Belgian guidelines for diagnosis and treatment of chronic myelomonocytic leukaemia

Collaboration of MDS and MPN committee of the BHS

M. Beckers, MD, PhD[1], S. Sid, MD[2], A. De Becker, MD[3], B. Heyrman, MD[4], N. Granacher, MD[5], D. Mazure, MD[6], S. Meers, MD, PhD[7], M-C. Vekemans, MD[8]

On behalf of the other members of MDS and MPN committee

SUMMARY

Chronic myelomonocytic leukaemia (CMML) is a rare haematological disease. Hallmark of the diagnosis is chronic monocytosis. Other clinical features include cytopenia, dysplasia with the associated complaints like fatigue or leucocytosis, splenomegaly with constitutional symptoms. Predicting prognosis and choosing the correct treatment can be challenging for the clinician. These guidelines cover the diagnosis and treatment of CMML and provide information on morphology, cytogenetics and molecular testing, clinical features including autoimmune manifestations, prognosis and risk assessment and a treatment algorithm for both the fit and unfit CMML patient.

(BELG J HEMATOL 2020;12(2):66-76)

INTRODUCTION

Chronic myelomonocytic leukaemia (CMML) is characterised by the presence of persistent monocytosis with features of myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN). Clinical features are heterogeneous. CMML is a rare disease with an estimated incidence of four cases per 100,000 persons per year.[1,2] The incidence increases with advancing age and the median age at diagnosis is 71-74 years.[2] There is a male predominance of the disease of about 1,5-3:1.[1] Treatment options vary from supportive care, cytoreductive therapy, hypomethylating agents and allogeneic stem cell transplantation. Apart from allogeneic stem cell transplantation, none of the other treatments are truly disease modifying, leaving allogeneic stem cell transplantation the only potential curative option. In general, overall prognosis is poor and risk of transformation to acute myeloid leukaemia (AML) in 15%-30% of cases.[1] Choice of therapy should be based on patient-related factors, symptoms and risk stratification.

DIAGNOSIS

Diagnostic criteria for CMML according to the WHO are reported in *Table 1.*

MORPHOLOGY

If CMML is suspected, a complete blood count and blood smear should be performed. Mild normocytic anaemia is common. The leukocyte count varies however; the leuko-

[1]Department of Hematology, University Hospital Leuven, Leuven, Belgium, [2]Department of Hematology, Hôpital de Jolimont, Haine-Saint-Paul, Belgium, [3]Department of Hematology, University Hospital Brussels, Brussels, Belgium, [4]Department of Hematology, ZNA Middelheim, Antwerp, Antwerp, Belgium, [5]Department of Hematology, ZNA Stuivenberg, Antwerp, Antwerp, Belgium, [6]Department of Hematology, University Hospital Gent, Gent, Belgium, [7]Department of Hematology, AZ Klina, Brasschaat, Belgium, [8]Department of Hematology, Cliniques universitaires Saint-Luc, UCL, Brussels, Belgium.

Please send all correspondence to: M. Beckers, MD, PhD, Department of Hematology, University Hospital Leuven, Herestraat 49, 3000 Leuven, Belgium, tel: +32 16 34 68 80, email: marielle.beckers@uzleuven.be.

Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

Keywords: chronic myelomonocytic leukaemia, CMML, diagnosis, guidelines, treatment.

TABLE 1. Diagnostic criteria for CMML according to WHO.[3]

Persistent peripheral blood monocytosis (≥1000/μL), with monocytes accounting for ≥10% of the WBC count
Not meeting WHO criteria for *BCR-ABL1*-positive CML, PMF, PV, or ET†
No evidence of *PDGFRA, PDGFRB,* or *FGFR1* rearrangement or *PCM1-JAK2* (should be specifically excluded in cases with eosinophilia)
<20% blasts (including myeloblasts, monoblasts, and promonocytes) in the blood and BM
Dysplasia in 1 or more myeloid lineages ***or*** If myelodysplasia is absent or minimal, but all other criteria are met, and: • an acquired clonal cytogenetic or molecular genetic abnormality is present in hematopoietic cells‡ or • the monocytosis has persisted for ≥3 months and all other causes of monocytosis have been excluded

† A previous documented history of MPN excludes CMML, whereas the presence of MPN features in the BM and/or of MPN-associated mutations (*JAK2, CALR,* or *MPL*) tend to support MPN with monocytosis rather than CMML.
‡ In the appropriate clinical context, mutations in genes often associated with CMML (e.g. *TET2, SRSF2, ASXL1* and *SETBP1*) support the diagnosis. However, some of these mutations can be age-related or present in other neoplasms; therefore, these genetic findings must be interpreted with caution.

