



Article  
scientifique

Revue de la  
littérature

2024

Published  
version

Public  
access

This is the published version of the publication, made available in accordance with the publisher's policy.

---

## Management of adult patients with CMML undergoing allo-HCT : recommendations from the EBMT PH&G Committee

---

Onida, Francesco; Gagelmann, Nico; Chalandon, Yves; Kobbe, Guido; Robin, Marie; Symeonidis, Argiris; de Witte, Theo; Itzykson, Raphael; Jentzsch, Madlen; Platzbecker, Uwe; Santini, Valeria; Sanz, Guillermo; Scheid, Christof; Solary, &nbsp;Eric [and 5 more]

### How to cite

ONIDA, Francesco et al. Management of adult patients with CMML undergoing allo-HCT :  
recommendations from the EBMT PH&G Committee. In: Blood, 2024, vol. 143, n° 22, p. 2227–2244. doi:  
10.1182/blood.2023023476

This publication URL: <https://archive-ouverte.unige.ch/unige:179659>

Publication DOI: [10.1182/blood.2023023476](https://doi.org/10.1182/blood.2023023476)

© This document is protected by copyright. Please refer to copyright holder(s) for terms of use.

Last deposit update in Archive ouverte UNIGE on 06.09.2024 11:52

# Management of adult patients with CMML undergoing allo-HCT: recommendations from the EBMT PH&G Committee

Francesco Onida,<sup>1,2</sup> Nico Gagelmann,<sup>3</sup> Yves Chalandon,<sup>4,5</sup> Guido Kobbe,<sup>6</sup> Marie Robin,<sup>7</sup> Argiris Symeonidis,<sup>8</sup> Theo de Witte,<sup>9</sup> Raphael Itzykson,<sup>10,11</sup> Madlen Jentzsch,<sup>12</sup> Uwe Platzbecker,<sup>12</sup> Valeria Santini,<sup>13</sup> Guillermo Sanz,<sup>14,15</sup> Christof Scheid,<sup>16</sup> Eric Solary,<sup>17,18</sup> Peter Valent,<sup>19,20</sup> Raffaella Greco,<sup>2,21</sup> Isabel Sanchez-Ortega,<sup>2</sup> Ibrahim Yakoub-Agha,<sup>2,22</sup> and Lisa Pleyer<sup>23-26</sup>

<sup>1</sup>Department of Oncology and Hemato-Oncology, Hematology and Bone Marrow Transplantation Unit, Azienda Socio Sanitaria Territoriale Fatebenefratelli-Sacco, University of Milan, Milan, Italy; <sup>2</sup>European Society for Blood and Marrow Transplantation Practice Harmonization and Guidelines Committee, Barcelona, Spain; <sup>3</sup>University Medical Center Hamburg-Eppendorf, Hamburg, Germany; <sup>4</sup>Division of Hematology, University Hospital of Geneva, Geneva, Switzerland; <sup>5</sup>Faculty of Medicine, University of Geneva, Geneva, Switzerland; <sup>6</sup>Department of Hematology, Oncology and Clinical Immunology, University Hospital Düsseldorf, Heinrich Heine University, Medical Faculty, Düsseldorf, Germany; <sup>7</sup>Service d'Hématologie Greffe, Hôpital Saint-Louis, L'Assistance Publique-Hôpitaux de Paris, Université de Paris Cité, Paris, France; <sup>8</sup>Department of Hematology, Olympion General Hospital and Rehabilitation Center, Patras, Greece; <sup>9</sup>Department of Tumor Immunology, Radboud Institute of Molecular Life Sciences, Radboud University Medical Center, Nijmegen, The Netherlands; <sup>10</sup>Université Paris Cité, Génomes, Biologie Cellulaire et Thérapeutique U944, INSERM, Centre National de la Recherche Scientifique, Paris, France; <sup>11</sup>Département Hématologie et Immunologie, Hôpital Saint-Louis, L'Assistance Publique-Hôpitaux de Paris, Paris, France; <sup>12</sup>Medical Clinic and Policlinic 1, Hematology and Cellular Therapy, University Hospital Leipzig, Leipzig, Germany; <sup>13</sup>Myelodysplastic Syndromes Unit, Hematology, Dipartimento di Medicina Sperimentale e Clinica, Azienda Ospedaliero-Universitaria Careggi, University of Florence, Florence, Italy; <sup>14</sup>University and Polytechnic Hospital La Fe and Health Research Institute La Fe, Valencia, Spain; <sup>15</sup>Centro de Investigación Biomedica en Red Cancer, Instituto de Salud Carlos III, Madrid, Spain; <sup>16</sup>Department of Internal Medicine I, University Hospital Cologne, Cologne, Germany; <sup>17</sup>Department of Hematology, INSERM Unité Mixte de Recherche 1287, Gustave Roussy Cancer Center, Villejuif, France; <sup>18</sup>Université Paris Saclay, Faculty of Medicine, Le Kremlin-Bicêtre, France; <sup>19</sup>Division of Hematology and Hemostaseology, Department of Internal Medicine I, and <sup>20</sup>Ludwig Boltzmann Institute for Hematology and Oncology, Medical University of Vienna, Vienna, Austria; <sup>21</sup>Unit of Hematology and Bone Marrow Transplantation, Istituto di Ricovero e Cura a Carattere Scientifico San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy; <sup>22</sup>Centre Hospitalier Universitaire de Lille, University of Lille, INSERM U1286, Infinite, Lille, France; <sup>23</sup>Austrian Group of Medical Tumor Therapy Study Group, Vienna, Austria; <sup>24</sup>Salzburg Cancer Research Institute, Center for Clinical Cancer and Immunology Trials, Salzburg, Austria; <sup>25</sup>3rd Medical Department with Hematology, Medical Oncology, Hemostaseology, Rheumatology and Infectiology, Oncologic Center, Paracelsus Medical University, Salzburg, Austria; and <sup>26</sup>Cancer Cluster Salzburg, Salzburg, Austria

