

# Management recommendations for chronic myelomonocytic leukemia: consensus statements from the SIE, SIES, GITMO groups

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## ABSTRACT

With the aim of reviewing critical concepts and producing recommendations for the management of chronic myelomonocytic leukemia, key questions were selected according to the criterion of clinical relevance. Recommendations were produced using a Delphi process and four consensus conferences involving a panel of experts appointed by the Italian Society of Hematology and affiliated societies. This report presents the final statements and recommendations, covering patient evaluation at diagnosis, diagnostic criteria, risk classification, first-line therapy, monitoring, second-line therapy and allogeneic stem cell transplantation. For the first-line therapy, the panel recommended that patients with myelodysplastic-type chronic myelomonocytic leukemia and less than 10% blasts in bone marrow should be managed with supportive therapy aimed at correcting cytopenias. In patients with myelodysplastic-type chronic myelomonocytic leukemia with a high number of blasts in bone marrow ( $\geq 10\%$ ), supportive therapy should be integrated with the use of 5-azacytidine. Patients with myeloproliferative-type chronic myelomonocytic leukemia with a low number of blasts ( $<10\%$ ) should be treated with cytoreductive therapy. Hydroxyurea is the drug of choice to control cell proliferation and to reduce organomegaly. Patients with myeloproliferative-type chronic myelomonocytic leukemia, and a high number of blasts should receive polychemotherapy. Both in myelodysplastic-type and myeloproliferative-type chronic myelomonocytic leukemia, allogeneic stem cell transplantation should be offered within clinical trials in selected patients.

## Introduction

Chronic myelomonocytic leukemia (CMML) is classified by the WHO as a clonal hematopoietic malignancy characterized by features of both a myeloproliferative neoplasm and a myelodysplastic syndrome.<sup>1</sup> CMML accounts for 10% of all cases of myelodysplastic syndromes;<sup>2,3</sup> affected patients are diagnosed at a median age of 65-75 years, and there is a 2 to 1 male predominance.<sup>3</sup> The most common symptoms of CMML are a reflection of the underlying cytopenia, hypercatabolic syndrome, splenomegaly, or organ infiltration of monocytes. The disease presents with variable clinical phenotypes, the prognosis is generally poor, and effective therapies are limited.<sup>2</sup> In recent years, array and sequencing technologies have provided new insights into the molecular pathogenesis of CMML.<sup>2</sup> Molecular discoveries, however, have not yet been translated into changes in disease management. Therefore, therapy for CMML remains a challenge. For this reason, the Italian Society of Hematology (SIE) and affiliated Societies (the Italian Society of Experimental Hematology, SIES, and the Italian Group for Bone Marrow Transplantation, GITMO) decided to review recent data regarding diagnostic criteria, evaluation needs at diagnosis, assessment of prognostic risk, and determinants of therapeutic

intervention, in order to produce recommendations aimed at helping to optimize and standardize CMML clinical management.

## Methods

An expert panel of 8 hematologists with a long experience and scientific interest in CMML was selected. During an initial meeting on December 2011, the areas of major concern in the management of CMML were identified. Clinical key-questions were generated and rank-ordered using the criterion of clinical relevance (Table 1).

Each panelist drafted statements that addressed the key questions, and the remaining panelists scored their agreement with those statements providing suggestions for re-phrasing. To exploit this phase of the process, the Delphi questionnaire method was used.<sup>4</sup> Finally, the panel met three times in Bologna, Italy, for consensus conferences. The nominal group technique<sup>5</sup> was used according to which participants were first asked to comment in round-robin fashion on their preliminary votes and then to propose a new vote.

## Results

### Patient evaluation at diagnosis

The diagnosis of CMML relies largely on findings of bone

marrow (BM) morphological dysplasia or clonal genetic abnormalities in patients with persistent peripheral blood monocytosis. Conventional cytogenetic analysis can allow clonal abnormalities to be identified, even if most patients with CMML exhibit a normal karyotype.<sup>6</sup> The most frequent abnormalities involve chromosome 7, mostly consisting of monosomy, trisomy 8, and a complex karyotype involving 3 or more abnormalities.<sup>7</sup>