Abbreviations: BM: bone marrow; CML: chronic myeloid leukaemia; ET: essential thrombocythemia; MPN: myeloproliferative neoplasms; PMF: primary myelofibrosis; PV: polycythemia vera; WBC: white blood cell.

cyte count is often increased due to monocytosis and neutrophilia. Moderate thrombocytopenia is often present. Presence of monocytosis ≥1000/μl for at least three months and accounting for more than 10% of the leucocytes is a prerequisite for the diagnosis of CMML.[4] Peripheral blood smear tends to show normal monocytes with occasionally aberrant monocytes (i.e. nuclear hyposegmentation or abnormal granulation); blasts and young myeloid precursor cells may be present. Based on the leukocyte count below or above 13000/μl, the FAB-group distinguishes a dysplastic and proliferative CMML-subgroup.[5]

Bone marrow aspirate should be assessed for monocytes, monoblasts and promonocytes.[6] Other myeloid cells and mast cells should be reported if present. It can sometimes be difficult to distinguish monocytes, promonocytes and monoblasts morphologically. Dysplasia should be present in at least 10% of cells (any of the myeloid cell lineages), and is most frequently seen in the megakaryocytic and granulocytic lineages. Myeloblasts, monoblasts as well as promonocytes should be included in the blast count. Based on these blast counts, WHO 2016 proposed a blast-based grouping (*Table 2*).[4]

Bone marrow biopsy is usually hypercellular with granulocytic proliferation. Hypocellularity is very rare. Immunohistochemistry including CD34 and the monocytic markers like CD14, CD68 and CD163 can be added.

TABLE 2. Blast-based grouping according to WHO 2016.[4]

CMML-0	<2% blasts in the blood and <5% blasts in the bone marrow, no Auer rods.
CMML-1	2-4% blasts in the blood or 5-9% blasts in the bone marrow, <5% blasts in the blood, <10% blasts in the bone marrow, and no Auer rods.
CMML-2	5-19% blasts in the blood, 10-19% blasts in the bone marrow or Auer rods are present, <20% blasts in the blood and marrow.

FLOW CYTOMETRY

In the WHO 2016 classification, flow cytometry is not a criterion for the diagnosis of CMML. Aberrant expression of surface makers on monocytes (e.g. CD56 and CD2) lacks the specificity and sensitivity to use them as a diagnostic marker for CMML.

Nevertheless, the monocytic subset distribution gains attention in the clinic. The monocyte subset distribution can distinguish CMML from healthy controls, benign reactive monocytosis and other hematological malignancies like MPN, MDS and AML.[7,8] In blood and bone marrow the monocytes can be subdivided in three subtypes based on the expression of CD14: classical or MO1 monocytes ($CD14^{bright}CD16^{-}$), intermediate or MO2 monocytes ($CD14^{bright}CD16^{+}$) and non-classical or MO3 monocytes ($CD14^{dim}CD16^{++}$).[9] In CMML patients, the percentages of MO1 monocytes are higher, while the percentages of MO3 monocytes are lower as compared to healthy controls and reactive monocytosis.[7,10,11] Using a cut-off value of >94%, MO1 monocytes in peripheral blood identifies CMML with a specificity of >95% and a sensitivity of >90%.[11,12] The monocyte subset percentage can also be used to diagnose CMML in bone marrow with a cut-off value of >90% MO1 monocytes.[8] A few studies have shown that during therapy the distribution of MO1, MO2, and MO3 returns to normal.[8,12] Based on the above, flow cytometry can contribute to the diagnosis of CMML in difficult cases and can be used to monitor therapy.

RECOMMENDATIONS

Complete blood count including peripheral blood smear, bone marrow aspirate and bone marrow biopsy should be performed. Immunohistochemistry including CD34 and the monocytic markers can be added. In order to distinguish CMML from reactive monocytosis and other hematological malignancies, analysis of peripheral monocyte subset distribution by flow cytometry can be useful in challenging cases.

CYTOGENETICS

Chromosomal abnormalities are reported in only 20-40% of CMML patients, a variability related to the small numbers and inclusion criteria of the published reports.[13,14] The abnormalities are not specific for CMML and are more frequently seen in CMML-2.[15] The most common aberrations concern trisomy 8, deletion Y and chromosome 7 abnormalities (either monosomy 7 or deletion 7q) while complex karyotypes are less frequent.[15-18] With the exception of deletion Y, these abnormalities are associated with a poor outcome and a high risk of evolution to AML.[16]

MOLECULAR TESTING

An average of ten to fifteen somatic mutations are recurrently reported in CMML patients[19], with more than 90% of patients carrying at least one mutation.[20,21] Mutations occur in genes involved in transcriptional regulators (*TET2* and *ASXL1*), spliceosome complex (*SRSF2*, less often *SF3B1, U2AF1*), cell signal transduction (*JAK2, KRAS, NRAS, CBL, FLT3*), and transcription factors and nucleosome assembly (*RUNX1, SETBP1*). The relative frequency of these mutations is reported in *Table 3*. *TET2* and *SRSF2* are frequently co-mutated and the combination is highly specific for CMML.[22]

Certain mutations are associated with clinical features like *ASXL1* and *SF3B1* with lower haemoglobin levels, *TET2* and *RUNX1* with thrombocytopenia, *ASXL1* and *NRAS* with higher WBC counts, *IDH2* and *U2AF1* with higher blast count and *CBL, NRAS, KRAS* and *ASXL1* with extramedullary disease.[21,22]

RECOMMENDATIONS

Cytogenetic analysis (at least twenty mitoses) of preferably bone marrow is mandatory in the diagnostic work-up of CMML. Mutational analysis, using a conventional myeloid panel should also be included. The test is recommended even in patients only eligible for hydroxyurea or supportive care since some genes like *IDH1, IDH2* and *FLT3*, even though infrequently mutated (≤5%), can be drug targets.