**Chronic myelomonocytic leukemia (CMML) is a heterogeneous disease presenting with either myeloproliferative or myelodysplastic features. Allogeneic hematopoietic cell transplantation (allo-HCT) remains the only potentially curative option, but the inherent toxicity of this procedure makes the decision to proceed to allo-HCT challenging, particularly because patients with CMML are mostly older and comorbid. Therefore, the decision between a non-intensive treatment approach and allo-HCT represents a delicate balance, especially because prospective randomized studies are lacking and retrospective data in the literature are conflicting. International consensus on the selection of patients and the ideal timing of allo-HCT, specifically in CMML, could not be reached in international recommendations published 6 years ago. Since then, new, CMML-specific data have been published. The European Society for Blood and Marrow Transplantation**

**(EBMT) Practice Harmonization and Guidelines (PH&G) Committee assembled a panel of experts in the field to provide the first best practice recommendations on the role of allo-HCT specifically in CMML. Recommendations were based on the results of an international survey, a comprehensive review of the literature, and expert opinions on the subject, after structured discussion and circulation of recommendations. Algorithms for patient selection, timing of allo-HCT during the course of the disease, pretransplant strategies, allo-HCT modality, as well as posttransplant management for patients with CMML were outlined. The keynote message is, that once a patient has been identified as a transplant candidate, upfront transplantation without prior disease-modifying treatment is preferred to maximize chances of reaching allo-HCT whenever possible, irrespective of bone marrow blast counts.**

## Introduction: current state of the art

Chronic myelomonocytic leukemia (CMML) is a hybrid or mixed myelodysplastic/myeloproliferative neoplasm characterized by

a large heterogeneity of clinical features with high variability of life expectation. Median age at diagnosis ranges from 70 to 75 years. Median survival in the largest reported series is in the 2- to 3-year range<sup>1</sup> but is <2 years in patients with higher-risk

disease according to various models of prognostication specifically developed for the disease.<sup>2,3</sup> To date, allogeneic hematopoietic cell transplantation (allo-HCT) remains the only potentially curative treatment strategy for eligible patients.<sup>4</sup> Overall survival for patients with CMML ranges from 30% to 40% at 5 years after allo-HCT, owing to cumulative incidences of relapse of 30% to 50% and nonrelapse mortality rates of 20% to 40%.<sup>5-12</sup> In the context of allo-HCT the absence of prospective data drags behind many uncertainties not only regarding patient selection but also possible pretransplant treatment strategies, the timing of allo-HCT, and the optimal overall transplant policy including donor selection, the choice and intensity of conditioning, graft-versus-host disease (GVHD) prophylaxis, stem cell source, and patient management in the posttransplant setting.

Given the aforementioned factors, the newly established European Society for Blood and Marrow Transplantation (EBMT) Practice Harmonization and Guidelines (PH&G) Committee included the best practice recommendation on the management of adult patients with CMML undergoing allo-HCT among the projects to be finalized during the second annual workshop, planned in Lille, France, on 25-26 September 2023. The methodology used is described in the supplemental Material, available on the *Blood* website.