Several molecular gene mutations have been found in CMML.<sup>8-10</sup> These mutations affect different cellular targets and processes, like RUNX1<sup>9,11,12</sup> (transcription regulation), isocitrate dehydrogenases IDH1/IDH2<sup>13</sup> (metabolism), KRAS, NRAS, CBL, and JAK2<sup>9,14-17</sup> (tyrosine-signaling pathways), TET2, DNMT3A, ASXL1, UTX, EZH2<sup>8,18-21</sup> (epigenetic regulatory mechanism), and SRSF2<sup>22</sup> (splicing regulation). Mutations involving the NRAS, KRAS, TET2, CBL and SRSF2 genes, and JAK2 V617F mutations are the most frequently reported.<sup>22</sup> A comprehensive mutation analysis revealed that 93% of all CMML patients carried at least one somatic mutation in 9 recurrently mutated genes.<sup>22</sup>

Flow cytometry immunophenotyping may detect aberrancies in the monocytic lineage, including abnormal CD11b/HLA-DR, CD36/CD14, abnormal intensity of CD13, CD14, CD16, CD33, CD36, CD64, expression of CD34 and lineage infidelity markers, and overexpression of CD56.<sup>23-25</sup> None of these aberrancies are specific for CMML.

### Recommendations

The diagnostic workup of a suspected CMML should include: patient's history aimed at excluding reactive causes of monocytosis (in particular, infectious diseases and solid tumors); physical examination (in particular, assessment of spleen size and search for cutaneous lesions); complete blood count and peripheral blood smear examination with differential leukocyte count; bone marrow aspiration and biopsy; conventional cytogenetic analysis; molecular assays to exclude bcr/abl fusion gene and rearrangement of PDGFRA and PDGFRB; any investigation necessary to exclude infectious diseases with monocytosis. A sample of bone marrow cells should be stored for possible further molecular analysis in centers where a certified tissue bank is available.

Useful diagnostic information gained from peripheral blood smear examination includes: monocyte count; presence of dysgranulopoiesis; presence of promonocytes, blasts, and neutrophil precursors. Useful diagnostic information from bone marrow aspiration is: presence of dysplasia in one or more myeloid lineages; granulocytic hyperplasia; percentage of blasts, that should include myeloblasts, monoblasts and promonocytes.

Staining of bone marrow biopsy sections should include hematoxylin-eosin or equivalent, immunostaining for CD34<sup>+</sup> and monocytic cells (CD68R and CD163), and Gomori's silver impregnation for fibrosis. Useful diagnostic information from BM biopsy is: marrow cellularity; dysplasia and hyperplasia of megakaryocyte compartment; blast count; and bone marrow fibrosis.

Conventional cytogenetic analysis should allow acquired clonal chromosomal abnormalities to be detected and t(9;22) and t(5;12) translocations excluded that are characteristic for chronic myeloid leukemia and MDS/MPN with eosinophilia, respectively.

In patients with negative t(9;22), bcr/abl fusion gene molecular assay should be performed to definitively exclude chronic myeloid leukemia. In the case of eosinophilia and negative t(5;12), the PDGFRA and PDGFRB rearrangement molecular assay should be performed in order to exclude MDS/MPN with eosinophilia.

The panel agreed that validation of potential diagnostic molecular biomarkers, like SRSF2, TET2, JAK2 or RAS mutations, and a better knowledge of their specificity is needed before they can be indicated for routine assessment in CMML patients at diagnosis.

### Comprehensive diagnostic criteria

Diagnostic criteria proposed by the FAB group in the 1980s included: blood monocytes > 1x10<sup>9</sup>/L; bone marrow blasts <20%, associated with dysplasia in erythroid, granulocytic, or megakaryocytic lineages; peripheral blasts < 5%; and absence of Auer rods in myeloid cells.<sup>26</sup> Due to the variability of this presentation, in 1994 the FAB group distinguished "dysplastic" (MD-CMML) and "proliferative" (MP-CMML) variants, considering a white blood cell (WBC) count of 13x10<sup>9</sup>/L as a cut-off point.<sup>27</sup> In most of the studies investigating the prognostic significance of such a subdivision,<sup>28-34</sup> median survival of patients with the MP-CMML turned out to be shorter than that of patients with the MD-variant, even though the observed differences were hardly ever statistically significant. On the contrary, the probability of transformation to acute myeloid leukemia (AML) was generally similar between the two subtypes of CMML.

