Chapter 6

Chronic Myelomonocytic Leukaemia

Andreas Himmelmann

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/63193

Abstract

The classification, pathobiology and clinical management of chronic myelomonocytic leukaemia (CMML) are reviewed. Three important issues are identified: (1) CMML should be recognised as a unique clinical entity and as distinct from myelodysplastic syndromes (MDSs). Somatic mutations of a restricted set of genes are frequent in CMML. (2) Risk stratification for CMML patients should utilise new CMML-specific prognostic scoring systems. (3) Until randomised clinical trials have defined the role of new drugs (especially of the hypomethylating agents), treatment must focus on the main symptoms and aim at quality-of-life improvement.

Keywords: chronic myelomonocytic leukaemia, myelodysplastic/myeloproliferative syndrome, somatic mutations, prognosis, therapy

1. Introduction

Chronic myelomonocytic leukaemia (CMML) is a rare haematological neoplasm characterised by a persistent peripheral blood monocytosis and both myelodysplastic and myeloproliferative features. Our understanding of this disease has undergone profound changes in recent years. Initially it was classified as a subtype of myelodysplastic syndromes (MDSs), and it is now recognised as a unique disease. This reclassification has been substantiated by recent advances in the genetic and molecular pathogenesis of CMML, which have confirmed that CMML is biologically distinct from MDS with a different pattern of somatic mutations and a different molecular ontogeny [1]. In addition, CMML-specific prognostic scoring systems (CPSSs) have been established by various groups. These differ from those commonly used in MDS and, for the first time, also include molecular markers. Hopefully, these efforts will culminate in CMML-specific treatments in the near future. The following chapter will summa-

rise these developments starting with a discussion of CMML classification and ending with an outlook on new treatment approaches.

2. Diagnosis and classification

The first reports comprising significant numbers of patients with CMML were published around 40 years ago [2, 3]. These early series already noted a considerable clinical diversity, describing myelodysplasia and cytopenia accompanied by leukocytosis and other myeloproliferative symptoms such as splenomegaly. Nevertheless, the first French–American–British (FAB) Cooperative Group classification of MDS in 1982 included CMML as a MDS subtype, emphasising its dysplastic features but not its diversity [4]. The diagnostic criteria proposed included more than 1×10^9/L blood monocytes, bone marrow blasts of 20% or less, peripheral blasts <5%, and bone marrow dysplastic features in at least one haematopoietic lineage (**Table 1**). To account for the clinical diversity mentioned earlier, the FAB group later introduced a subclassification by dividing patients into two groups based on the leukocyte count at diagnosis [5]. Patients with a leukocyte count above 13×10^9/L were considered to have a myeloproliferative form (MPD-CMML), those with a leukocyte count below 13×10^9/L a myelodysplastic form (MDS-CMML). This arbitrary threshold has been controversial, and its clinical relevance was tested in several cohorts of patients with CMML. In a retrospective analysis of 158 patients (81 patients with MDS-CMML and 77 patients with MPD-CMML), Germing et al. found no significant difference in 2-year overall survival (OS) between these subgroups. The likelihood of transformation to AML was higher in the MDS-CMML group, but this difference was not statistically significant [6]. Voglova et al. [7] described the frequent transition of MDS-CMML to MPD-CMML, suggesting that the two subgroups might represent different stages of the same disease rather than two different entities. Onida et al. analysed a cohort of 213 patients with CMML (35% with MDS-CMML and 65% with MPD-CMML) and could also not find a statistically significant difference in survival after 12 months. There was, however, a trend for a better survival of patients with MPD-CMML after 16 months [8]. To resolve these diagnostic inconsistencies, the WHO (2001) classification of myeloid neoplasms defined a new group of overlap syndromes called myelodysplastic/myeloproliferative diseases (MDS/MPS). Besides CMML, atypical (bcr-abl negative) CML (aCML), juvenile myelomonocytic leukaemia (JMML) and myelodysplastic/myeloproliferative disease, unclassifiable (MDS/MPS-U) were placed in this group [9]. The details of the diagnostic criteria for CMML are listed in **Table 1**. Further, two CMML subtypes were recognised: CMML-1 with PB blast <5% and <10% BM blasts and CMML-2 with 5–19% PB blasts and 10–19% BM blasts. The prognostic significance of these subgroups was confirmed in a reanalysis of the Düsseldorf registry of 300 CMML patients. The 5-year risk of transformation to AML was 63% for patients with CMML-2 compared to only 18% for patients with CMML-1 [10]. More recently, the same group found that further subclassification of CMML based on medullary blast count could provide additional prognostic information [11]. Patients with the new subtype of CMML-0 (defined as <5% medullary blasts) had a better prognosis than those with CMML-1 (OS 31 vs. 19 months). These results have not yet been reproduced in an independent cohort.

The 2008 revision of the WHO classification has maintained the main diagnostic criteria for CMML, with one additional feature [12]. In particular, the recognition of an associated eosinophilia is an important clue to an underlying rearrangement of the platelet-derived growth factor receptor, alpha or beta polypeptide (*PDGFRA*/*B*) gene. If this molecular lesion is found, the case should be classified as a myeloid neoplasm with eosinophilia associated with *PDGFRA*/*B* rearrangement. These patients often respond exquisitely to imatinib [13].

Diagnostic difficulties most commonly arise in the distinction between CMML and aCML, because a monocytosis can be present in the latter. In difficult cases, the pattern of somatic mutations might be exploited in the future [14, 15]. For example, the co-existence of a serine/arginine-rich splicing factor 2 (*SRSF2*) and a ten–eleven translocation-2 (*TET2*) mutation suggests CMML, a SET nuclear proto-oncogene binding protein1 (*SETBP1*) mutation points towards aCML.

