the only randomized clinical trial focusing on CMML has been published in 1996 [2].

Recent progresses in the molecular characterization of CMML have led to a better understanding of the pathogenesis of CMML, with frequent mutations in genes encoding regulators of DNA methylation (*TET2*), histone modifications (*ASXL1*), splicing (*SRSF2*) or GM-CSF signaling (*NRAS*, *KRAS*, *CBL*), to name a few [3]. These progresses have led to a regained interest for this orphan neoplasm, with an International Working Group now fostering research in CMML [4].

In light of the recent molecular data in CMML, we will review the recent progresses made in the diagnostic, prognostic and therapeutic management of CMML, and propose a scheme for the pathogenesis of a disease which remains difficult to treat.

Epidemiology

CMML is a rare myeloid neoplasm of the elderly, with an annual incidence of about 4 cases per million in Western countries, a male predominance, and a median age at diagnosis close to 75 years [5–7]. CMML is very infrequent before the age of 50, and prognosis appears superior in

younger patients, possibly because of a broader access to disease-modifying treatments such as allogeneic stem cell transplantation [8].

Etiological clues on CMML are scarce, and in fact mutational signatures suggest that in most cases, CMML arises because of the natural aging of hematopoietic stem cells (HSC) [9]. CMML may arise from a previously stage of clonal hematopoiesis of indeterminate potential (CHIP, also called Age Related Clonal Hematopoiesis, ARCH) [10], or in some cases from a previous MDS, with, in the latter case, seemingly distinct molecular routes than de novo CMML [11]. Therapy-related cases of CMML have been reported [12].

Diagnostic criteria

The current diagnostic criteria of CMML have recently been updated by the 2016 WHO classification [1] and are summarized in Table 1. Persistent monocytosis defined both as an absolute count $>1 \times 10^9$/L and as a proportion >10% of white blood cell (WBC) count is the cornerstone of diagnosis. Increased neutrophils and presence of circulating immature myeloid cells (IMC) can also be seen in CMML. Interestingly, even cells with morphology of *bona fide* monocytes can correspond to clonal immature dysplastic granulocytes with phenotypic and functional features reminiscent of myeloid derived immunosuppressive cells (MDSC) [13, 14]. How these MDSC contribute to the pathogenesis of the disease is currently being investigated.

The formal inclusion of the >10% WBC rule in the diagnosis of CMML better helps delineating it from atypical Chronic Myeloid Leukemia (aCML) or unclassified MDS/MPN (MDS/MPNu), where absolute monocytosis is often present but where granulocytic hyperplasia is predominant, though from a molecular perspective, it is likely that a continuum exists between these entities [15, 16], raising questions on genotype/phenotype correlates in myeloid neoplasms [17]. The WHO recommends stratifying CMML into three groups based on bone marrow and peripheral blood blast count: CMML-0 [blasts <2% in peripheral blood (PB) and <5% in bone marrow (BM)], CMML-1 (2–4% in PB, 5–9% in BM) and CMML-2 (5–19% in PB, 10–19% in BM, or presence of Auer rods). Importantly, promonocytes, which are sometimes difficult to distinguish from immature monocytes, must be included in the blast count of CMML [18].

CML and classical MPNs such as ET, PV and PMF, where monocytosis can be present and often carries poor prognosis [19], must be excluded, as well as eosinophilia and a *PDGFRA/B* rearrangements. CMML can also be concomitantly diagnosed with mast cell [20], histiocytic [21], and blastic plasmocytoid dendritic cell disorders [22], with clonal relationship proved or strongly suspected in most cases.

The WHO classification requires the presence of significant bone marrow dysplasia, or a cytogenetic abnormality to confirm the diagnosis of CMML. Dysplasia can be difficult to assess on the monocytic lineage, predominates on the granulocytic lineage, but can be missing.