In 2001, the WHO classification definitively separated

**Table 1.** The nine key questions selected by the panel and deemed to be relevant for the management of CMML.

1.	Patient evaluation at diagnosis
2.	Comprehensive diagnostic criteria
3.	Prognosis and risk classification
4.	Determinants of therapeutic interventions, including investigations to be done before planning therapy
5.	Response criteria
6.	Goals of therapy
7.	Monitoring patients not candidates for treatment
8.	First-line therapy
9.	Second-line therapy and stem cell transplantation

**Table 2.** WHO diagnostic criteria of chronic myelomonocytic leukemia.<sup>1</sup>

1.	Persistent peripheral blood monocytosis (> 1x10 <sup>9</sup> /L);
2.	No Philadelphia chromosome or <i>BCR-ABL1</i> fusion gene;
3.	No arrangement of <i>PDGFRA</i> or <i>PDGFRB</i> (these rearrangements should be specifically excluded in cases with eosinophilia);
4.	Less than 20% blasts in the peripheral blood and the bone marrow (blasts includes myeloblasts, monoblasts, and promonocytes);
5.	At least one of the following: (a) dysplasia in one or more cell lines, (b) an acquired clonal cytogenetic abnormality or molecular genetic abnormality present in hematopoietic cells, or (c) persistence of monocytosis for at least 3 months and no evidence of other causes of monocytosis (such as infection, inflammation or malignancy).

CMML from MDS.<sup>35</sup> A new group of diseases with both myelodysplastic and myeloproliferative features was established, named “myelodysplastic/myeloproliferative diseases” including CMML, atypical CMML, and juvenile CMML. WHO committees chose not to maintain the distinction between MD and MP CMML, but to divide CMML into two prognostic categories based on blast number: CMML-1 (blasts < 5% in blood and < 10% in BM) and CMML-2 (blasts 5-19% in blood and/or 10-19% in BM). A diagnostic sub-category of “CMML with eosinophilia” was recommended in cases where peripheral eosinophil counts resulted over  $1.5 \times 10^9/L$ .

The WHO classification was reviewed in 2008<sup>1</sup> and “myelodysplastic/myeloproliferative diseases” were renamed “myelodysplastic/myeloproliferative neoplasms”. A new subgroup, “myeloid and lymphoid neoplasm with eosinophilia and abnormalities of PDGFRA, PDGFRB and FGFR1”, was added. “CMML with eosinophilia” harboring PDGFRA or PDGFRB rearrangement was included in this new entity.

### Recommendations

Diagnostic criteria for CMML are clearly set out in the WHO 2008 classification and their use is recommended (Table 2). We suggest that the distinction of CMML into MP- and MD-variants should be maintained in the diagnostic workup, since it retains importance due to the different therapeutic options that this may involve. For the time being, although arbitrary, a white blood cell count of  $13 \times 10^9/L$  is considered an appropriate cut-off point for this distinction.

### Prognosis and risk classification

In the past, patients with CMML were usually assessed for risk using scoring systems developed for MDS.<sup>36</sup> In 2002, a specific prognostic scoring system was developed at the University of Texas MD Anderson Cancer Center (MDACC).<sup>37</sup> This study identified a hemoglobin level (<12 vs.  $\geq 12$  g/dL), absolute number of lymphocytes (>2.5 vs.  $\leq 2.5 \times 10^9/L$ ), the presence of immature myeloid cells (IMC) in the peripheral blood and marrow blast percentage ( $\geq 10$  vs. <10%) as the variables independently associated to prognosis that could identify four subgroups of patients (low, intermediate-1, intermediate-2, and high risk, with median survival times of 26, 14, 9, and 5 months, respectively) showing significantly different life expectations (MDAPS). The association of higher lymphocyte counts with shorter survival has been confirmed by the MDS Düsseldorf Registry.<sup>38</sup> A few years later, a slight modification of the MDAPS was proposed (MDAPS M1) replacing BM blasts with LDH, which allowed a slightly better stratification in four risk groups to be obtained in comparison to the original MDAPS.<sup>39</sup>

The presence of cytogenetic aberrations has been associated to shorter survival in CMML,<sup>37</sup> in particular in patients with high-risk disease.<sup>39</sup> A recent multivariate analysis of 414 CMML patients included in the Spanish MDS Registry confirmed the independent association of an abnormal karyotype (reported in 27% of patients) with poorer overall survival and a higher risk of AML evolution.<sup>40</sup>

Independent associations of molecular abnormalities with prognosis have been recently identified.<sup>14</sup> Indeed, the presence of RAS point mutations appears to be significantly higher in MP-CMML than in MD-CMML (40% vs.