CLINICAL FEATURES AND AUTOIMMUNE MANIFESTATIONS

The clinical features of CMML are heterogeneous. Patients suffering from the dysplastic CMML-variant will most often present with cytopenias and the resulting symptoms of fatigue, bleeding and recurrent infections. Patients diagnosed with the proliferative CMML-variant will present with leucocytosis, splenomegaly and constitutional symptoms (weight loss, fever, night sweats).[23]

Additionally, patients with CMML often present with autoimmune disorders (AID). Large studies have also described this for MDS.[24,25] Since CMML is a rare disease, findings on AID in CMML are most often published as case reports, such as acquired thrombotic thrombocytopenic purpura

or acquired haemophilia A complicating CMML.[26,27] However, the Mayo Clinic and the Moffitt Cancer Center have published retrospective analyses on the incidence of AID in CMML, as have a French group.[28-30] *Table 4* provides an overview of AID reported in CMML patients.

TABLE 3. Relative frequencies of somatic mutations in CMML patients.[2]

Major classes of gene mutations	Gene	Frequency of mutations
Epigenetic control		
Histone modification	***ASXL1***	**40%**
	EZH2	5%
DNA methylation	***TET2***	**60%**
	DNMT3A	5%
	IDH1	1%
	IDH2	5-10%
Cell signaling	*JAK2*	5-10%
	CBL	**15%**
	NRAS	**15%**
	KRAS	10%
	PTPN11	5%
	FLT3	<5%
Splicing	***SFRF2***	**50%**
	SF3B1	5-10%
	U2AF1	5-10%
	ZRSR2	5%
Transcription and nucleosome assembly	***RUNX1***	**15%**
	SETBP1	15%
DNA damage	*TP53*	1%
	PHF6	5%

TABLE 4. Overview of AID described in CMML patients.

AID	References
Systemic vasculitis	
Polyarteritis nodosa	28,30,31
Giant cell arteritis	30
Cryoglobulinemia	30
Behçet's disease	30,32
Aortitis	33
Systemic rheumatoid diseases	
Sjögren's syndrome	28-30
Recurrent polychondritis	30
Polymyalgia rheumatica	28-30
Rheumatoid arthritis	28,29
Ankylosing spondylitis	28,34
Systemic lupus	35
Undifferentiated	30
Hematologic	
Immune mediated thrombocytopenia	28-30,36-39
Pure red cell aplasia	28
Auto-immune haemolytic anaemia	28,29
Acquired thrombotic thrombocytopenic purpura	26
Acquired haemophilia A	27
Uveitis	28
Christian Weber panniculitis	28
Dermatologic	
Psoriasis	28,29
Neutrophilic dermatosis	28,30
Granuloma annulare	28,29
Generalized palisaded neutrophilic and granulomatous dermatitis	40
Inflammatory bowel disease	28
Neurologic	
Chronic inflammatory demyelinating polyneuropathy	28,41
Myasthenia gravis	28
Multiple sclerosis	29
Expressive aphasia	42
Thyroid	
Hashimoto thyroiditis	28
Graves' disease	28
Retroperitoneal fibrosis	30

TABLE 5. Prognostic scoring systems for CMML.

Score	GFM[21]	Mayo[13]	CPSS[44]	MADPS[45]	CPSS-Mol[46]
Clinical features	Age >65	No	RBC-TD	No	RBC-TD
Morphology	WBC >15000/µl; Anaemia; Platelets <100000/µl	Increased AMC >10000/µl; Presence of circulating IMC; Hb <10 g/dl; Platelets <100000/µl	WBC; Blasts %	Hb <12 g/dl; Circulating IMC; ALC >2500/µl; BM blasts >10%	WBC ≥13000/µl BM blasts ≥5%
Cytogenetics	No	No	Yes	Yes	Yes
Molecular analysis	*ASXL1*	No	No	No	Yes
Risk groups	3	3	4	4	4
Median OS (months)	14-60	10-32	5-72	5-26	18- > 144
External validation	Yes	Yes	Yes	No	Yes

Note: The CPSS-mol is based on cytogenetic risk groups and presence of ASXL1/NRAS/SETPBP1/RUNX1 mutations. Cytogenetic risk groups are defined as: low; normal, and isolated –Y; intermediate, other abnormalities; and high, trisomy 8, complex karyotype (≥3 abnormalities), and abnormalities of chromosome 7. CPSS-mol score of 0 for low cytogenetics and absence of mutations, a score of 1 for intermediate risk cytogenetics and mutations involving ASXL1/SETBP1 and NRAS, and a score of 2 for high risk cytogenetics and RUNX1 mutations. CMML patients can be stratified into low risk (zero risk factors), intermediate-1 (one risk factor), intermediate-2 (two or three risk factors) and high (four or more risk factors).

Abbreviations: ALS, absolute lymphocyte count; AMC, absolute monocyte count; BM, bone marrow; CMML, chronic myelomonocytic leukaemia; CPSS, CMML prognostic scoring system; GFM, groupe francophone des myélodysplasies; Hb, haemoglobin; IMC, immature myeloid cells; MADPS, MD Anderson prognostic score; RBC-TD, red blood cell transfusion dependence; WBC, white blood cells.