Cytogenetics are normal in two-thirds of patients and the most frequent cytogenetic alterations including trisomy 8, -7/del7q and del20q are not specific [23]. A suspicion of CMML without significant dysplasia and normal cytogenetics is thus a frequent situation. In these instances, the WHO requires persistence of monocytosis for at least 3 months to confirm the diagnosis, a delay that may be sub-optimal in case of significant cytopenias or myeloproliferation. Using a small list of 10–20 genes, all but one (*ASXL1*) easily analyzed by most NGS methods, a recurrent mutation with higher allelic frequency than seen in CHIP/ARCH can be detected in >90% of CMML patients [3, 9, 24]. Even though none of these genes is specific of CMML, the identification of mutations in one or several of these genes detailed below can contribute to the diagnosis per WHO recommendations [1]. Finally, as NGS is not yet available in all centers and results can be delayed, Selimoglu-Buet et al. have proposed a rapid approach to validate the diagnosis of CMML, based on flow cytometry assessment of normal monocytic populations in peripheral blood. Reactive monocytoses, e.g., caused by chronic infections or inflammation, are associated with expansion of intermediate (CD14+/CD16+) and non-classical (CD14−/CD16+) monocytes, whereas a proportion of 'classical' CD14+/

Table 1 Diagnosis criteria of CMML according to WHO 2016

Persistent monocytosis $\geq 1 \times 10^9$/L and monocytes ≥10% of WBC in peripheral blood

No criteria and no previous history of CML, ET, PV and PMF

If eosinophilia, neither *PDGFRA, PDGFRB, FGFR1* rearrangements nor *PMC1-JAK2* translocation

<20% blasts in peripheral blood and bone marrow aspiration

≥1 following criteria:

Dysplasia in ≥1 myeloid lineage

Acquired clonal cytogenetic or molecular abnormality in hematopoietic cells

Monocytosis persistent for at least 3 months, with other causes excluded

CD16− monocytes >94% predicts CMML with good accuracy (Fig. 1) [25].

Clinical presentation

The clinical features of CMML are variable. Cytopenias including macrocytic or normocytic anemia and thrombopenia are seen more frequently than neutropenia. Thrombocytopenia can also be of peripheral, auto-immune origin. Myeloproliferative features are dominated by splenomegaly, but can include skin lesions for which different patterns of infiltration can be seen, requiring systematic skin biopsy, notably to exclude *bona fide* leukemia cutis corresponding to extramedullary transformation to AML [26]. Other extra-medullary lesions include pleuro-pericardic effusions, hepatomegaly, or lymph node infiltration.

The FAB classification defined two subtypes of CMML based on WBC. Patients with WBC < 13 G/L were considered to have myelodysplastic CMML (MD-CMML) and those with ≥13 G/L myeloproliferative CMML (MP-CMML). This stratification was re-instated by the recent WHO 2016 classification [1]. It is convenient, matches well with the clinical prioritization of management of cytopenias in MD-CMML and of cytoreduction in MP-CMML. Finally, this cut-off is included in the labeling of azacitidine in CMML in Europe [27].

CMML may present with general symptoms akin to those seen in patients with non-CML MPN such as PMF [4]. To date there is no validated questionnaire for CMML patients, but recent biological findings suggest that plasma levels of inflammatory cytokines can also be elevated in CMML [28], paving the way for dedicated therapeutic intervention such as JAK inhibition [29].

Auto-immune or inflammatory disorders (AID) can also be present at the diagnosis of CMML, predating the diagnosis, or less frequently occurring during the follow-up of CMML. The clinical spectrum of these AIDs, notably including immune thrombocytopenia or seronegative arthritis, is somewhat distinct from that associated to MDS, with a higher frequency of systemic vasculitis [30, 31]. These AIDs can be treated conventionally with steroids, and hypomethylating agents (HMA) can also prove useful [32].

The relationship of AID with clonal myeloid neoplasms such as CMML is a chicken-and-egg issue. A history of infection or inflammatory condition is associated with an increased risk of CMML [33], raising intriguing questions as to the connection between inflammation in the bone marrow milieu and clonal emergence or selection amongst HSCs [34]. Conversely, abnormal immune populations may be present in MDS and CMML. *TET2* mutations can be present in T cells in CMML [35] and are frequent in cases with AID (Itzykson et al. unpublished observation). TET enzymes have been involved in normal innate and adaptive immunity [36, 37], but how *TET2* mutations affect the function of normal T cells remains unclear.