The presence of a peripheral blood monocytosis is a diagnostic prerequisite for the diagnosis of CMML but can also be caused by a number of reactive conditions. In patients with clinical or laboratory signs of inflammation, such as fever, arthritis, increased C-reactive protein or elevated erythrocyte sedimentation rate, the diagnosis of CMML should be made with caution. Often, re-evaluation is necessary once the signs of inflammation have subsided. A recent study suggests that the distinction between reactive monocytosis and CMML might be possible by immunophenotyping, but this finding needs further confirmation in independent studies [16].

FAB classification	WHO classification
Myelodysplastic syndrome	MDS/MPD overlap syndrome
PB Monocytosis >1 × 10^9/L	PB Monocytosis >1 × 10^9/L
Myeloblasts <5% in PB, <20% in BM	Myeloblasts <20% in BM
Dysplasia in one or more haematopoietic lineage	No BCR-ABL1 fusion gene
	No PDGFRA/PDGFRB rearrangement
	Dysplasia in one or more myeloid lineage
	If lacking: acquired clonal cytogenetic abnormality
Subclassification	*Subclassification*
MDS-CMML: WBC < 13 × 10^9/L	CMML-1: Blasts PB < 5%, BM < 10%
MPD-CMML: WBC > 13 × 10^9/L	CMML-2: Blasts PB 5–19%, BM 10–19%

FAB, French-American-British; PB, peripheral blood; BM, bone marrow.

Table 1. Comparison of the FAB and WHO classifications of CMML.

3. Epidemiology and clinical features

CMML is a rare disease of the elderly. Two recent population-based studies found a similar age standardised annual incidence rate of approximately 0.3–0.4/100,000/year [17, 18]. Median

age was 70–75 years, and there was a slight male predominance. The study from the Netherlands found that the diagnosis was made in a non-university setting in 78%, indicating that many patients are managed by practising haematologists. This observation emphasises the need to perform clinical studies also in a community-based setting to include as many patients as possible. The 5-year relative survival was poor (16–20%) in this study and did not improve over time. Therapy-related CMML (t-CMML), defined as occurring after chemotherapy, radiotherapy or both, is considered rare but was found in 10% in a recent MD Anderson Cancer Centre (MDACC) series. Patients with t-CMML had a significantly worse median OS compared to patients with de novo disease (13 vs. 20 months), most likely due to a higher rate of intermediate- or high-risk cytogenetic abnormalities [19]. Similar results were reported in a series from the Mayo Clinic (median OS 11 vs. 20 months) [20].

3.1. Clinical features

Monocytosis can be an incidental finding in an otherwise asymptomatic patient. In other cases, it is accompanied by anaemia (in about 50% of patients at diagnosis) and/or thrombocytopenia. Frequently, a haematological prodrome, for example an unclear thrombocytopenia, can be observed. In about 30–60% of patients, leukocyte counts $>13 \times 10^9$/L are found, often with clinical signs of myeloproliferation such as splenomegaly in around 30% [8]. Hepatosplenomegaly is more frequent (25–50% of patients) in the myeloproliferative variant [21]. Many patients experience constitutional symptoms, fatigue, night sweats and occasionally bone pain.

In contrast to MDS, involvement of various organ systems has been described in CMML patients. Skin lesions can be an indicator of leukemic transformation [22]. Serosal infiltration causing pleural or pericardial effusion is quite frequent and can be difficult to treat [23]. Local instillation of mitoxantrone, in combination with systemic chemotherapy, has been used with some success in such cases. A case of widespread gastric involvement mimicking metastatic gastric carcinoma was recently seen in our practice (own unpublished observation). Cases of uncontrollable haematuria caused by CMML involvement of the urogenital tract have also been described [24, 25].

An association with autoimmune-mediated disorders is frequently seen in CMML. For example, in a study of 123 CMML patients, 20% had at least one associated disorder, most commonly immune thrombocytopenia (ITP), gout or psoriasis [26]. Importantly, ITP seems to respond well to standard treatment used in primary ITP, such as steroids and splenectomy [27].

Over time transformation into acute myeloid leukaemia occurs in approximately 30% of patients. The rate of transformation varies according to the risk profile at diagnosis. A sudden rise in the leukocyte count does not necessarily indicate leukemic transformation but can be an expression of increased myeloproliferation. A careful evaluation of the blast count is important in this situation.

3.2. Laboratory and pathologic findings

In the peripheral blood, monocytes can be normal or display atypical features such as fine nuclear chromatin or abnormal nuclear lobulations. In the myeloproliferative variant, median

absolute monocyte counts ranging from 4.2×10^9 to 7.7×10^9/L have been reported [21]; in general, the median monocyte count is around 2×10^9–3×10^9/L. Morphologic evidence of dysgranulopoesis is often seen in CMML, while dysmegakaryopoiesis and dyserythropoiesis are less frequent. The bone marrow is usually hypercellular with an elevated myelopoiesis-to-erythropoiesis ratio. By definition, the blast count is <20%. When enumerating blasts, monoblasts and promonocytes should be included. A helpful morphological classification of monocytic precursors, particularly defining promonocytes in CMML, is available [28]. Monocytic precursors including monoblasts are frequently CD34 negative. Therefore, there is a risk of underestimating the blast number by relying only on CD34 staining in bone marrow biopsies or flow cytometry. The medullary blast count should be determined in good quality bone marrow aspirates that have also been stained for esterase.