The Mayo Clinic performed a retrospective analysis on occurrence of AID in CMML patients diagnosed between 1994 and 2016. Of 377 patients included, 20% had at least one episode of AID. It preceded the diagnosis of CMML in 58%, was concomitant in 20% or occurred after the diagnosis was made in 17% of patients. The vast majority of these patients only developed one type of AID. In 61% of the cases, the AID was linked to CMML, and inflammatory arthritis was the most common form encountered.[28]
The Moffitt Cancer Center published an overview of 123 cases diagnosed and/or treated with CMML between 1991 and 2011. They found that 19,5% of these patients had a history of AID. The most frequent manifestations were immune mediated thrombocytopenia (ITP) and systemic rheumatoid diseases.[29]
The French published an overview of 26 cases of CMML presenting with AID after reviewing case reports of CMML and AID between 1993 and 2013, from fifteen departments of Hematology/Internal Medicine in France. The most common type of AID was systemic vasculitis. They found that CMML and AID were diagnosed concomitantly in 35% of cases. In 46%, AID preceded CMML diagnosis, while in 23% AID presented later in the course of CMML. The median interval between diagnosis of CMML and AID was 0,5 months, ranging from 0-44 months.[30]
It has been postulated that chronic inflammation and autoimmunity might be risk factors for the development of CMML. A Danish group conducted a case-control study on 112 CMML patients diagnosed between 2003 and 2012; controls were unmatched chronic lymphocytic leukaemia (CLL) patients. Sixteen comma one percent of CMML patients had a history of AID compared to 6,5% of CLL patients and this correlated with a significantly increased risk of CMML. At the individual level the association was significant for polymyalgia rheumatica and ITP.[43]

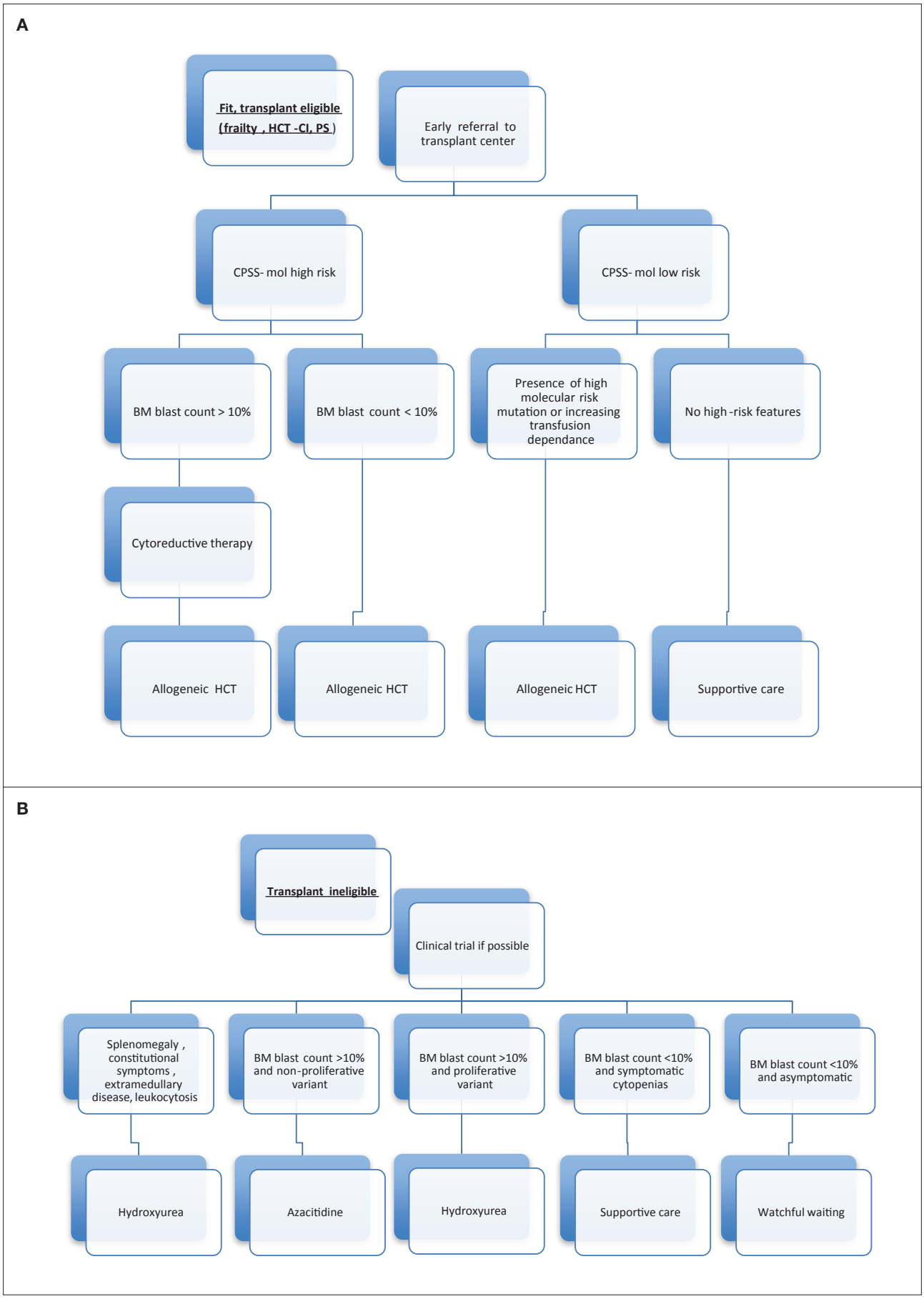

FIGURE 1. Treatment overview of CMML patients. **A.** Transplant eligible patients. **B.** Transplant ineligible patients.

PROGNOSIS AND RISK STRATIFICATION

The general prognosis of patients with CMML is poor with an expected median survival of approximately 30 months. Despite treatment, most patients will ultimately develop cytopenias resulting in infections or fatal bleeding or, in about 25% of cases, progress to AML.