Molecular lesions and pathogenesis

CMML harbor an average of ~500 somatic mutations (substitutions and small insertion/deletions) per genome, including ~15 in coding sequences (exomes), and an average of 2 mutations in the top twenty recurrent oncogenes [3, 9, 24]. Copy-neutral loss of heterozygosity (LOH) is frequent in CMML, most often targeting hemizygous mutated tumor suppressors such as *TET2* or *CBL*, but recurrent copy number alterations in regions lacking formally identified oncogenes have also been reported [38].

Recurrent oncogenes can be broadly stratified into four distinct families, with a certain degree of mutual exclusion
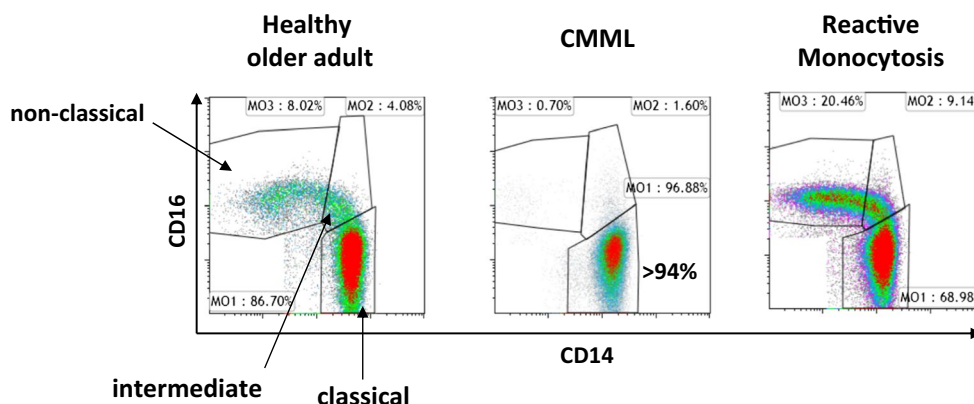
Fig. 1 Patterns of monocyte sub-populations based on CD14 and CD16 expression in normal peripheral blood, CMML, and reactive monocytosis. Reproduced and modified from [25]

within each of these families (Fig. 2). Recurrent oncogenes affect the DNA methylation pathway (*TET2*, *IDH1/2*, *DNMT3A*), the histone modification machinery (*ASXL1*, *EZH2*, *UTX*), the spliceosome complex (*SRSF2*, *SF3B1*, *U2AF1* and *ZRSR2*) and signal transduction molecules, mostly thought to affect GM-CSF signaling in CMML (*NRAS*, *KRAS*, *JAK2*, *CBL*, *RIT1*). Finally, mutations in the transcription factor *RUNX1* are seen in 10–15% of cases, notably in patients with thrombocytopenia. Mutations in *SETBP1* are also found in ~5% of CMML cases, and these cases often harbor a phenotype close to that of aCML, with predominant granulocytic over monocytic hyperplasia [15]. Finally, an intriguing feature of CMML is the scarcity of mutations in *TP53* in contrast to other myeloid neoplasms.

Mutations in *TET2*, *SRSF2* and *ASXL1* are by far the most frequent, being present in ~30–50% of cases each, and even though none of these oncogenes is specific of CMML amongst other myeloid neoplasms, the combination of *TET2/SRSF2* mutations is highly suggestive of CMML [39]. As discussed below, mutations in signaling transduction genes are more frequent in patients with MP-CMML. Overall, this relatively homogeneous molecular fingerprint of CMML contrasts with its heterogeneous clinical presentation, stressing the fact that the latter also

reflects other features of clonal architecture such as patterns of clonal expansion, and non-genetic factors [17].