4. Cytogenetics

Clonal chromosomal abnormalities occur in approximately 30% of patients with CMML [29, 30]. The most frequent abnormalities are +8 (20–25%), -Y (20%), monosomy 7 and deletion 7q (14%), deletion 20q (8%). A complex karyotype was found in 11%. In contrast to MDS, del5q is very rare. Patients with an abnormal karyotype tended to be older, more anaemic and had a higher peripheral blood and bone marrow blast count [30]. Additional sex combs like 1 (*ASXL1*) mutations were associated with an abnormal karyotype, *SRSF2* mutations with a normal karyotype [31]. Cytogenetic abnormalities were also found to be of prognostic relevance (see Section 6).

5. Molecular findings

Large-scale sequencing studies in myeloid malignancies have lead to important insights into disease biology. These studies have shown one of the highest rates of acquired somatic mutations in CMML patients. For example, in a study by Meggendorfer et al. [31], at least one mutation in 9 recurrently mutated genes was found in 93% of 275 CMML patients. This study and several others also identified clear differences in frequency of mutations in key cellular pathways between CMML and MDS. In addition, the genomic landscape in CMML demonstrates a much smaller molecular heterogeneity compared to a more diffuse mutation profile in MDS [32].

Table 2 summarises the frequency of mutations sorted by the cellular pathway affected [33]. In contrast to MDS, genes serving in different signalling pathways are frequently mutated in CMML. As a biological correlate, an increased sensitivity to GM-CSF has been found in vitro. It appears to be mediated by the STAT pathway, since inhibition of proliferation was observed by the JAK2 inhibitor ruxolitinib [34], indicating the therapeutic potential of these agents or anti GM-CSF monoclonal antibodies.

Cellular pathway	Gene	Frequency (%)
Signalling	*KRAS*	8%
	NRAS	11%
	CBL	10%
	JAK2	10%
	SETBP1	10%
RNA splicing	*SRSF2*	46%
	ZRR2	10%
	U2AF35	10%
Epigenetic regulation	*TET2*	58%
	ASXL1	50%
	EZH2	8%
Transcription	RUNX1	15%

Numbers based on Refs. [1, 33].

Table 2. Frequency of somatic mutations in CMML.

Significant differences were also found in the frequency of mutations affecting RNA splicing. While mutations in *SRSF2* are very common in CMML (40–45%), they are found in <10% of MDS patients, with an enrichment in subtypes with blast excess [31, 32]. Similarly, mutations in epigenetic regulators, among them *TET2* and *ASXL1*, occur much more frequently in CMML than in MDS. For example, using next generation sequencing, *TET2* mutations were found in only 39 of 320 patients with MDS (12%) but in 16 of 35 patients with CMML (46%) [35].

TET2 belongs to the ten–eleven translocations family of proteins and participates in the conversion of 5-methylcytosine to 5-hydroxymethylcytosine. TET2 function depends on the presence of alpha-ketoglutarate, which is produced by isocitrate dehydrogenase 1 and 2 (IDH1/2). *TET2* and *IDH1/2* mutations are mutually exclusive and lead to promoter *hyper*methylation [36], providing a potential explanation for the mode of action of the hypomethylating agents (HMAs). *TET2* mutations appear to be particularly important for CMML pathophysiology and development of its characteristic phenotype. In a series of elegant experiments with samples from CMML patients, Itzykson et al. [37] have shown that early clonal dominance, particularly in a *TET2*-mutated clone, promotes granulomonocytic differentiation. Knockdown experiments of *TET2* in human cord blood CD34+ cells have also found perturbation of myeloid development with promotion of the granulomonocytic lineage [38]. Furthermore, the early occurrence of *TET2* mutations could predetermine the acquisition of secondary mutations, for example in *SRSF2*, leading to characteristic mutational combinations. Besides its role in understanding disease biology and classification, mutational analysis is

likely to impact on various clinical aspects, for example prognostication (discussed below) and prediction of treatment response.

6. Prognosis

6.1. Individual parameters

The importance of the medullary blast count as a prognostic variable was discussed before and forms the basis of the subclassification of CMML into CMML-1 and CMML-2. The prognostic significance of cytogenetic abnormalities was first described by the Spanish MDS group in a cohort of 414 CMML patients. Three risk cytogenetic categories were identified in that study: low risk (normal karyotype and loss of chromosome Y as single abnormality), intermediate (all other single or double abnormalities) and high risk (trisomy 8, abnormalities of chromosome 7 and complex karyotype). The OS at 5 years for these risk groups was 35, 24 and 4%, respectively [29]. In a recent large collaborative analysis of 409 patients with CMML, slightly different cytogenetic risk groups were defined: low risk [normal, sole -Y, sole der(3q)], intermediate (all karyotypes not belonging to high or low risk group) and high risk (complex and monosomal karyotype). In contrast to the Spanish study, trisomy 8 was placed in the intermediate risk group. The median OS was 41, 20 and 3 months, respectively [30]. The mutational status of several genes has also shown to be of prognostic relevance, although conflicting results were found in different cohorts. For example, mutations in *TET2* were associated with no effect on outcome in one study [35] and with an adverse outcome in another study [39]. In a large series of 312 patients tested for a number of genes, only *ASXL1* mutations had a negative prognostic value in multivariate analysis [40]. This finding was confirmed in a larger cohort of 466 patients (including the 312 patients from the original series) [41]. In another large study of 275 CMML patients, no effect of *SRSF2* mutations on survival was observed [31]. In summary, *ASXL1* mutational status has emerged as a robust prognostic variable and has thus been incorporated into CPSSs, as discussed below.