Numerous prognostic scores have been developed using clinical features and laboratory findings, and more recently cytogenetic and molecular analysis.

Historically, the International Prognostic Scoring System (IPSS) and the Revised IPSS (IPSS-R) scoring systems developed for MDS were used, as some CMML-patients were included during the development of both scoring systems. These scores already highlighted the negative impact of an excess of medullary blasts or pronounced cytopenias. This is also reflected by the blast-based grouping in the WHO 2016 classification (*Table 2*).[4]

The proliferative character of the disease is also considered unfavourable, although without consensus what the exact leukocyte threshold is. Patients with a leukocyte count above 13000/μl are considered having a proliferative variant and those below a dysplastic variant.[5] Subsequently, specific CMML-scores appeared based on blast percentage, leukocyte count and age; and later on cytogenetics were also taken into account. A selection of these scores is mentioned in *Table 5*.

With the arrival of NGS techniques, new prognostic systems have been developed taking into account the recurring mutations in CMML and their prognostic impact. One of the latest models developed is the "CPSS-Mol model" of the Italian group (*Table 5*).[46] In this model, the presence of karyotypic abnormalities as well as mutations of *ASXL1, RUNX1, NRAS* and *SETBP1* are taken into account, together with bone marrow blasts, leukocyte count and transfusion dependence. The authors ultimately identified four risk groups whose overall survival ranged from eighteen months to more than 144 months.

RECOMMENDATIONS

All patients should have a risk stratification assessment, preferably according to the CPSS-Mol. For treatment purposes we regard CPSS-Mol low and int-1 as 'low-risk CMML', and CPSS-Mol int-2 and high as 'high-risk CMML'.

If mutational analysis is not available, it is recommended to use any of the clinical CMML-specific scoring systems (*Table 5*).

In addition to these models requiring cytogenetic or molecular testing, the Mayo CMML prognostic model remains useful because it requires only four variables already available in peripheral blood sampling (haemoglobin, platelet count, monocytosis and the presence of immature erythroid precursors).[13]

TREATMENT *(Figure 1)*

Besides allogeneic stem cell transplantation (HCT), there is no curative treatment. Other treatment options are designed to alleviate symptom burden and ameliorate cytopenias or leucocytosis. Therefore, we highly recommend including patients in clinical trials if available.

SUPPORTIVE CARE

Many CMML patients will develop cytopenias during their disease course; these should be managed appropriately.

In case of symptomatic anaemia with low transfusion burden and low endogenous EPO-level (<200U/L), erythropoietin stimulating agents (ESA) are a valuable option in the non-proliferative CMML patient with IPSS-score low or int-1. In patients with higher transfusion burden, iron chelation should be considered.

Prophylactic antibiotics can be considered for neutropenic patients with recurrent infections. Pneumococcal vaccination should be updated and annual influenza vaccine is recommended.

Platelet transfusion is recommended according to local guidelines. As in all chronic malignancies, quality of life and psychosocial aspects are not to be forgotten. Geriatric assessment should be part of the initial work-up.

RECOMMENDATIONS

Manage cytopenias appropriately.

CYTOREDUCTIVE THERAPY

CHEMOTHERAPY

Cytoreduction is required in frontline setting in patients presenting with leucocytosis >50000/μl, constitutional symptoms, splenomegaly or extramedullary haematopoiesis. In case fast debulking is not required (i.e. no bridging strategy to allogeneic transplantation), first choice is hydroxyurea (HU). Management of side effects occurring with HU is well implemented since it is commonly used in myeloproliferative diseases. In the absence of a well-established target for leukocyte or monocyte counts, a general goal is to reduce the leukocyte count below 15000/μl. HU has the

TABLE 6. CPSS-Mol risk score.[46] **A.** Calculation of the cytogenetic risk.

	Spanish cytogenetic risk[1]	*ASXL1*	*NRAS*	*RUNX1*	*SETBP1*
0	low	unmutated	unmutated	unmutated	unmutated
1	intermediate	mutated	mutated	-	mutated
2	high	-	-	mutated	-

Cytogenetic risk score	
0	low
1	int-1
2	int-2
≥3	high

[1]Spanish cytogenetic risk:
low: normal, -Y
intermediate: other
high: trisomy 8, chromosome 7 abnormalities, complex karyotype.

B. Calculation CPPS-Mol.

	0	1	2	3
CPSS genetics	low	int-1	int-2	high
BM blasts	<5%	≥5%	–	–
Leukocyte count	<13000/µl	≥13000/µl	–	–
Transfusion dependence	no	Yes	–	–

CPSS-Mol score	Risk	med OS (mo)
0	low	NR
1	int-1	68
2-3	int-2	30
≥4	high	17

potential to regress and control myeloproliferative features, thereby contributing to a better quality of life. There is no disease modifying effect and therefore it has no effect on hard study endpoints like OS and PFS.

Intravenous chemotherapy can be an option to obtain a fast debulking in eligible patients. '7+3' type induction chemotherapy is the therapy of choice for proliferative CMML with blast excess above 10% as induction for transplantation.

HYPOMETHYLATING AGENTS

Hypomethylating agents (HMA) have no effect on the mutated allele burden and will not prevent accumulation of genetic damage or disease evolution and therefore have no effect on overall survival. The goal of HMA in CMML is to restore a balanced haematopoiesis thereby improving cytopenias and quality of life.