## Workshop recommendations

### Patient selection for allo-HCT

Before going into further details as to which classification system, which prognostic scoring system, and which other disease- and patient-related factors define the indication(s) for, and the most appropriate timing of, allo-HCT, it is critical that patients are at all assessed for their eligibility for allo-HCT. Up to 21% of patients with myelodysplastic neoplasms (MDS) or acute myeloid leukemia (AML) in a large registry-based study were not receiving assessment or consideration for allo-HCT,<sup>6</sup> indicating the need for heightening nontransplant specialists' awareness in this regard. In addition, there is also a significant proportion (up to one-third) of patients failing to reach allo-HCT after the decision to transplant has been made,<sup>7-13</sup> indicating the need for better patient selection strategies, more efficacious pretransplant treatment modalities, faster procedure to transplant, and/or increasing the rates of upfront transplantations. Careful, holistic risk assessment and patient selection is essential to recognize patient eligibility for allo-HCT on the one hand, and, on the other, to maximize patient benefit while minimizing treatment-related morbidity and mortality.

**Classification of CMML** The recently published International Consensus Classification (ICC)<sup>14</sup> and the 2022 World Health Organization<sup>15</sup> Classification have made mostly similar adaptations in CMML (ie, elimination of CMML-0, lowering of the monocyte threshold to  $\geq 0.5 \times 10^9/L$ , and reiteration of the myelodysplastic and myeloproliferative subtype distinction), while retaining the same blast count thresholds, and can thus both be recommended. Neither classification has as yet defined CMML subtypes based on mutational signatures.

However, the threshold of blasts required for the definition of AML was lowered or eliminated when certain mutations are present. AML defined by mutations includes AML with mutated

*NPM1* (World Health Organization-2022 [no blast count threshold required])<sup>15</sup> and AML with mutated bZIP *CEBPA* (ICC-2022 [ $\geq 10\%$  blasts required]).<sup>14</sup> As such, patients with CMML harboring these mutations should be considered and treated as AML.

When mutations in *TP53*, *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *STAG2*, *U2AF1*, or *ZRSR2* are present, ICC-2022 proposes a new disease category MDS/AML defined by 10% to 19% blasts, that can be treated either as MDS or as AML.<sup>14</sup> This however, does not affect patients with CMML as yet.

**Patient-related factors** Prospective data have confirmed survival benefits for patients at higher risk for MDS aged 60 to 70 years, or  $\geq 65$  years<sup>12,16</sup> undergoing allo-HCT. Thus, although age alone should not preclude patients from being considered as transplant eligible,<sup>17</sup> it must nevertheless be considered. Other patient-related factors that need to be considered for identifying patients eligible for allo-HCT include: performance status (PS) assessment by the Eastern Cooperative Oncology Group or Karnofsky PS scale, HCT-specific comorbidity index,<sup>18,19</sup> frailty assessment,<sup>20</sup> comprehensive geriatric assessments,<sup>21,22</sup> and/or combinations thereof.<sup>23-25</sup>

**Recommendations** Figure 1 gives an overview of patient-, disease-, and transplant-related factors that need to be considered and carefully weighed. This panel considers the following factors to be required in patients deemed "fit for transplant" (Figure 1):