6.2. Prognostic scoring systems

A number of prognostic scoring systems for CMML patients have been developed in the past, none of which however was universally used [42]. This is in contrast to MDS where the International Prognostic Scoring System (IPSS) and its recently revised version (IPSS-R) form the basis of treatment decisions in studies as well as in clinical practice. More recently, novel CMML-specific scoring systems have been described that incorporate cytogenetic or molecular information. These scores appear to be more precise and will be discussed further. First, the CPSS has been developed by the Spanish MDS group in a cohort of 558 patients [43]. It uses WHO/FAB subtype, a CMML-specific cytogenetic risk categorisation and transfusion dependence to divide patients into four risk groups (low, intermediate-1 or intermediate-2, and high) with a median OS of 72, 31, 13 and 5 months, respectively). This model demonstrated for the first time that cytogenetic abnormalities are of prognostic relevance in CMML. Notably, it highlights that the significance of individual cytogenetic abnormalities can vary between

CMML and MDS. For example, trisomy 8 carries an adverse prognosis in CMML but not in MDS. The CPPS has been externally validated in a cohort of 274 patients. Second, the French cooperative MDS group (GFM) developed a prognostic model that included the presence of *ASXL1* mutations, age (>65 years being an adverse prognostic factor), and haematological parameters (WBC > 15×10^9/L, platelet count <100×10^9/L and haemoglobin <11 g/dl being adverse factors). It stratifies patients into 3 risk categories with a median OS of not reached, 38.5 and 14.4 months, respectively, and has also been externally validated [40]. Lastly, the group from the Mayo Clinic has improved on their original prognostic model by incorporating *ASXL1* mutational status. This new score has been termed Mayo Molecular Model (MMM) and was developed in corporation with the GFM [41]. Five risk factors affected median survival in multivariate analysis*: ASXL1* mutation status, absolute monocyte count >10×10^9/L, haemoglobin levels <10 g/dl, platelet count <100×10^9/L, and circulating immature myeloid cells. It divides patients into four risk categories with median survival of 97, 59, 37 and 16 months, respectively. Importantly, this new score can identify low risk patients (by the original Mayo Clinic score) with a high risk of progression (without or with *ASXL1* mutation: median survival 99 vs. 44 months).

Particularly when considering allogeneic stem cell transplantation, prognostication in younger CMML patients, defined as younger than 65 years, is crucial. A retrospective analysis of 261 such patients has identified several adverse prognostic factors that differ from those in the general CMML population. In addition to anaemia and *ASXL1* mutations, an increased circulating blast count, *SRSF2* mutations and the cytogenetic risk classification of the Mayo-French consortium were independently prognostic. In this study, *ASXL1* and *SRSF2* mutation status did not influence response to HMAs or transplantation outcome [44].

In summary, it is evident that CPSSs that include cytogenetic and/or molecular parameters should be employed in the future.

7. Therapy

7.1. General considerations

Although providing little prognostic information, the concept of a myelodysplastic and a myeloproliferative variant of CMML is helpful in guiding treatment. In particular, patients suffering mainly from uncontrolled myeloproliferation may require rapidly acting cytoreductive treatment. On the other hand, patients with symptoms due to marrow failure require treatment aiming at restoring adequate peripheral blood counts. No treatment so far has been shown to prolong survival or to alter the natural history of the disease. However, randomised studies in CMML patients have not yet been performed, with one exception [45]. Typically, CMML patients (excluding those with MPD-CMML) were included in MDS trials, albeit in small numbers precluding a meaningful statistical analysis. For example, in the AZA-001 trial that led to the registration of azacitidine in higher risk MDS only 16 of the 358 enrolled patients had CMML [46].

For the treatment of lower risk patients with symptomatic anaemia, erythropoiesis-stimulating agents (ESA) might be helpful. A 64% erythroid response rate and transfusion independence in 33% of patients was recently reported in a retrospective analysis of 94 CMML patients. Low/intermediate-1 CPSS and low endogenous erythropoietin levels were predictors of response [47]. ESA's should be used with caution in patients with myeloproliferative CMML because of the risk of splenic enlargement or rupture.

Younger patients with high-risk features (for example intermediate-2 or high risk in the MMM) should be evaluated for eligibility for allogeneic stem cell transplantation. Whether high-risk patients benefit from early treatment with HMAs, as in high-risk MDS, must be tested in prospective randomised trials.

7.2. Stem cell transplantation

Allogeneic stem cell transplant (allo-SCT) still remains the only curative option for patients with CMML and should be considered in younger patients with high-risk disease. So far all reports on allo-SCT in CMML have been retrospective and many included patients with CMML as well as MDS. CMML-specific patient series have only been recently reported, with the EBMT series comprising 513 patients being by far the largest [48]. The median age was 53 years, clearly younger than the median age of CMML patients in general. The non-relapse mortality at 1 and 4 years was 31 and 41%, respectively. The incidence of relapse at 4 years was 32%, resulting in an estimated 4-year relapse free survival of 27% and OS of 33%, respectively. Of note, no influence of procedure-related parameters such as stem cell source, type of donor or T-cell depletion on outcome was found. Importantly, the only significant parameter associated with an improved outcome was the presence of a complete remission at the time of transplantation. A similar trend was also found in a smaller study [49]. Thus, allo-SCT can provide long-term remissions in about 30% of younger patients. The procedure should be performed after achievement of the best possible remission status, either with combination chemotherapy or with HMAs. Although the best preparatory regimen is not known, a recent retrospective study of 83 patients from the MDACC supports the use of HMA before allo-SCT. The study found a significantly lower incidence of relapse at 3 years post transplant in patients treated with HMA, compared to patients treated with other agents (22 vs. 35%, $p = 0.03$), resulting in a better 3-year progression-free survival [50]. A selection bias might confound these interesting results, since patients who do not progress while treated with HMA (median of 6 cycles in the study) are likely to have a less aggressive disease.