5-Azacytidin (AZA), but not decitabin, is reimbursed only for non-proliferative (<13000/µl) CMML-2 with 10-29%

bone marrow blasts as this form resembles poor risk MDS. The regimen is the same as in MDS with 75 mg/m^2 for seven consecutive days or in a 5+2 regimen with a pause during the weekend every four weeks.

First approval of AZA in MDS and CMML was based on a large phase III study, which only included fourteen CMML patients. Later data confirmed efficacy of AZA in CMML.[47] Response rates are variable and range between 30-60% using IWG criteria, highlighting that these criteria are developed for MDS and may not be well suited for CMML patients.[48] Somatic mutations are not predictive for response. Continued reimbursement requires at least stable bone marrow blast count without worsening of transfusion need at twelve months.

AZA can be an option to reduce disease burden before transplantation.[49] This strategy is adopted from current evidence in AML, although there are no prospective trials in CMML. In Belgium, AZA is only reimbursed in non-transplant eligible patients. Transplant eligibility, however, can vary over time because of disease and patient evolution. If possible, bringing the patient to allogeneic stem cell transplantation should remain the goal since outcome is better with HCT then AZA.

Response assessment of any treatment should be based on blood counts and bone marrow re-evaluation. There are no prospectively validated specific response criteria for CMML; therefore, the IWG criteria for MDS are commonly used. Alternatively, the response criteria for MDS/MPN can be applied since it takes also myeloproliverative features in consideration. However, the MDS/MPN response criteria are only retrospectively validated and prospective validation is needed.[50]

RECOMMENDATIONS

In non-transplant eligible patients, hydroxyurea is the treatment of choice to reduce leucocytosis, constitutional symptoms, splenomegaly and extramedullary haematopoiesis. In non-transplant eligible patients with a dysplastic CMML-2 (up till 29% bone marrow blasts), AZA is a reimbursed treatment option.

Transplant eligible patients with a blast count >10% benefit from induction therapy before transplantation. Both intensive chemotherapy or hypomethylating agents are an option; choice to be made based on patient characteristics, disease characteristics (e.g. cytogenetics) and urgency in the need of response.

ALLOGENEIC STEM CELL TRANSPLANTATION

Allogeneic hematopoietic stem cell transplantation is the only potentially curative treatment for CMML.[51] The decision whether or not to perform HCT must be guided by patient comorbidities (HCT-comorbidity index, frailty and performance status), donor availability and disease aggressiveness. Data concerning HCT in CMML patients are scarce due to smaller patient cohorts and retrospective nature of the studies. The longest follow-up data reach up to nineteen years with a sustained probability of survival of 40% at ten years; however, this comes at a cost of high non-relapse mortality.[52,53]

There is a consensus that patients with high blast count (CMML-2) will benefit from blast reduction to blast count <10% before proceeding to transplantation. The achievement of complete remission at time of transplantation has a favourable influence on overall and event-free survival, mainly because of lower non-relapse mortality.[54]

Taking these two into account, we recommend giving patients with >10% blasts cytoreductive treatment, keeping in mind that early transplant is also important for survival. All young patients and fit high-risk patients should be referred to a transplant centre at diagnosis.

Referral of elderly, but still HCT eligible low risk patients should be considered in the presence of high-risk molecular mutations (e.g. *ASXL1* and *RUNX1*) or in predefined clinical circumstances such as increasing transfusion dependency.

HLA-matched donors, both related and unrelated, are the most reported donor source in CMML. Very few data are available for alternative donor sources (e.g. cord blood and haplo-identical donors).[53,55]

Both myeloablative and reduced intensity conditioning regimens are reported.[51,52] Therefore, the choice of conditioning intensity should be made according to local institutional protocol and based on patient's age and comorbidity.

RECOMMENDATIONS

Early referral to a transplant centre is important for all young patients, and fit high-risk patients. Transplant-eligible elderly low-risk patients should be referred in the presence of high-risk somatic mutations or severe cytopenias.

Cytoreductive therapy pre-transplant is recommended to achieve <10% blasts.

KEY MESSAGES FOR CLINICAL PRACTICE

1. **Diagnosis of CMML relies on the presence of monocytosis with bone marrow dysplasia.**
2. **Cytogenetic abnormalities are present in 20-40% of patients, while gene mutations occur in more than 90% of patients. Most common reported mutations are TET2, SFRF2 and ASXL1.**
3. **Several autoimmune manifestations can occur prior, concomitantly to or after CMML diagnosis.**
4. **Preferable the CPSS-Mol prognostic scoring system is used for risk stratification. If mutational analysis is not available, other prognostic tools based on clinical features and laboratory results may be used.**
5. **Allogeneic stem cell transplantation is the only curative treatment option. Young, and fit high-risk patients and transplant-eligible elderly low-risk patients with high-risk somatic mutations or severe cytopenia should be referred to a transplant center.**
6. **For non-transplant eligible patients, supportive care like transfusions and hydroxyurea in case of myelo-proliferation can be used. For patients with dysplastic CMML-2, AZA is a reimbursed treatment option.**

FUTURE DIRECTIONS

Given the limited effectiveness of current treatments and the poor prognosis of this pathology, many potential treatments are currently under investigation. They include drugs targeting cytokine signalling pathways as agents targeting GM-CSF (lenzilumab) or blocking the RAS pathway (tipifarnib or trametinib). Another therapeutic target could be the spliceosome with an inhibitor of SF3B1 under development (H3B-8800). Immunomodulators such as lenalidomide are also being tested alone or in combination with other agents.