These mutations mostly arise spontaneously as a result of replicative stress in aging HSCs [9, 10]. Mutations accumulate in a linear fashion in those, with lesions in epigenetic and splicing regulators often predating mutations in signaling pathways. Clonal branching can also arise as a result of mitotic recombination, resulting in LOH, or because of parallel evolution, for instance when independent clones harboring distinct mutations in the RAS pathway arise. Clonal burden of HSCs seems particularly high in CMML compared to MPNs or even MDS, with >90% of clonality in the most immature CD34+/CD38− cells, which could explain why current therapeutic strategies fail to achieve clonal eradication [9, 35]. Finally, clonal architecture is remodeled during myeloid differentiation, with cytokine-mediated expansion of RAS-mutated clones. Genetic interrogation of total bone marrow mononucleated cells is, therefore, not an accurate depiction of the clonal composition of CMML stem cells [35, 40].

Molecular and functional studies suggest that at least two distinct mechanisms lead to the granulomonocytic expansion that is the phenotypic cornerstone of CMML (Fig. 3). Historically, the first identified, notably by colony assays
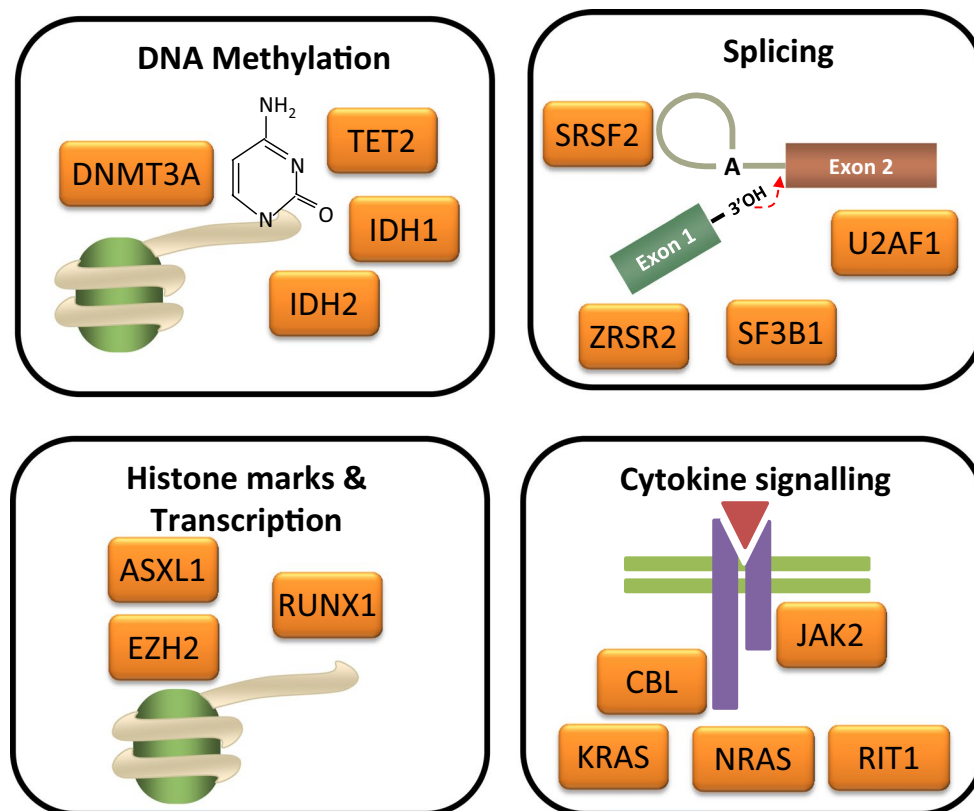
Fig. 2 Oncogene families in CMML
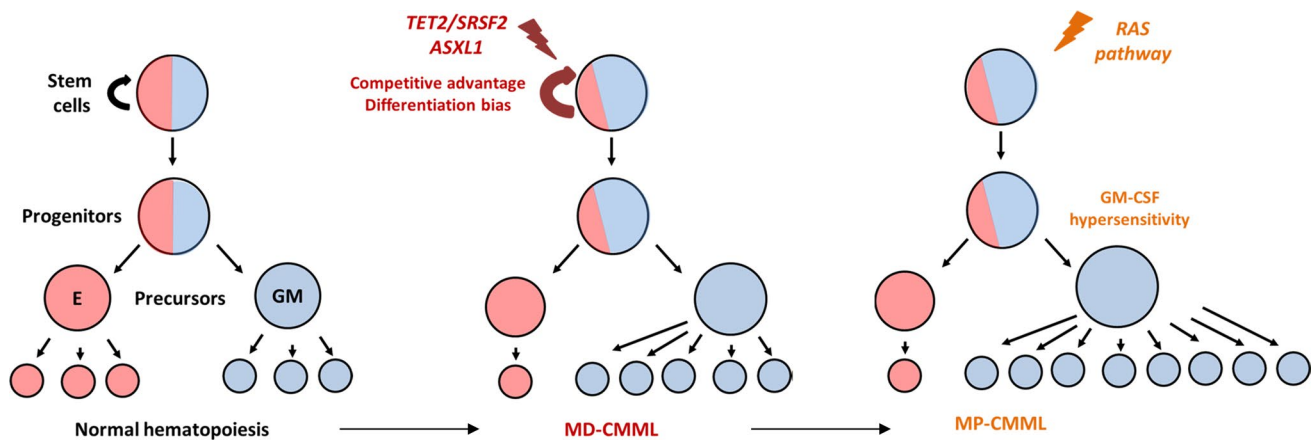
Fig. 3 A model of CMML pathogenesis with a two-step acquisition of the granulomonocytic lineage based on differentiation bias and GM-CSF hypersensitivity