7.3. Cytoreductive treatment

In patients with symptoms mainly caused by myeloproliferation, cytoreductive treatment is indicated. Several studies have demonstrated the effect of the topoisomerase-I inhibitor topotecan in patients with CMML. As a single-agent, complete response rates of up to 28% have been described [51]. Similarly, clinically meaningful responses, including improvement of life threatening pericardial and pleural effusions, as well as cytopenias were reported for the topoisomerase-II inhibitor etoposide [52]. However, in a randomised study of 105 patients from 43 European centres, hydroxyurea was found to be superior to etoposide in terms of the

response rate (60 vs. 36%) and OS (20 vs. 9 months) and has thus remained the treatment of choice for palliative cytoreduction in CMML patients [45]. The experience with intensive chemotherapy in CMML has been disappointing [53]. AML-like induction therapy is only rarely used, usually as a preparatory regimen before allogeneic stem cell transplantation in patients with an aggressive disease.

7.4. Hypomethylating agents

The introduction of the HMAs azacitidine and decitabine is likely to transform clinical management of CMML. A growing number of studies have shown considerable single agent activity with very low toxicity. In the largest study so far (76 patients from France, Cleveland Clinic and Lee Moffitt Cancer Center), a response rate of 43%, with 17% complete remissions, was found [54]. Of note, 46% had a proliferative form of CMML, as defined by a leukocyte count of $>13 \times 10^9$/L. In that study, the presence of more than 10% bone marrow blasts and palpable splenomegaly had a negative impact on survival. A smaller Italian retrospective study analysed the response in 31 patients with CMML (42% with CMML-1, 58% with CMML-2) who were treated with azacitidine at a dose of 75 or 50 mg/m^2 for 7 days. The overall response rate was 51%, including 45% achieving complete remission [55]. A study from the Austrian Azacitidine registry reported on the outcome of 48 patients treated with azacitidine at 11 different centres [56]. Mean age was 71 years; 40% had CMML-1; 60% had CMML-2; and splenomegaly was found in 48%. Even in this unselected cohort with several high-risk features, there was a surprising response rate of 70%, including 22% complete responses. Matched paired analysis suggested a better 2-year-survival when compared to best supportive care (62 vs. 41%, $p = 0.067$).

Other studies have examined the activity of the related HMA decitabine in CMML. One of the first reports was published by the MDACC group on 19 patients with CMML, and a complete response rate of 58% was found. The dose of decitabine was 100 mg/m^2 per course, given in three different treatment schedules [57]. In a phase 2 trial from the GFM, 39 patients with advanced CMML were treated with decitabine at a dose of 20 mg/m^2 for 5 days. The median number of treatment cycles was 10 and the overall response rate 38%, OS at 2 years was 48%. Interestingly, the presence of *ASXL1* mutations had no significant impact on response or survival in that study [58]. A review of CMML patients that were included in several phase 2 and one phase 3 trials of decitabine in MDS was done by Wijermans et al. [59]. Among a total of 271 patients, 31 CMML patients were identified. The overall response rate was 25% with 14% CR, and 39% had stable disease. The treatment schedule was different than in the GFM study, and many patients received only a few cycles of therapy (median of four cycles).

Reliable and easily available predictors of response to treatment with HMA have not yet been identified. Although a correlation of response with *TET2* mutational status would seem plausible, this was not found in two different studies [58, 60]. Likewise, no other somatic mutation frequent in CMML proved to be predictive of response.

A small retrospective analysis has shown activity of decatibine and azacitidine in reducing spleen size in CMML patients. Spleen size was measured by physical examination, and complete or partial spleen response was found in 5 of 11 patients (45%) [61].

Although these data are promising and have led to the registration of both drugs for the treatment of CMML, data from phase 3 trials demonstrating a survival benefit are not yet available. Also, the optimal treatment schedule and treatment duration need to be defined. The results of an ongoing randomised trial (DACOTA trial) comparing hydroxyurea to decitabine in patients with advanced proliferative CMML are, therefore, eagerly awaited. This trial is conducted in three countries (France, Italy and Germany) and will include about 160 patients. The primary endpoint is progression-free survival.

7.5. Investigational agents

A large number of investigational agents have been tested in CMML, among them tyrosine kinase inhibitors, farnesyltransferase inhibitors, immunomodulators and most recently JAK2 inhibitors. The experience with many of these approaches is limited to small phase 1 or phase 2 studies that have not been further developed, either because of limited activity or because of significant toxicity.

Imatinib has shown no effect in CMML patients without a *PDGFRB* rearrangement. Because CMML cells often have *RAS* activating mutations, drugs targeting this pathway have been tested. In a phase 2 trial, 35 patients with CMML were treated with lonafarnib (200–300 mg twice daily), one CR and 7 haematological improvements were reported. Major toxicities were gastrointestinal, fatigue, fever and hypokalemia [62]. Similar results were observed for tipifanib in a study of 10 CMML patients [63]. In several patients treated with lonafarnib, a significant increase in the white blood cell count was noted, sometimes accompanied by oedema and respiratory symptoms. This complication resolved quickly after discontinuation of lonafarnib and treatment with dexamethasone [64]. Disappointingly, translational studies have shown no correlation between responses and inhibition of farnesyl transferase.

Interesting results have been found in a study targeting angiogenesis in MDS and CMML patients with a combination consisting of melphalan (2 mg/day) and lenalidomide (10 mg/day). Changes in circulating endothelial cells and plasma VEGF levels served as biomarkers of angiogenesis. The response rate was 33% in CMML patients (3/9), all of which had a proliferative form of the disease. Interestingly, there was a correlation between response and angiogenesis inhibition in these patients. Dose reductions were frequently necessary, but many patients were cytopenic already at baseline [65].