Regarding cytopenias, already available molecules are being tested including luspatercept and eltrombopag to improve anaemia and thrombocytopenia respectively. Finally, molecular target inhibitors such as ruxolitinib or *IDH2*-inhibitors that have already proven their efficacy in other malignancies, are now being tested in CMML.

REFERENCES

1. Swerdlow SH. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon: International Agency for Research on Cancer, 2008.
2. Patnaik MM, et al. Chronic Myelomonocytic leukaemia: 2020 update on diagnosis, risk stratification and management. Am J Hematol. 2020;95(1):97-115.
3. Arber DA, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukaemia. Blood. 2016;127(20):2391-405.
4. Orazi A, et al. Chronic myelomonocytic leukaemia. In: Swerdlow S, Campo E, Harris N, et al., eds. WHO Classification of Tumours of Haematopoeitic and Lymphoid Tissues. Lyon: IARC Press; 2017.
5. Bennett JM, et al. Proposals for the classification of the acute leukaemias French-American-British (FAB) co-operative group. Br J Haematol. 1976; 33(4):451-8.
6. Goasguen JE, et al. Morphological evaluation of monocytes and their precursors. Haematologica. 2009;94(7):994-7.
7. Selimoglu-Buet D, et al. Characteristic repartition of monocyte subsets as a diagnostic signature of chronic myelomonocytic leukaemia. Blood. 2015; 125(23):3618-26.
8. Picot T, et al. Evaluation by Flow Cytometry of Mature Monocyte Subpopulations for the Diagnosis and Follow-Up of Chronic Myelomonocytic Leukemia. Front Oncol. 2018;8:109.
9. Ziegler-Heitbrock L, et al. Nomenclature of monocytes and dendritic cells in blood. Blood. 2010;116(16):e74-80.
10. Talati C, et al. Monocyte subset analysis accurately distinguishes CMML from MDS and is associated with a favorable MDS prognosis. Blood. 2017;129(13):1881-3.
11. Selimoglu-Buet D, et al. Accumulation of classical monocytes defines a subgroup of MDS that frequently evolves into CMML. Blood. 2017;130(6):832-5.
12. Hudson CA, et al. Clinical Utility of Classical and Nonclassical Monocyte Percentage in the Diagnosis of Chronic Myelomonocytic Leukemia. Am J Clin Pathol. 2018;150(4):293-302.
13. Patnaik MM, et al. Mayo prognostic model for WHO-defined chronic myelomonocytic leukaemia: ASXL1 and spliceosome component mutations and outcomes. Leukemia. 2013;27(7):1504-10.
14. Tang G, et al. MLL gene amplification in acute myeloid leukaemia and myelodysplastic syndromes is associated with characteristic clinicopathological findings and TP53 gene mutation. Hum Pathol. 2015;46(1):65-73.
15. Germing U, et al. Risk assessment in chronic myelomonocytic leukaemia (CMML). Leuk Lymphoma. 2004;45(7):1311-8.
16. Such E, et al. Cytogenetic risk stratification in chronic myelomonocytic leukaemia. Haematologica. 2011;96(3):375-83.
17. Onida F, et al. Prognostic factors and scoring systems in chronic myelomonocytic leukaemia: a retrospective analysis of 213 patients. Blood. 2002;99(3):840-9.
18. Solé F, et al. Incidence, characterization and prognostic significance of chromosomal abnormalities in 640 patients with primary myelodysplastic syndromes. Grupo Cooperativo Español de Citogenética Hematológica. Br J