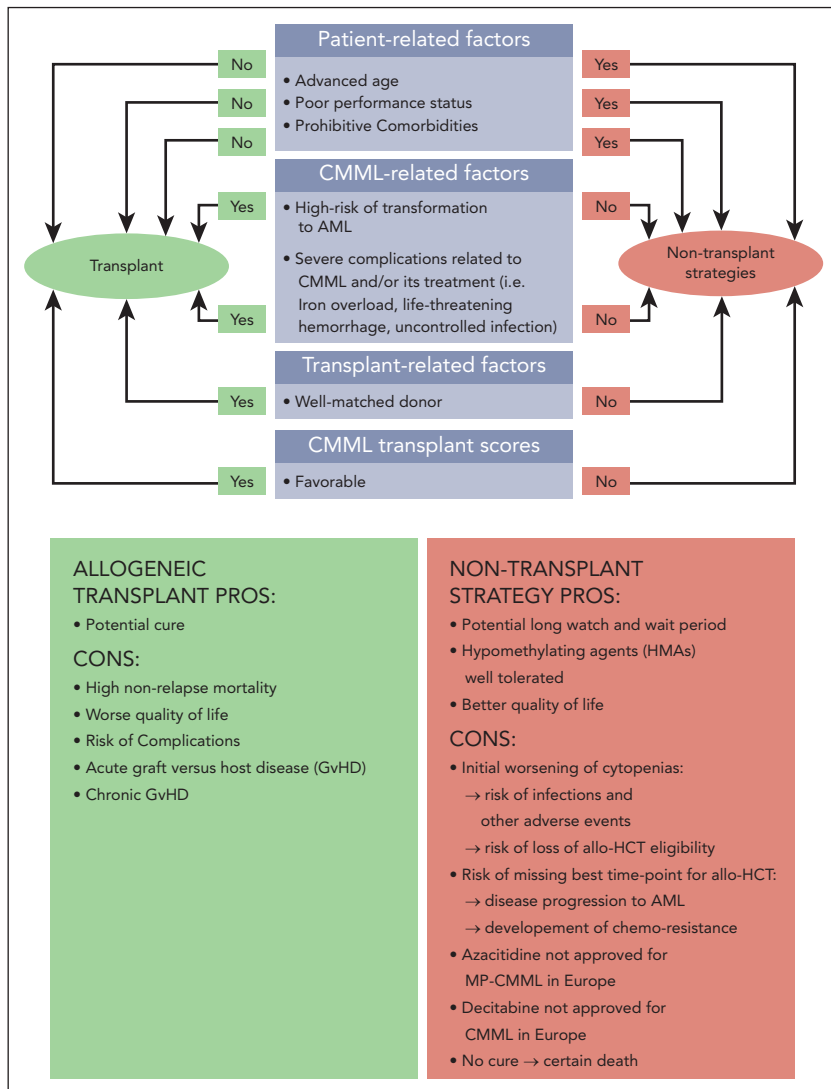
- Age of  $\leq 70$  years (in select cases  $\leq 75$  years)
- Eastern Cooperative Oncology Group PS of  $< 2$  or Karnofsky index of  $\geq 70\%$
- HCT-comorbidity index of  $< 3$
- Lack of any comorbidity that the transplant specialist judges to be incompatible with intensive chemotherapy (IC), for example, as suggested by Ferrara et al.<sup>26</sup>

### Timing of allo-HCT

Once the decision to proceed to allo-HCT has been made, timing is a crucial consideration, because delaying transplant may result in disease progression and/or acquisition of additional comorbidities, and/or toxicities (if the patient receives pretransplant treatment) that may preclude transplant. To date, no randomized clinical trial has addressed this important question in CMML. Expert panels could not reach a solid consensus regarding the indication for pretransplant treatment in patients candidate for allo-HCT for CMML so far,<sup>27</sup> and 2018 European Hematology Association/European LeukemiaNet (ELN) recommendations<sup>28</sup> were largely extrapolated from data obtained in patients with MDS.<sup>28-32</sup>

**Risk stratification to identify transplant candidates** Risk stratification dictates the management of patients with CMML. Allo-HCT is the only treatment that can offer cure in this disease. Identifying those patients that will have the most benefit and the least harm from allo-HCT is thus critical. A myriad of scoring systems used in CMML have evolved from MDS-based models (International Prognostic Scoring System (IPSS),<sup>33</sup> revised IPSS (IPSS-R),<sup>34</sup>) to CMML-specific scores predicting outcomes (Düsseldorf score,<sup>35</sup> MD-Anderson Prognostic

Figure 1. Patient selection for allo-HCT.



Score,<sup>36</sup> modified Bournemouth score,<sup>37</sup> CMML-specific Prognostic Scoring System [CPSS],<sup>38</sup> and Mayo model<sup>39</sup>) or estimating time to first treatment,<sup>40</sup> most of which have been found to be valid and with comparable performance.<sup>1,2,41-44</sup> Updated versions of some of these scores have been published, incorporating molecular data: IPSS molecular (IPSS-M),<sup>45</sup> Groupe Francophone des Myelodysplasies score (ASXL1),<sup>46</sup> Mayo Molecular Model (ASXL1),<sup>47</sup> CPSS molecular (CPSS-Mol; ASXL1, RUNX1, NRAS, and SETBP1).<sup>48</sup> ELN and 2018 European Hematology Association guidelines recommend 5 of these scores (MD-Anderson Prognostic Score; CPSS, in case of unavailability of molecular data; Groupe Francophone des Myelodysplasies; and Mayo Molecular and CPSS-Mol when molecular data are available).<sup>28</sup> It needs to be born in mind, that above mentioned prognostic scores were mostly devised in either untreated historic patient cohorts, and/or were not assessed for their predictive capacity on specific treatment outcomes in general, and on allo-HCT outcomes in particular.