Most recently, a multicentre phase 1 trial (only published in abstract form) tested the JAK2 inhibitor ruxolitinib in 19 CMML patients. All patients had CMML-1 and those with significant cytopenias were excluded. No dose limiting toxicity was noted. Although there were few haematologic responses, a frequent improvement of splenomegaly and B symptoms was found. A phase 2 trial testing ruxolitinib at a dose of 20 mg BID is planned [66].

8. Summary and outlook

CMML is a rare myeloid neoplasm with an overall poor prognosis. Important progress has been made in recent years in several aspects. First, the recognition of CMML as a unique disease

entity, separated from the myelodysplastic syndromes, is an important step towards optimising clinical management. Second, the introduction of CPSSs will improve patient selection in clinical trials. Phase 3 clinical trials in CMML patients will soon define the role of HMA in treatment. The elucidation of the mutational landscape in CMML has not provided disease-specific mutations but highly characteristic mutational combinations, particularly of *TET2* and *SRSF2*. These insights into molecular pathology are very likely to provide the basis for the development of novel therapeutic agents. Individualised therapies based on the predominant gene mutations could be envisaged. For example, while patients with *TET2* mutations are treated with HMA, in patients with mutations affecting signalling, specific pathway inhibitors might be more potent. Clearly, novel strategies and agents are needed for this still difficult to treat disease.

Author details

Andreas Himmelmann*

Address all correspondence to: andreas.himmelmann@hirslanden.ch

Haematology Practice Lucerne, Clinic St. Anna, Lucerne, Switzerland

References

[1] Benton CB, Nazha A, Pemmaraju N, Garcia-Manero G. Chronic myelomonocytic leukemia: forefront of the field in 2015. Crit Rev Oncol Hematol 2015;95:222–42.

[2] Geary CG, Catovsky D, Wiltshaw E, Milner GR, Scholes MC, Van Noorden S, et al. Chronic myelomonocytic leukaemia. Br J Haematol 1975;30:289–302.

[3] Miescher PA, Farguet JJ. Chronic myelomonocytic leukemia in adults. Semin Hematol 1974;11:129–39.

[4] Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, et al. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol 1982;51:189–99.

[5] Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick H, et al. The chronic myeloid leukaemias: guidelines for distinguishing chronic granulocytic, atypical chronic myeloid, and chronic myelomonocytic leukaemia. Proposals by the French–American–British Cooperative Leukaemia Group. Br J Haematol 1994;87:746–54.

[6] Germing U, Gattermann N, Minning H, Heyll A, Aul C. Problems in the classification of CMML—dysplastic versus proliferative type. Leuk Res 1998;22:871–8.

[7] Voglová J, Chrobák L, Neuwirtová R, Malasková V, Straka L. Myelodysplastic and myeloproliferative type of chronic myelomonocytic leukemia—distinct subgroups or two stages of the same disease? Leuk Res 2001;25:493–9.

[8] Onida F, Kantarjian HM, Smith TL, Ball G, Keating MJ, Estey EH, et al. Prognostic factors and scoring systems in chronic myelomonocytic leukemia: a retrospective analysis of 213 patients. Blood 2002;99:840–9.

[9] Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. Blood 2002;100:2292–302.

[10] Germing U, Strupp C, Knipp S, Kuendgen A, Giagounidis A, Hildebrandt B, et al. Chronic myelomonocytic leukemia in the light of the WHO proposals. Haematologica 2007;92:974–7.

[11] Schuler E, Schroeder M, Neukirchen J, Strupp C, Xicoy B, Kündgen A, et al. Refined medullary blast and white blood cell count based classification of chronic myelomonocytic leukemias. Leuk Res 2014;38:1413–9.

[12] Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood 2009;114:937–51.

[13] Apperley JF, Gardembas M, Melo JV, Russell-Jones R, Bain BJ, Baxter EJ, et al. Response to imatinib mesylate in patients with chronic myeloproliferative diseases with rearrangements of the platelet-derived growth factor receptor beta. N Engl J Med 2002;347:481–7.

[14] Li B, Gale RP, Xiao Z. Molecular genetics of chronic neutrophilic leukemia, chronic myelomonocytic leukemia and atypical chronic myeloid leukemia. J Hematol Oncol 2014;7:93.

[15] Meggendorfer M, Haferlach T, Jeromin S, Haferlach C, Kern W, Schnittger S. Molecular analyses of MDS/MPN overlap entities according to WHO classification reveal a distinct molecular pattern for MDS/MPN, unclassifiable. Blood 2014;124:4618–8.

[16] Selimoglu-Buet D, Wagner-Ballon O, Saada V, Bardet V, Itzykson R, Bencheikh L, et al. Characteristic repartition of monocyte subsets as a diagnostic signature of chronic myelomonocytic leukemia. Blood 2015;125:3618–26.

[17] Visser O, Trama A, Maynadié M, Stiller C, Marcos-Gragera R, De Angelis R, et al. Incidence, survival and prevalence of myeloid malignancies in Europe. Eur J Cancer 2012;48:3257–66.

[18] Dinmohamed AG, van Norden Y, Visser O, Posthuma EFM, Huijgens PC, Sonneveld P, et al. The use of medical claims to assess incidence, diagnostic procedures and initial treatment of myelodysplastic syndromes and chronic myelomonocytic leukemia in the Netherlands. Leuk Res 2015;39:177–82.

[19] Takahashi K, Pemmaraju N, Strati P, Nogueras-Gonzalez G, Ning J, Bueso-Ramos C, et al. Clinical characteristics and outcomes of therapy-related chronic myelomonocytic leukemia. Blood 2013;122:2807–11.

[20] Subari S, Patnaik M, Alfakara D, Gangat N, Elliott M, Hogan W, et al. Patients with therapy-related CMML have shorter median overall survival than those with De Novo CMML: Mayo Clinic long-term follow-up experience. Clin Lymphoma Myeloma Leuk 2015;15:546–9.