20%).<sup>41</sup> The presence of *EZH2* implies an unfavorable prognosis<sup>8</sup> while mutation of *ASXL1* correlates with evolution to AML and a shorter overall survival.<sup>18</sup> The impact of *TET2* mutations remains controversial.<sup>9,42</sup> No impact of *SRSF2* mutation on survival was observed.<sup>22</sup> However, in the *RUNX1* mutated sub-cohort, *SRSF2* Pro95His had a favorable impact on overall survival.<sup>22</sup> Most important, a recently concluded phase II trial in which 39 CMML patients were treated with decitabine suggested that lower *CJUN* and *CMYB* gene expression levels were independently associated with an improved overall outcome and survival.<sup>43</sup> However, the value of somatic gene mutations in the prognosis of CMML has not been validated and no scoring system including such molecular aberrations has been developed.

### Recommendations

Because life expectancy is so heterogeneous in CMML, risk assessment is highly recommended for clinical decision making in individual patients.

The CMML-1 and CMML-2 WHO classification is recommended for prognostic implications but it should not be considered sufficient on its own to discriminate between low- and high-risk patients. Additional clinical criteria should be taken into account to decide the timing and modalities of therapeutic interventions.

At present, there is no universally used validated CMML-specific risk classification system. The use of CMML specific risk-oriented systems (i.e. MDAPS, MDAPS-M1, Düsseldorf or Spanish Registry scores) for individual patient risk assessment is recommended, in particular for patients who are candidates for allogeneic HSCT or enrolled in clinical trials.

### Determinants of therapeutic intervention

Although criteria for starting therapy in CMML have not yet been fully established, the panel reasoned that clinical relevance should be considered when deciding the criteria for starting therapy. Thus empirical values were selected for the severity of anemia, thrombocytopenia, percentage of blasts and immature myeloid cells. The panel agreed on the following recommendations.

### Recommendations

Therapy should be started when the disease is symptomatic or progressive, and, in particular, when one of these events occurs: a) severe anemia (Hb less than 10 g/dL); b) percentage of blasts in peripheral blood >5% (including myeloblasts, monoblasts and promonocytes); c) platelet count  $\leq 50 \times 10^9/L$ ; d) WBC count  $\geq 30 \times 10^9/L$ ; e) immature granulocytes  $\geq 10\%$  in peripheral blood; f) extramedullary manifestations of the disease, such as cutaneous or lymphnodal; g) symptomatic splenomegaly.

### Response criteria and definition of resistance

In 1996, Wattel *et al.* proposed five grades of response (clinical remission, good response, minor response, progression and stable disease) based on blood count, bone marrow aspirate and biopsy, and karyotype. However, these criteria were not used thereafter.<sup>44</sup> Stressing the need for response criteria that are specific for CMML, the panel concluded that, at present, either the IWG 2006 response criteria for MDS or the IWG response criteria for myelofibrosis are appropriate for CMML in the myelodysplastic and myeloproliferative variants, respectively.<sup>45,46</sup> (Tables 3

and 4). There is no universally applied standardized definition of resistance/intolerance to first-line therapy (either hydroxyurea or 5-azacytidine) in CMML.

#### Recommendations

Response to treatment should be assessed according to the MD- and MP-disease classification at the time of treatment. For patients with MD-CMML, the IWG 2006 criteria for MDS (Table 3) should be applied. For patients with MP-CMML, the same set of IWG criteria of response used for primary myelofibrosis should be applied (IWG 2009 - Table 4). In both variants of the disease, the distinction of patients according to the WHO classification (CMML-1 vs. CMML-2) does not imply modifications of response criteria.

In MD-CMML, the absence of hematologic improvement after at least six cycles of 5-azacytidine and without progression of the disease should be defined as resistance. In MP-CMML, the same criteria used for defining resistance to hydroxyurea in myelofibrosis may be used<sup>47</sup> (Table 5).