Risk stratification has been used to identify at which time point during the course of the disease a patient should undergo

transplantation. Of note, almost all data published to date used older scoring systems (IPSS, IPSS-R, or CPSS) that did not incorporate molecular data in attempts to identify the “sweet spot” at which an allo-HCT bears the most benefit for the patient while doing the least potential harm to the patient. It remains unclear whether these data can be transferred to newer molecular scores (IPSS-M and CPSS-Mol) in patients with CMML, but the IPSS-M has recently been shown to correlate with allo-HCT outcomes in MDS.<sup>49-52</sup> These retrospective analyses indicated that allo-HCT improves outcomes for the (very) high-risk IPSS-M groups. Very recently the 1102 Study of the Blood and Marrow Transplant Clinical Trials Network was reanalyzed after inclusion of molecular data enabling re-stratification of patients according to IPSS-M.<sup>45</sup> This trial identified patients with MDS with high-risk IPSS-M to be ideal candidates for early transplantation.<sup>45</sup> In the largest cohorts of patients with CMML who had received transplantation with molecular data available (n = 313<sup>53</sup> and n = 240<sup>54</sup>), the CPSS-Mol was shown to be significantly associated with post-allogeneic disease-free survival and/or overall survival.

Although transplantation of early-stage lower-risk disease offers the lowest rate of nonrelapse mortality, it exposes patients who might have had a long period without disease progression to immediate morbidity and mortality. Because life expectancy of patients with CMML with lower-risk disease is >5 years,<sup>48</sup> it is generally accepted that the risks of allo-HCT outweigh the potential benefits. Markov models applied to patients with MDS indicate that allo-HCT should be delayed in patients with lower-risk MDS (according to IPSS, WPSS [WHO-based prognostic scoring system], or R-IPSS) until disease progression to a higher risk category, whereas HCT should be immediately offered to patients with higher-risk disease.<sup>29-32</sup> In corroboration thereof, retrospective studies exclusively analyzing patients with CMML have confirmed the absence of significant survival benefit of allo-HCT for patients with CMML with lower-risk disease as categorized by the CPSS.<sup>4,55</sup> Although allo-HCT provides modest survival benefit as compared with all other treatment modalities including IC for patients after having transformed from CMML to AML,<sup>4,56</sup> most evidence underscores the importance of early transplantation before transformation to AML.<sup>57-59</sup> The latter coincides with disease progression and an increased potential for the acquisition of contraindications for transplantation. It also needs to be kept in mind, that although high-risk features are indications for allo-HCT in CMML, they also adversely affect allo-HCT outcomes.<sup>5,55,60-63</sup>

This panel acknowledges the recent developments in, and increasing importance of, molecular data. The CPSS-Mol (Table 1) has been shown to outperform the CPSS in all patients with CMML for both overall survival and cumulative incidence of AML evolution (Table 2).<sup>48</sup> The panel acknowledges that specific data for the use of the CPSS-Mol in patient selection and timing decisions for allo-HCT are lacking. However, very recently, data generated in 8326 MDS cases with semi-Markov multistate decision models were presented, showing clinical relevance and statistically significant superiority of using the IPSS-M over the IPSS-R regarding the optimal timing of allo-HCT in the transplant decision making process.<sup>64</sup> Different from other molecularly

integrated CMML-specific prognostic models, only considering nonsense/frameshift ASXL1 mutations as independent adverse factors,<sup>44,45</sup> the CPSS-Mol relies on a more comprehensive genetic risk score. In light of these data, and after much internal discussion, the panel ultimately decided to recommend the use of the CPSS-Mol, wherever possible, to stratify patient risk and to identify the optimal timing of allo-HCT in patients with CMML. Taking the possibility for posttransplant interventions into account, it may be important to dissect those disease features that affect cumulative incidences or relapse from those that can portend higher nonrelapse mortality (see also "Risk-stratification to predict post-HCT outcomes").

**Risk-stratification to predict post-HCT outcomes** Although both CPSS risk stratifications<sup>53,61</sup> have been significantly associated with posttransplant relapse and/or overall survival, risk stratification by CPSS<sup>5,55</sup> or CPSS-Mol<sup>5</sup> alone has limitations in predicting posttransplant outcomes.<sup>55</sup> Dynamic use of prognostic scores (IPSS-R,<sup>65</sup> CPSS, or CPSS-Mol<sup>61,62</sup>) at the time of transplant (rather than at initial diagnosis) may be more relevant for the prediction of allo-HCT outcome, but this remains to be validated. Of note, aberrations of several genes (eg, *TP53*), although infrequent in CMML, have also been acknowledged as adverse molecular predictors of outcome, but are not captured by current molecularly integrated prognostic models. These are discussed in "Cytogenetics and gene mutations."