[21] Onida F, Beran M. Chronic myelomonocytic leukemia: myeloproliferative variant. Curr Hematol Rep 2004;3:218–26.

[22] Mathew RA, Bennett JM, Liu JJ, Komrokji RS, Lancet JE, Naghashpour M, et al. Cutaneous manifestations in CMML: indication of disease acceleration or transformation to AML and review of the literature. Leuk Res 2012;36:72–80.

[23] Morita Y, Ohyama Y, Rai S, Kawauchi M, Yamaguchi T, Shimada T, et al. A case of chronic myelomonocytic leukemia who developed pericardial effusion during stably controlled leukocytosis. Intern Med 2011;50:1737–40.

[24] Bane AL, Enright H, Sweeney EC. Chronic myelomonocytic leukemia revealed by uncontrollable hematuria. Arch Pathol Lab Med 2001;125:657–9.

[25] Hyams ES, Gupta R, Melamed J, Taneja SS, Shah O. Renal involvement by chronic myelomonocytic leukemia requiring nephroureterectomy. Rev Urol 2009;11:33–7.

[26] Peker D, Padron E, Bennett JM, Zhang X, Horna P, Epling-Burnette PK, et al. A close association of autoimmune-mediated processes and autoimmune disorders with chronic myelomonocytic leukemia: observation from a single institution. Acta Haematol 2015;133:249–56.

[27] Hadjadj J, Michel M, Chauveheid M-P, Godeau B, Papo T, Sacre K. Immune thrombocytopenia in chronic myelomonocytic leukemia. Eur J Haematol 2014;93:521–6.

[28] Goasguen JE, Bennett JM, Bain BJ, Vallespí T, Brunning R, Mufti GJ. Morphological evaluation of monocytes and their precursors. Haematologica 2009;94:994–7.

[29] Such E, Cervera J, Costa D, Solé F, Vallespí T, Luño E, et al. Cytogenetic risk stratification in chronic myelomonocytic leukemia. Haematologica 2011;96:375–83.

[30] Wassie EA, Itzykson R, Lasho TL, Kosmider O, Finke CM, Hanson CA, et al. Molecular and prognostic correlates of cytogenetic abnormalities in chronic myelomonocytic leukemia: a Mayo Clinic-French Consortium Study. Am J Hematol 2014;89:1111–5.

[31] Meggendorfer M, Roller A, Haferlach T, Eder C, Dicker F, Grossmann V, et al. SRSF2 mutations in 275 cases with chronic myelomonocytic leukemia (CMML). Blood 2012;120:3080–8.

[32] Haferlach T, Nagata Y, Grossmann V, Okuno Y, Bacher U, Nagae G, et al. Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. Leukemia 2014;28:241–7.

[33] Zoi K, Cross NCP. Molecular pathogenesis of atypical CML, CMML and MDS/MPN-unclassifiable. Int J Hematol 2015;101:229–42.

[34] Padron E, Painter JS, Kunigal S, Mailloux AW, McGraw K, McDaniel JM, et al. GM-CSF-dependent pSTAT5 sensitivity is a feature with therapeutic potential in chronic myelomonocytic leukemia. Blood 2013;121:5068–77.

[35] Smith AE, Mohamedali AM, Kulasekararaj A, Lim Z, Gäken J, Lea NC, et al. Next-generation sequencing of the TET2 gene in 355 MDS and CMML patients reveals low-abundance mutant clones with early origins, but indicates no definite prognostic value. Blood 2010;116:3923–32.

[36] Figueroa ME, Abdel-Wahab O, Lu C, Ward PS, Patel J, Shih A, et al. Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, disrupt TET2 function, and impair hematopoietic differentiation. Cancer Cell 2010;18:553–67.

[37] Itzykson R, Kosmider O, Renneville A, Morabito M, Preudhomme C, Berthon C, et al. Clonal architecture of chronic myelomonocytic leukemias. Blood 2013;121:2186–98.

[38] Pronier E, Almire C, Mokrani H, Vasanthakumar A, Simon A, da Costa Reis Monte Mor B, et al. Inhibition of TET2-mediated conversion of 5-methylcytosine to 5-hydroxymethylcytosine disturbs erythroid and granulomonocytic differentiation of human hematopoietic progenitors. Blood 2011;118:2551–5.

[39] Kosmider O, Gelsi-Boyer V, Ciudad M, Racoeur C, Jooste V, Vey N, et al. TET2 gene mutation is a frequent and adverse event in chronic myelomonocytic leukemia. Haematologica 2009;94:1676–81.

[40] Itzykson R, Kosmider O, Renneville A, Gelsi-Boyer V, Meggendorfer M, Morabito M, et al. Prognostic score including gene mutations in chronic myelomonocytic leukemia. J Clin Oncol 2013;31:2428–36.

[41] Patnaik MM, Itzykson R, Lasho TL, Kosmider O, Finke CM, Hanson CA, et al. ASXL1 and SETBP1 mutations and their prognostic contribution in chronic myelomonocytic leukemia: a two-center study of 466 patients. Leukemia 2014;28:2206–12.

[42] Mughal TI, Cross NCP, Padron E, Tiu RV, Savona M, Malcovati L, et al. An International MDS/MPN Working Group's perspective and recommendations on molecular pathogenesis, diagnosis and clinical characterization of myelodysplastic/myeloproliferative neoplasms. Haematologica 2015;100:1117–30.

[43] Such E, Germing U, Malcovati L, Cervera J, Kuendgen A, Porta Della MG, et al. Development and validation of a prognostic scoring system for patients with chronic myelomonocytic leukemia. Blood 2013;121:3005–15.