[41] and phospho-flow cytometry [42] is hypersensitivity of myeloid progenitors to GM-CSF signaling, with increased phospho-STAT5 activity as a critical transducer of this phenotype. However, recent studies have stressed that this mechanism is not universal and in fact appears restricted to the 35–50% of CMML cases that harbor somatic mutations in cytokine signaling pathway [43–45]. These cases partly, but not fully, correspond to MP-CMML. Alternative mechanisms are, therefore, involved in the remaining cases. Data from murine models and from in vitro studies on primary human cells suggest that early clonal expansion of *TET2*-mutated clones in immature multipotent progenitors can lead to a significant differentiation bias with both a mild granulomonocytic expansion and impaired erythroid differentiation, a phenotype reminiscent of MD-CMML. This differentiation bias seems to be an evolutionary neutral 'by-product' of the competitive advantage provided in HSCs by *TET2* loss of function [40]. This model has yet to be formally demonstrated, but is in keeping with the role of TET enzymes in embryonic stem cells [46].

Non-cell autonomous mechanisms involving dialogue between clonal differentiated cells and clonal HSCs, or between leukemic cells and the micro-environment may also contribute to the disease. For instance, TET2-deficient macrophages have increased NLRP3 inflammasome–mediated interleukin-1β secretion [47], and interleukin-1β have been suggested to contribute to leukemic cell expansion [48].

Prognosis

There is limited prospective data on the natural history of CMML. Overall survival in recent retrospective series of CMML is in the range of 24–36 months, comparable to that of older cohorts suggesting limited improvement over the last decades. Conversely, registry data suggest an improvement in disease-specific mortality of CMML since ~2006 in the US, roughly corresponding to the introduction of HMA and broader availability of allogeneic stem cell transplantation (ASCT) [49].

Roughly 25% patients will progress to AML and these secondary AML are notoriously difficult to treat. Other causes of death in CMML are related to cytopenias, including fatal bleeding and infections, mostly in treated patients, or less frequently to extra-medullary disease.

Historical prognostic scores for CMML, including the Bournemouth, Lille, MD Anderson and Dusseldorf prognostic scores stressed the key prognostic roles of cytopenias, myeloproliferative features, and blast excess in CMML [50–53]. A dedicated prognostic stratification of cytogenetic lesions was then proposed, that differs from MDS classifications in the poor prognostic value attributed to trisomy 8 [23], even though this point remains controversial [54].