#### Monitoring patients not candidates for treatment

The frequency of clinical and laboratory monitoring in patients who are not candidates for treatment should be initially set according to the individual disease characteristics and then adjusted depending on the natural clinical course.

#### Recommendations

Patients with MD-CMML who are not candidates for treatment should be monitored with a full blood count one month after diagnosis to assess the hematologic stability. These patients should then be monitored by full blood count and clinical examination every three months.

Patients with MP-CMML at diagnosis or evolving from an MD-CMML and not candidates for treatment, should be monitored monthly by full blood count for the first three months from diagnosis to exclude a rapid rise in WBC count or significant changes in other hematologic parameters, then by complete whole blood count and clinical examination every three months. Clinical examination should aim to evaluate spleen size, and the appearance of lymphadenomegalies or extrahematologic involvement (e.g. skin).

In cases of disease evolution from MD- to MP-CMML, as well as in cases of a significant increase in WBC count or a considerable spleen size enlargement in patients with a previously stable MP-CMML, hematologic and cytogenetic re-evaluation is recommended. Molecular evaluation should be considered, storing marrow cell DNA for further studies.

In patients not candidates for stem cell transplantation or any other possible experimental treatment, BM examination for blast count and cytogenetics should be performed once a year and in cases of relevant hematologic changes.

#### First-line therapy

Management of CMML is usually focused on supportive care and cytoreductive therapy, depending on the characteristics of individual patient's disease (MD- vs. MP-CMML). Wattel *et al.* compared 1,000 mg/day of oral hydroxyurea (HU) to 150 mg/week of oral etoposide in 105 patients.<sup>44</sup> After a median follow up of 11 months, 60% of patients in the HU arm responded compared with 36% in the etoposide arm. Median overall survival (OS) was statistically superior in the HU arm leading to the trial ending early.

Two randomized studies established the efficacy and safety of hypomethylating agents (5-azacytidine and

**Table 3.** Modified IWG response criteria in myelodysplasia.<sup>45</sup>

Category	Response criteria (responses must last at least 4 weeks)
Complete remission	Bone marrow: $\leq 5\%$ myeloblasts with normal maturation of all cell lines Persistent dysplasia will be noted Peripheral blood: Hb $\geq 11$ g/dL, platelets $\geq 100 \times 10^9/L$ , neutrophils $\geq 1.0 \times 10^9/L$ , blasts 0%
Partial remission	All CR criteria if abnormal before treatment except: bone marrow blasts decreased by $\geq 50\%$ over pre-treatment but still $> 5\%$ cellularity and morphology not relevant
Marrow CR	Bone marrow: $\leq 5\%$ myeloblasts and decrease by $\geq 50\%$ over pre-treatment Peripheral blood: if HI responses, they will be noted in addition to marrow CR
Stable disease	Failure to achieve at least PR, but no evidence of progression for $> 8$ weeks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pre-treatment
Relapse after CR or PR	At least 1 of the following: return to pre-treatment bone marrow blast percentage; decrement of $\geq 50\%$ from maximum remission/response levels in granulocytes or platelets; reduction in Hb concentration by $\geq 1.5$ g/dL or transfusion dependence
Cytogenetic response	Complete: disappearance of the chromosomal abnormality without appearance of new ones Partial: at least 50% reduction of the chromosomal abnormality
Disease progression	For patients with: less than 5% blasts: $\geq 50\%$ increase in blasts to $> 5\%$ blasts 5%-10% blasts: $\geq 50\%$ increase to $> 10\%$ blasts 10%-20% blasts: $\geq 50\%$ increase to $> 20\%$ blasts 20%-30% blasts: $\geq 50\%$ increase to $> 30\%$ blasts Any of the following: at least 50% decrement from maximum remission/response in granulocytes or platelets; Reduction in Hb by $\geq 2$ g/dL; transfusion dependence