Once the decision to proceed to transplant has been made, it is necessary to differentiate the use of prognostic scores for the identification of transplant eligibility on the one hand, and, on the other hand, for the prediction of posttransplant outcomes. For the former, we propose the use of the CPSS-Mol, as discussed earlier. For the latter, transplantation-specific scores to predict transplant outcomes have been developed for patients with CMML<sup>54,66</sup> or validated in patients with CMML,<sup>67</sup> and outperform scores typically used in the nontransplant setting. The CMML transplant score,<sup>54</sup> which incorporates both molecular (*ASXL1* and *NRAS* mutations) and clinical information (bone

**Table 1. CPSS-Mol genetic risk group**

Variable score points	CPSS cytogenetic risk group	ASXL1	NRAS	RUNX1	SETBP1
0	Normal karyotype, isolated -Y	Unmutated	Unmutated	Unmutated	Unmutated
1	All other abnormalities	Mutated	Mutated	—	Mutated
2	Trisomy 8, complex karyotype (≥3 abnormalities), abnormalities of chromosome 7	—	—	Mutated	—
Genetic risk group category					
Total score points	CPSS genetic risk group				
0	Low				
1	Intermediate-1				
2	Intermediate-2				
≥3	High				

Adapted from Elena et al.<sup>48</sup>  
-Y, loss of chromosome Y.

**Table 2. CPSS-Mol score**

Score points	Genetic risk group*	Bone marrow blasts	WBC count	Red blood cell transfusion dependency
0	Low	<5%	<13 × 10 <sup>9</sup> /L	No
1	Intermediate-1	≥5%	≥13 × 10 <sup>9</sup> /L	Yes
2	Intermediate-2	—	—	—
3	High	—	—	—
CPSS-Mol risk group category				
Total score points	CPSS-Mol risk group	Median overall survival, † mo	Cumulative incidence of transformation to AML at 48 mo, † %	
0	Low	Not reached	0	
1	Intermediate-1	64-68	3 (8)	
2-3	Intermediate-2	30-37	21 (24)	
≥4	High	17-18	48 (52)	

Adapted from Elena et al.<sup>48</sup>

\*As reported in Table 1.

†In the training and validation cohorts, respectively.

marrow blasts and increasing comorbidity index), was prognostic in patients specifically undergoing transplantation and may facilitate personalized counseling. In particular, the CMML-specific transplant score was designed and validated in a cohort of 240 patients with CMML undergoing allo-HCT. Five risk groups were identified with 5-year survival rates ranging from 81% to 19%, and nonrelapse mortality rates ranging from 5% to 51% for an increasing transplant score.<sup>54</sup> The score retained performance after validation, and predictions were significant and superior to existing scores incorporating molecular data (including the CPSS-Mol) designed in the nontransplant setting.<sup>54</sup> In addition, the endothelial activation and stress index score might help to predict nonrelapse mortality,<sup>67</sup> whereas a more recent score has been criticized because of inclusion of GVHD as a risk factor without adjusting for inherent statistical bias.<sup>66</sup> The inclusion of donor type and source as well as conditioning intensity might further refine transplant-specific prognostic scores.

**Recommendations** **Choice of transplant candidates and timing of allo-HCT** The panel recommends the use of the CPSS-Mol together with additional patient- and disease-related risk factors to identify transplant candidates, and for the optimal timing of allo-HCT during the course of the disease.

- Patients with high-risk CPSS-Mol disease have a median overall survival of 17 to 18 months and a cumulative incidence of transformation to AML at 48 months of 48% to 52% (Table 2).<sup>48</sup> The panel recommends that they should proceed to transplant as soon as possible (Figure 2), preferably without disease-modifying treatment to maximize chances of reaching allo-HCT (for the discussion on how the recommendation for upfront transplant was reached please see “Role of pretransplant therapy”).