[44] Patnaik MM, Wassie EA, Padron E, Onida F, Itzykson R, Lasho TL, et al. Chronic myelomonocytic leukemia in younger patients: molecular and cytogenetic predictors of survival and treatment outcome. Blood Cancer J 2015;5:e270.

[45] Wattel E, Guerci A, Hecquet B, Economopoulos T, Copplestone A, Mahé B, et al. A randomized trial of hydroxyurea versus VP16 in adult chronic myelomonocytic leukemia. Groupe Français des Myélodysplasies and European CMML Group. Blood 1996;88:2480–7.

[46] Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol 2009;10:223–32.

[47] Xicoy B, Germing U, Jimenez M-J, Garcia O, Garcia R, Schemenau J, et al. Response to erythropoietic-stimulating agents in patients with chronic myelomonocytic leukemia. Eur J Haematol 2015. doi:10.1111/ejh.12679. [Epub ahead of print].

[48] Symeonidis A, van Biezen A, de Wreede L, Piciocchi A, Finke J, Beelen D, 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;98:983–91.

[49] Warlick ED, Cioc A, Defor T, Dolan M, Weisdorf D. Allogeneic stem cell transplantation for adults with myelodysplastic syndromes: importance of pretransplant disease burden. Biol Blood Marrow Transplant 2009;15:30–8.

[50] Kongtim P, Popat U, Jimenez A, Gaballa S, Fakih El R, Rondon G, 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;22:47–53.

[51] Beran M, Kantarjian H, O'Brien S, Koller C, Al-Bitar M, Arbuck S, et al. Topotecan, a topoisomerase I inhibitor, is active in the treatment of myelodysplastic syndrome and chronic myelomonocytic leukemia. Blood 1996;88:2473–9.

[52] Oscier DG, Worsley A, Hamblin TJ, Mufti GJ. Treatment of chronic myelomonocytic leukaemia with low dose etoposide. Br J Haematol 1989;72:468–71.

[53] Wattel E, De Botton S, Luc Laï J, Preudhomme C, Lepelley P, Bauters F, et al. Long-term follow-up of de novo myelodysplastic syndromes treated with intensive chemotherapy: incidence of long-term survivors and outcome of partial responders. Br J Haematol 1997;98:983–91.

[54] Ades L, Sekeres MA, Wolfromm A, Teichman ML, Tiu RV, Itzykson R, et al. Predictive factors of response and survival among chronic myelomonocytic leukemia patients treated with azacitidine. Leuk Res 2013;37:609–13.

[55] Fianchi L, Criscuolo M, Breccia M, Maurillo L, Salvi F, Musto P, et al. High rate of remissions in chronic myelomonocytic leukemia treated with 5-azacytidine: results of an Italian retrospective study. Leuk Lymphoma 2013;54:658–61.

[56] Pleyer L, Germing U, Sperr WR, Linkesch W, Burgstaller S, Stauder R, et al. Azacitidine in CMML: matched-pair analyses of daily-life patients reveal modest effects on clinical course and survival. Leuk Res 2014;38:475–83.

[57] Aribi A, Borthakur G, Ravandi F, Shan J, Davisson J, Cortes J, et al. Activity of decitabine, a hypomethylating agent, in chronic myelomonocytic leukemia. Cancer 2007;109:713–7.

[58] Braun T, Itzykson R, Renneville A, de Renzis B, Dreyfus F, Laribi K, et al. Molecular predictors of response to decitabine in advanced chronic myelomonocytic leukemia: a phase 2 trial. Blood 2011;118:3824–31.

[59] Wijermans PW, Ruter B, Baer MR, Slack JL, Saba HI, Lubbert M. Efficacy of decitabine in the treatment of patients with chronic myelomonocytic leukemia (CMML). Leuk Res 2008;32:587–91.

[60] Meldi K, Qin T, Buchi F, Droin N, Sotzen J, Micol J-B, et al. Specific molecular signatures predict decitabine response in chronic myelomonocytic leukemia. J Clin Investig 2015;125:1857–72.

[61] Subari S, Patnaik M, Alfakara D, Zblewski D, Hook C, Hashmi S, et al. Hypomethylating agents are effective in shrinking splenomegaly in patients with chronic myelomonocytic leukemia. Leuk Lymphoma 2015;1–7 [Epub ahead of print].

[62] Feldman EJ, Cortes J, DeAngelo DJ, Holyoake T, Simonsson B, O'Brien SG, et al. On the use of lonafarnib in myelodysplastic syndrome and chronic myelomonocytic leukemia. Leukemia 2008;22:1707–11.

[63] Kurzrock R, Kantarjian HM, Cortes JE, Singhania N, Thomas DA, Wilson EF, et al. Farnesyltransferase inhibitor R115777 in myelodysplastic syndrome: clinical and biologic activities in the phase 1 setting. Blood 2003;102:4527–34.

[64] Buresh A, Perentesis J, Rimsza L, Kurtin S, Heaton R, Sugrue M, et al. Hyperleukocytosis complicating lonafarnib treatment in patients with chronic myelomonocytic leukemia. Leukemia 2005;19:308–10.

[65] Buckstein R, Kerbel R, Cheung M, Shaked Y, Chodirker L, Lee CR, et al. Lenalidomide and metronomic melphalan for CMML and higher risk MDS: a phase 2 clinical study with biomarkers of angiogenesis. Leuk Res 2014;38:756–63.

[66] Padron E, Dezern A, Andrade-Campos M, Vaddi K, Scherle P, Zhang Q, et al. A multi-institution phase 1 trial of ruxolitinib in patients with chronic myelomonocytic leukemia (CMML). Clin Cancer Res 2016

IntechOpen