**Table 4. International Working Group (IWG) consensus criteria for treatment response in myelofibrosis.<sup>46</sup>**

1. Complete remission (CR)	<ul style="list-style-type: none"> <li>i. Complete resolution of disease-related symptoms and signs including palpable hepatosplenomegaly.</li> <li>ii. Peripheral blood count remission defined as hemoglobin level at least 110 g/L, platelet count at least <math>100 \times 10^9/L</math>, and absolute neutrophil count at least <math>1.0 \times 10^9/L</math>. In addition, all 3 blood counts should be no higher than the upper normal limit.</li> <li>iii. Normal leukocyte differential including disappearance of nucleated red blood cells, blasts, and immature myeloid cells in the peripheral smear, in the absence of splenectomy.</li> <li>iv. Bone marrow histological remission defined as the presence of age-adjusted normocellularity, no more than 5% myeloblasts, and an osteomyelofibrosis grade no higher than 1.</li> </ul>
2. Partial remission (PR)	Requires all of the above criteria for CR except the requirement for bone marrow histological remission. However, a repeat bone marrow biopsy is required in the assessment of PR and may or may not show favorable changes that do not however fulfill criteria for CR.
3. Clinical improvement (CI)	<p>Requires one of the following in the absence of both disease progression (as outlined below) and CR/PR assignment (CI response is validated only if it lasts for no fewer than 8 weeks)</p> <ul style="list-style-type: none"> <li>i. A minimum 20-g/L increase in hemoglobin level or becoming transfusion independent (applicable only for patients with baseline hemoglobin level of less than 100 g/L).</li> <li>ii. Either a minimum 50% reduction in palpable splenomegaly of a spleen that is at least 10 cm at baseline or a spleen that is palpable at more than 5 cm at baseline becomes not palpable.</li> <li>iii. A minimum 100% increase in platelet count and an absolute platelet count of at least <math>50\,000 \times 10^9/L</math> (applicable only for patients with baseline platelet count below <math>50 \times 10^9/L</math>).</li> <li>iv. A minimum 100% increase in ANC and an ANC of at least <math>0.5 \times 10^9/L</math> (applicable only for patients with baseline absolute neutrophil count below <math>1 \times 10^9/L</math>).</li> </ul>
4. Progressive disease (PD)	<p>Requires one of the following:</p> <ul style="list-style-type: none"> <li>i. Progressive splenomegaly that is defined by the appearance of a previously absent splenomegaly that is palpable at greater than 5 cm below the left costal margin or a minimum 100% increase in palpable distance for baseline splenomegaly of 5-10 cm or a minimum 50% increase in palpable distance for baseline splenomegaly of greater than 10 cm.</li> <li>ii. Leukemic transformation confirmed by a bone marrow blast count of at least 20%.</li> <li>iii. An increase in peripheral blood blast percentage of at least 20% that lasts for at least 8 weeks.</li> </ul>
5. Stable disease (SD)	None of the above.
6. Relapse	Loss of CR, PR, or CI. In other words, a patient with CR or PR is considered to have undergone relapse when he or she no longer fulfills the criteria for even CI. However, changes from either CR to PR or CR/PR to CI should be documented and reported.

decitabine) in a total of 361 patients with MDS.<sup>48,49</sup> However, only 14 patients with CMML were enrolled in each of these studies. Although the responses for CMML patients were not reported separately in the trials, it was reported that there were no significant differences in response rates among patients with refractory anemia as compared to CMML. Only one out of the 7 CMML patients randomized to the decitabine arm had a response. 5-azacitidine and decitabine have been approved by the US FDA for the treatment of CMML. More restricted approval was given by the EMA who indicated 5-azacitidine for the treatment of CMML-2 in absence of myeloproliferative aspects ( $<13 \times 10^9/L$  WBC) therefore allowing a treatment indication only in 10-20% of patients. Recently, Costa *et al.* retrospectively reviewed 38 CMML patients treated with two different schedules of 5-azacitidine and reported a 39% overall response rate (ORR) and a significantly improved survival in responders *versus* non-responders.<sup>50</sup> In a retrospective study, clinical data of 31 patients with CMML consecutively treated with 5-azacitidine were collected.<sup>51</sup> 5-azacitidine was administered at 75 mg/m<sup>2</sup> or 50 mg/m<sup>2</sup> daily for 7 days, or at 100 mg daily for 5 or 7 days, every 4 weeks. Overall, 51% of the patients responded to the drug, with a high rate of complete remissions (CR), while hematologic improvement (HI) was obtained in 2 patients. The disease remained stable in 7 patients (SD, 23%) while 8 patients (26%) were resistant to the drug. Patients responding to