In recent years, various retrospective studies have reported the prognostic role of gene mutations in CMML, often in univariate analysis. If *ASXL1 RUNX1* and *SETBP1* mutations appear detrimental in most series [3, 15, 55–57], the prognosis of *TET2*, *SRSF2* and *RAS/CBL* mutations seems more controversial, perhaps because of interactions with other gene mutation status [58], clinical variables such as myeloproliferative features, or with treatment. Finally, rare mutations such as those in *EZH2* or *DNMT3A* are probably of poor prognosis [59, 60], but only very large series will allow to incorporate them into molecular stratifications.

Recently, a second wave of prognostic stratifications have been proposed in CMML, most of which have been validated in independent cohorts. Amongst them, the

CMML Prognostic Scoring System (CPSS) remains the easiest to use because it does not account for molecular biology, but instead relies on simple criteria, namely blast excess, WBC, cytogenetics and RBC transfusion dependence [61]. We developed the GFM score by integrating clinical data with mutation status in 19 oncogenes, identifying the independent poor prognostic value of higher WBC, anemia, thrombocytopenia, older age and *ASXL1* mutations [3]. The GFM score can thus be used in centers relying on Sanger sequencing. Recently, the CPSS was integrated with molecular data to derive CPSS-mol that accounts for the poor prognosis of *ASXL1*, *RUNX1*, *NRAS* and *SETBP1* mutations, and thus requires access to NGS for practicality [57]. Two other scores integrating clinical and molecular features, one from the Mayo clinic and the other from an international consortium have also been proposed [62, 63]. All of these recent scores seem to perform similarly, and an international consensus has yet to emerge. Importantly, prognostic scores are dependent on the therapeutic context, and stratification tools will perhaps differ in patients eligible for ASCT [64], or treated with HMA (Duchmann et al., manuscript in preparation).

Treatment

Despite various national guidelines, internationally validated treatment algorithms for CMML are still lacking and treatment remains loosely codified. Progress in this direction is ongoing, with for instance a recent proposal for consensus response criteria in CMML [4], that

have been retrospectively validated (Duchmann et al., in press). Akin to MDS, it is tempting to stratify CMML as high-risk and low-risk disease, with high-risk cases requiring disease-modifying interventions, and low-risk disease eligible for symptomatic treatment aiming mostly at dampening myeloproliferation or improving cytopenias in MP-CMML and MD-CMML, respectively. A tentative algorithm is summarized in Fig. 4.

In lower-risk CMML, treatment of anemia can rely on Erythropoiesis Stimulating Agents (ESAs) with MDS regimens [65], whereas thrombopoietin agonists seem more difficult to use, and still require prospective evaluation [66]. In patients with proliferative features, hydroxyurea remains a standard of care [2].

ASCT remains the only curative option in CMML, but its feasibility is limited by patients older age. There is to date no retrospective study to delineate the best timing for ASCT in CMML, but experts recommend to proceed to transplant in eligible patients with intermediate-2 or high CPSS risk [67]. Patients with blasts >10% likely benefit from some form of treatment prior to transplant, and this increasingly relies on HMA. Relapse rates remain high (up to 30%) after ASCT, and prophylactic or preemptive strategies to prevent relapse, e.g., with HMA, have to be studied prospectively.

Conventional cytotoxic drugs have limited activity in CMML, and 7 + 3 regimens yield ~40–50% complete responses lasting only a few months [68]. The hypomethylating agents (HMA) azacitidine (AZA) and decitabine (DAC) seem active in CMML, though they have mostly been explored retrospectively [69, 70], reporting overall