Haematol. 2000;108(2):346-56.
19. Merlevede J, et al. Mutation allele burden remains unchanged in chronic myelomonocytic leukaemia responding to hypomethylating agents. Nat Commun. 2016;7:10767.
20. Meggendorfer M, et al. SRSF2 mutations in 275 cases with chronic myelomonocytic leukaemia (CMML). Blood. 2012;120(15):3080-8.
21. Itzykson R, et al. Prognostic score including gene mutations in chronic myelomonocytic leukaemia. J Clin Oncol. 2013;31(19):2428-36.
22. Malcovati L, et al. Driver somatic mutations identify distinct disease entities within myeloid neoplasms with myelodysplasia. Blood. 2014;124(9):1513-21.
23. Hunter AM, et al. Current Management and Recent Advances in the Treatment of Chronic Myelomonocytic Leukemia. Curr Treat Options Oncol. 2018; 19(12):67.
24. Montoro J, et al. Autoimmune disorders are common in myelodysplastic syndrome patients and confer an adverse impact on outcomes. Ann Hematol. 2018;97(8):1349-56.
25. Mekinian A, et al. Systemic inflammatory and autoimmune manifestations associated with myelodysplastic syndromes and chronic myelomonocytic leukaemia: a French multicentre retrospective study. Rheumatology (Oxford). 2016;55(2):291-300.
26. Krecak I, et al. Coombs-positive refractory acquired thrombotic thrombocytopenic purpura in a patient with chronic myelomonocytic leukaemia successfully treated with rituximab. Acta Clin Belg. 2019:1-5.
27. Araki T, et al. A Case of Acquired Haemophilia A in a Patient with Chronic Myelomonocytic Leukaemia. Case Rep Hematol. 2019;2019:8612031.
28. Zahid MF, et al. Spectrum of autoimmune diseases and systemic inflammatory syndromes in patients with chronic myelomonocytic leukaemia. Leuk Lymphoma. 2017;58(6):1488-93.
29. Peker D, et al. A close association of autoimmune-mediated processes and autoimmune disorders with chronic myelomonocytic leukaemia: observation from a single institution. Acta Haematol. 2015;133(2):249-56.
30. Grignano E, et al. Autoimmune and inflammatory diseases associated with chronic myelomonocytic leukaemia: A series of 26 cases and literature review. Leuk Res. 2016;47:136-41.
31. Georgiou C, et al. Spontaneous bilateral renal aneurysm rupture secondary to Polyarteritis Nodosa in a patient with chronic myelomonocytic leukaemia: A case report study. Int J Surg Case Rep. 2016;26:61-4.
32. Mantzourani MG, et al. Coexistence of Behcet's disease and chronic myelomonocyte leukaemia with trisomy 8: a case report and review of the literature. Clin Exp Rheumatol. 2009;27(2 Suppl 53):S85-7.
33. Sasinowska S, et al. A Rare Case of Paraneoplastic Aortitis Associated with Chronic Myelomonocytic Leukemia. Case Rep Hematol. 2017;2017:3091973.
34. Matsumoto T, et al. A case of chronic myelomonocytic leukaemia complicated with spondyloarthritis. Mod Rheumatol. 2018;28(2):373-5.
35. Moura CA, et al. Chronic myelomonocytic leukaemia mimicking hematologic systemic lupus erythematosus. Lupus. 2017;26(2):204-7.
36. Modi Y, et al. Successful treatment of severe thrombocytopenia with the use of thrombopoeitin receptor agonist eltrombopag in a patient with chronic myelomonocytic leukaemia. J Oncol Pharm Pract. 2015;21(1):74-5.
37. Hadjadj J, et al. Immune thrombocytopenia in chronic myelomonocytic leukaemia. Eur J Haematol. 2014;93(6):521-6.
38. Mainwaring CJ, et al. Not all cases of idiopathic thrombocytopenic purpura [correction of pupura] are what they might first seem. Clin Lab Haematol. 2002;24(4):261-2.
39. Bourgeois E, et al. Role of splenectomy in the treatment of myelodysplastic syndromes with peripheral thrombocytopenia: a report on six cases. Leukemia. 2001;15(6):950-3.
40. Federmann B, et al. Generalized palisaded neutrophilic and granulomatous dermatitis-a cutaneous manifestation of chronic myelomonocytic leukaemia? A clinical, histopathological, and molecular study of 3 cases. Hum Pathol. 2017;64:198-206.
41. Isoda A, et al. Chronic inflammatory demyelinating polyneuropathy accompanied by chronic myelomonocytic leukaemia: possible pathogenesis of autoimmunity in myelodysplastic syndrome. Int J Hematol. 2009;90(2):239-42.
42. Yeung DF, et al. Expressive aphasia in a patient with chronic myelomonocytic leukaemia. Springerplus. 2014;3:406.
43. Elbæk MV, et al. Chronic inflammation and autoimmunity as risk factors for the development of chronic myelomonocytic leukaemia? Leuk Lymphoma. 2016;57(8):1793-9.
44. Such E, et al. Development and validation of a prognostic scoring system for patients with chronic myelomonocytic leukaemia. Blood. 2013;121(15):3005-15.
45. Kantarjian H, et al. Proposal for a new risk model in myelodysplastic syndrome that accounts for events not considered in the original international prognostic scoring system. Cancer. 2008;113(6):1351-61.
46. Elena C, et al. Integrating clinical features and genetic lesions in the risk assessment of patients with chronic myelomonocytic leukaemia. Blood. 2016;128(10):1408-17.
47. Costa R, et al. Activity of Azacitidine (AZA) in Chronic Myelomonocytic Leukemia. Cancer. 2011;117(12):2960-6.
48. Solary E, let al. How I treat chronic myelomonocytic leukaemia. Blood. 2017;130(2):126-36.
49. Kongtim P, et al. Treatment with Hypomethylating Agents before Allogeneic Stem Cell Transplant Improves Progression-Free Survival for.Patients with Chronic Myelomonocytic Leukemia. Biol Blood Marrow Transplant. 2016;22(1):47-53.
50. Savona MR, et al. An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in adults. Blood. 2015 Mar 19;125(12):1857-65.0
51. de Witte T, et al. Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel. Blood. 2017;129(13):1753-62.
52. Bell JA, et al. Systematic Literature Review of Treatment Options and Clinical Outcomes for Patients With Higher-Risk Myelodysplastic Syndromes and Chronic Myelomonocytic Leukemia. Clin Lymphoma Myeloma Leuk. 2018;18(4):e157-e166.
53. Eissa H, et al. Allogeneic hematopoietic cell transplantation for chronic myelomonocytic leukaemia: relapse-free survival is determined by karyotype and comorbidities. Biol Blood Marrow Transplant. 2011;17(6):908-15.
54. Symeonidis A, et al. Achievement of complete remission predicts outcome of allogeneic haematopoietic stem cell transplantation in patients with chronic myelomonocytic leukaemia. A study of the Chronic Malignancies Working Party of the European Group for Blood and Marrow Transplantation. Br J Haematol. 2015;171(2):239-46.
55. Liu HD, et al. Allogeneic Hematopoietic Cell Transplantation for Adult Chronic Myelomonocytic Leukemia. Biol Blood Marrow Transplant. 2017;23(5):767-75.