- Patients with intermediate-2 risk CPSS-Mol disease have a median overall survival of 30 to 37 months and a cumulative incidence of transformation to AML at 48 months of 21% to 24% (Table 2).<sup>48</sup> The panel recommends that patients with ≥1 additional risk factor should proceed to upfront transplant preferably without disease-modifying treatment to maximize chances of reaching allo-HCT (Figure 2). Such risk factors include extramedullary involvement, (hyper)leukocytosis, iron overload, splenomegaly, as well as adverse cytogenetics and/or gene mutations. Further details on additional disease-related risk factors are discussed in “Additional disease-related risk factors” and “Pretransplant management of disease symptoms.”
- Patients with intermediate-2 risk CPSS-Mol disease without additional risk factors: a watch and wait strategy with dynamic assessment should be followed whenever possible. Nontransplant treatment strategies, if deemed necessary, should be discussed with the transplant center. Dynamic reassessment every 3 months, or sooner in case of suspected disease progression, should occur. In the presence of rapidly increasing white blood cell count (WBC; increases of >10 000/μL within ≤3 months) in the absence of signs of active inflammation and or infection, rapidly increasing peripheral blood or bone marrow blasts, and/or worsening of cytopenias, we recommend accurate serial restaging of disease and/or response status, which not only includes bone marrow workups (including cytology, histology, flow cytometry, conventional cytogenetics, fluorescence in situ hybridization, and next generation sequencing)<sup>68</sup> but also increasingly relies on analyses of the peripheral blood.<sup>69,70</sup> Reclassification and renewed calculation of CPSS-Mol risk should ensue (Figure 2).
- Patients with low and intermediate-1 CPSS-Mol disease have a median overall survival of 64 to 68 months and a cumulative incidence of transformation to AML at 48 months