5-azacitidine had a better survival than those with SD or progression. The use of 5-azacitidine in MP-CMML is debated because at low doses the drug primarily acts as a demethylating agent, with minimal cytotoxicity that is unable to control high proliferation rates.<sup>52</sup> In contrast to this observation, a recent study on a small group of 10 CMML patients treated with 5-azacitidine reported an ORR of 60%. Response was increased in proliferative CMML, with good control of leukocytosis and achievement of transfusion independence in 66% of the patients.<sup>53</sup>

Phase II studies using decitabine showed ORRs ranging from 38% to 70%.<sup>54,55</sup> A recent trial of decitabine 20 mg/m<sup>2</sup>/day for 5 days carried out on a median of 10 cycles in CMML patients with advanced myeloproliferative or myelodysplastic features indicated an ORR of 38% and suggested that a lower CJUN and CMYB expression could be predictive of response.<sup>45</sup>

Intensive chemotherapy with intermediate doses of Ara-C and topotecan was investigated in a phase II trial in CMML, obtaining a CR rate of 44%, with a median remission duration of 33 weeks and a median survival of 41 weeks.<sup>56</sup> Therapy with topotecan as single agent induced CR in 28% of CMML patients, with a median survival time of 10.5 months, and a median CR duration of 7.5 months.<sup>57</sup> In a more recent trial in 90 patients with MDS and CMML treated with oral topotecan following 2 different schedules, the response rate in CMML patients was

**Table 5.** Definition of resistance/intolerance to hydroxyurea.<sup>47</sup>

1. Failure to: (i) reduce massive (organ extending by more than 10 cm from the costal margin), or progressive (organ increasing by more than 3 cm in the last 3 months) splenomegaly, by more than 50% as measured by palpation, OR, (ii) completely relieve symptoms of splenomegaly after 3 months of at least 2 g/day of hydroxyurea
2. Uncontrolled myeloproliferation, i.e. platelet count  $>400 \times 10^9/L$  and white blood cell count  $>10 \times 10^9/L$  after 3 months of at least 2 g/day of hydroxyurea, OR
3. Absolute neutrophil count  $<1.0 \times 10^9/L$ , or platelet count  $<50 \times 10^9/L$  at the lowest dose of hydroxyurea required to achieve a complete or major clinico-hematologic response, OR.
4. Presence of leg ulcers or other unacceptable hydroxyurea-related non-hematologic toxicities, such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis or fever at any dose of hydroxyurea

50%, but no CR was reached.<sup>58</sup>

As CMML, especially in its proliferative variant, has the highest frequency of N- and K-RAS mutations among hematologic malignancies, farnesyl transferase inhibitors were considered potential effective drugs. Tipifarnib and lonafarnib were the most closely studied: unfortunately, both drugs, as single agents, were effective in only a few patients, resulting in limited disease control and leading to sporadic CR.<sup>59,60</sup>

In a pilot study, bendamustine was utilized in 15 pre-treated elderly patients with AML or high-risk MDS.<sup>61</sup>

#### Recommendations

Patients who start therapy later than three months from the diagnosis should have a pre-treatment re-evaluation, including BM aspiration, BM biopsy, and cytogenetic analysis. HLA typing is recommended for patients aged under 65 years. Serum erythropoietin should be determined in all patients with severe anemia ( $Hb \leq 10$  g/dL).

The treatment strategy should be decided first according to the disease hematologic phenotype, in particular whether it is an MP or MD phenotype, and to the number of blasts in BM.

Patients with MD-CMML and less than 10% blasts in BM should be managed with supportive therapy aimed at correcting cytopenias. Patients with severe anemia ( $Hb \leq 10$  g/dL and with serum erythropoietin  $\leq 500$  mU/dL) should be treated with erythropoietic stimulating agents. Myeloid growth factors may be considered only for patients with febrile severe neutropenia.

In patients with MD-CMML with high number of blasts ( $\geq 10\%$  in BM,  $\geq 5\%$  in the blood), the supportive therapy should be integrated with the use of hypomethylating agents (5-azacytidine or decitabine). In selected patients, allo-SCT may be offered within clinical trials.

Patients with MP-CMML with a low number of blasts should be treated with cytoreductive therapy. Hydroxyurea is the drug of choice to control proliferative myelomonocytic cells and to reduce organomegaly.

Patients with MP-CMML and a high number of blasts should receive blastolytic therapy with polychemotherapy followed, when possible, by allo-SCT.