Fig. 4 A tentative scheme of therapeutic stratification in CMML. Items indicated in ?? require further clinical studies. Const. constitutional. JAKi JAK inhibitors, TPO thrombopoietin, HY hydroxyurea
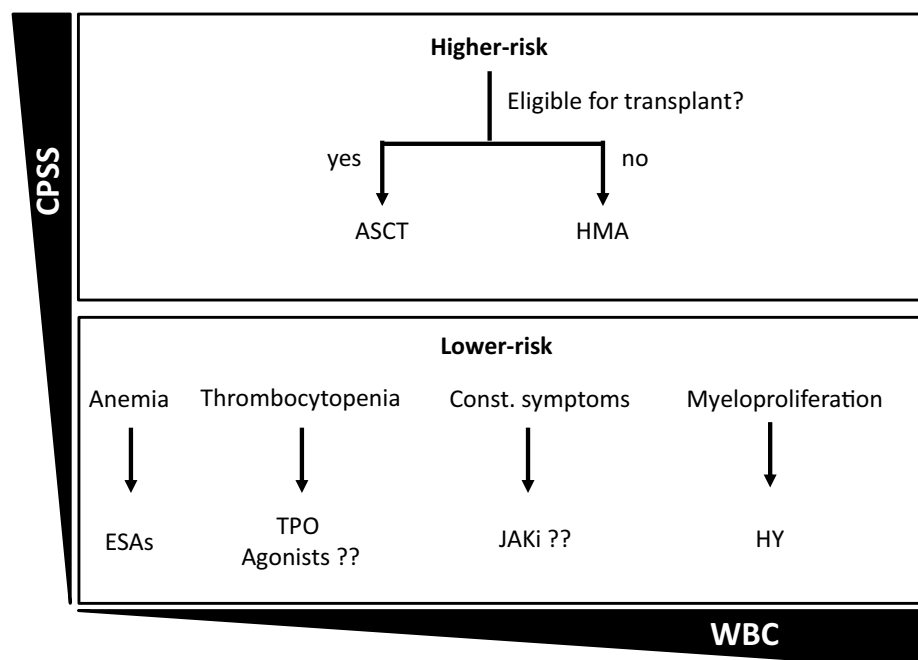
response rates in the 40–70% range. In retrospective studies controlling for biases, there does seem to be a significant difference between DAC and AZA in this population (Duchmann et al., *manuscript in preparation*), even though several authors have suggested that DAC could be beneficial in proliferative CMML [70, 71], possibly because standard regimens of DAC are slightly more myelotoxic than AZA regimens. HMA also seem active in patients with extra-medullary disease [71]. Limited prospective data is available: AZA is licensed in Europe in CMML-2 patients with WBC <12 G/L, on the basis of the MDS AZA-001 trial where only few CMML patients were randomized [27]. A phase II study of DAC in high risk population of MP-CMML provided interesting results [71] prompting an ongoing randomized phase III trial addressing the role of DAC as upfront treatment of MP-CMML in the presence of adverse prognostic features (NCT02214407). As in other myeloid neoplasms, response to HMA remains difficult to predict in CMML with clinical variables or with gene mutations. A DNA methylation signature predictive of response has been proposed that still warrants validation [72]. The poor prognostic value of *ASXL1* and *RUNX1* mutations is not abrogated by HMAs (Duchmann et al., *manuscript in preparation*). Their mechanism of action also remains unclear, but do not rely on clonal eradication [9]. Finally, outcome after failure of HMA in CMML, when half of patients have progressed to AML, remains very difficult, with overall survival of ~6 months [70]. Newer treatment options are thus needed in CMML. Ongoing pre-clinical and clinical trials are testing newer ways to induce hypomethylation (e.g., guadecitabine), to impair GM-CSF hypersensitivity (e.g., tipifarnib, lenzilumab, ruxolitinib), or specifically target founder mutations (e.g., IDH inihibitors, or splice inhibitors in patients with mutations in spliceosome genes), to name only a few.

Conclusion

CMML is a rare disease with a heterogeneous clinical presentation. The recent advances in the molecular deciphering of the disease have led to renewed collaborative efforts in this disease. Current basic and translational research aims at better understanding how the specific clonal architecture of CMML drives its clinical phenotype, identify therapeutic strategies to eradicate ancestral mutations such as those in the spliceosome [73], and derive relevant pre-clinical models to allow unbiased therapeutic screens. Clinical studies are ongoing to derive uniform risk stratification and therapeutic evaluation tools. A coordinated academic effort will be necessary to translate our recent molecular and cellular findings into scientifically informed trials in this rare yet difficult to treat disease.

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