If allo-SCT is not a possible option, patients should be informed that, although not curative, chemotherapy is recommended to maintain Quality of Life.

#### Second-line treatment

In the absence of any scientific evidence that could address the decision on second-line therapy in patients

refractory or intolerant to first-line treatment, the panel approved the following recommendations.

#### Recommendations

Patients with MD-CMML with a high number of blasts, resistant or intolerant to 5-azacytidine, and not eligible for transplant, should be treated with supportive therapy and enrolled in experimental therapeutic studies.

In patients with MP-CMML and resistant or intolerant to hydroxyurea (Table 5) without blasts ( $<10\%$ ), cytolytic therapy should be given to control the disease and avoid a rapid increase in WBC count. VP16, low-dose ARA-C, thioguanine as single agents are reported to be efficacious. Hypomethylating agents should be used in the context of clinical trials. Patients with MP-CMML with a high blast count resistant to conventional blastolytic therapies should be treated with new and experimental therapies. Topoisomerase I inhibitors, farnesyl-transferase inhibitors or other drugs like bendamustine seem to have little effect as single agents.

#### Hematopoietic stem cell transplantation

Allo-SCT is the only strategy that may lead to cure in patients with CMML. However, due to the advanced age of the vast majority of patients, this treatment option is rarely feasible. Recently,<sup>62</sup> a literature search was performed and data from adult CMML patients undergoing allo-SCT were reviewed. In all, 197 patients from eight studies<sup>63-70</sup> met the final inclusion criteria. All studies were retrospective, 6 out of 8 (71%) being single institution experiences. The overall results of allogeneic SCT following myeloablative conditioning in CMML patients were disappointing, indicating a manifest excess mortality. The overall survival (OS) at 2-10 years ranged from 18% to 75% for all studies: relapse-free survival (RFS) ranged from 18% to 67%. Reduced intensity conditioning (RIC) transplant improved non-relapse mortality, OS and RFS without increasing the relapse rate.

#### Recommendations

The panel agreed that allo-SCT should be considered a therapeutic option in CMML for fit patients aged under 60 years with high-risk CMML requiring treatment. Its use should be considered experimental under a controlled strategy that investigates new pre-transplant therapies and transplant protocols. In MP-CMML and a high number of blasts, allo-SCT should be preceded by polychemotherapy, whereas in MD-CMML, 5-azacytidine may be considered before enrolling patients in a program of allo-SCT.

## Discussion

Few recommendations in this work were grounded on strong scientific evidence, thus most of them reflect the uncertainty surrounding many issues in CMML. A critical issue in the disease assessment derives from recent comprehensive studies of somatic gene mutations. In these analyses, more than 80% of patients were found to have gene aberrations, and it has been hypothesized that such mutations, especially in the *SRSF2*, *TET2*, *ASXL* genes, represent disease-associated diagnostic markers. The panel concluded that these aberrancies must be validated before entering clinical practice. The hope is that integrating genetic lesions with traditional prognostic markers could lead to a better definition of risk classes, improving the indications for different therapeutic strategies.

The second issue is reflected in the recently revised WHO classification of CMML, which specifies hematologic, morphological and molecular parameters distinguishing two clinical CMML types on the basis of the number of blasts. However, the experts in this work considered that this distinction is not fully exploitable in therapeutic decision making. They believe that the previously reported distinction between myelodysplastic and myeloproliferative characteristics retains a clinical relevance in therapeutic decision making and that a validation of this distinction and correlation with genetic or molecular characteristics of the disease could improve patients' stratification for therapy.

A difficult therapeutic decision is that of advising patients about allo-SCT. The panel recommended that allo-SCT should be performed as an experimental proce-

dure. Nevertheless, by significantly reducing toxicities and extending the allo-SCT option to older patients, approaches based on reduced intensity conditioning transplant are definitely worth investigating in CMML.

### Last-minute addendum

Since submission of the paper, a new CMML-specific prognostic scoring system (CPSS) has been published by Such *et al.*<sup>71</sup> The most relevant variables for overall survival and evolution to acute myeloblastic leukemia were FAB and WHO CMML subtypes, CMML-specific cytogenetic risk classification, and RBC transfusion dependency. CPSS was able to segregate patients into four clearly different risk groups for OS and risk of AML evolution.

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