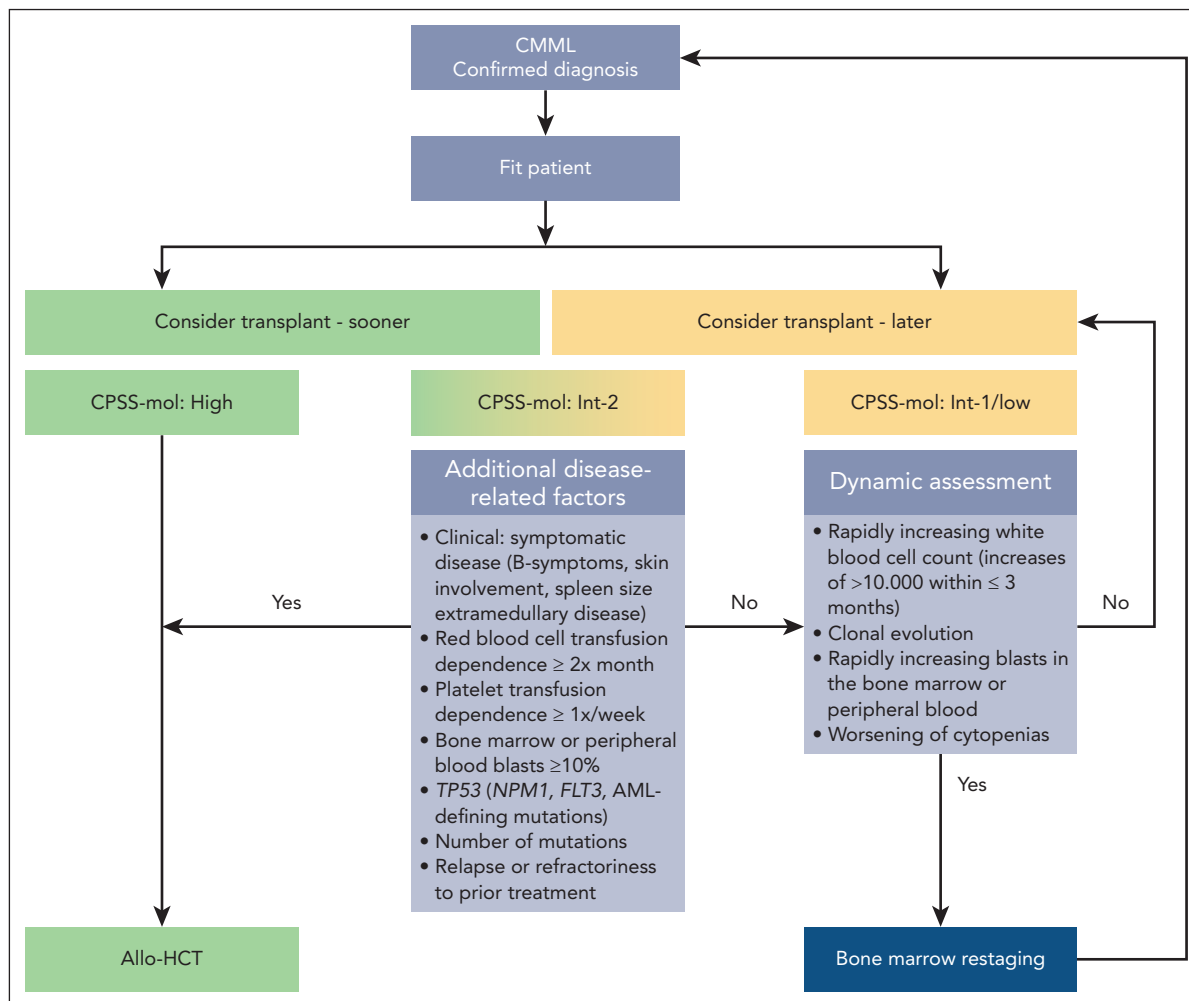


Figure 2. Timing of allo-HCT.

of 3% to 8% (Table 2).<sup>48</sup> The panel recommends that these patients should be managed with nontransplant approaches. Allo-HCT should be deferred until progression to higher-risk disease and/or the occurrence of  $\geq 1$  additional risk factor. To this end, dynamic reassessment should be performed as stated earlier (Figure 2).

For transplant ineligible patients, current guidelines<sup>28</sup> and more recent data<sup>13,71</sup> are applicable.

#### Prediction of posttransplant outcomes

- Based on aforementioned data, the panel recommends the use of the CMML transplant score<sup>54</sup> to predict posttransplant outcomes for patients that have been previously identified as transplant candidates with the CPSS-Mol.

#### Additional disease-related risk factors

As mentioned above, the presence or emergence of additional risk factors should result in upfront transplantation whenever possible in patients with CPSS-Mol intermediate-2 risk disease, and should result in dynamic reassessment in patients with CPSS-Mol intermediate-1 and low-risk disease (Figure 2; "Choice of transplant candidates and timing of allo-HCT").

**Clinical symptoms** General symptoms (such as drenching night sweats, unintended weight loss, and unexplained fever) are acknowledged signs of higher disease activity and potentially pending/imminent disease progression in many cancer types and may be early signs of transformation to AML. Bone marrow fibrosis adversely affects survival and correlates with higher relapse rates and delayed engraftment in patients with MDS and CMML.<sup>72-79</sup> Extramedullary disease with involvement of the skin,<sup>80,81</sup> pericardium,<sup>82,83</sup> pleura,<sup>84-86</sup> kidney,<sup>87,88</sup> and other sites<sup>89</sup> has been associated with disease acceleration or transformation.<sup>90,91</sup> Transfusion dependence, high transfusion burden, hyperleukocytosis,<sup>5,92</sup> splenomegaly, and iron overload (which may be confounded by prolonged anemia and complications resulting therefrom) are acknowledged adverse risk factors in CMML and are discussed in "Pretransplant management of disease symptoms."

**Cytogenetics and gene mutations** The genetic landscape and its prognostic relevance have been explored in CMML. Cytogenetic risk stratifications and somatic mutations guide prognosis.<sup>5,47,48,93-100</sup> High-risk aberrations are considered an indication for transplant. Not only the type, but potentially also the mutational burden (ie, the total number of mutational abnormalities and their variant allele frequency) may

be relevant to prognosis. High overall mutation burden ( $\geq 10$  mutations), and  $\geq 4$  mutated epigenetic regulatory genes have been linked to increased risk of relapse after transplant in patients with CMML.<sup>101</sup> However, the spectrum of molecular aberrations in CMML seems to be more restricted than in MDS or AML, and the clinical heterogeneity of the disease is thought to exceed genetic heterogeneity.<sup>102</sup> As such, the impact of somatic aberrations may be less straightforward than in MDS or AML.

Although several mutations have already been incorporated into molecular scores (*ASXL1*, *RUNX1*, *NRAS*, and *SETBP1*),<sup>48</sup> their prognostic impact in the transplant setting remains less clear. For example, mutations typically associated with altered risk in the nontransplant setting could not predict post-HCT survival in several studies: *ASXL1*,<sup>5,57,101</sup> *RUNX1*,<sup>5,101</sup> *SRSF2*,<sup>57</sup> and *SETBP1*,<sup>101</sup> with conflicting results for *TET2*.<sup>5,57,101</sup> In contrast, abnormal karyotype or adverse cytogenetics had an adverse impact on outcomes of patients with CMML who underwent transplants in most,<sup>57,63,101,103</sup> but not all<sup>5</sup> studies. However, a recent multicenter cohort identified *ASXL1* and *NRAS* as potential strong molecular predictors of posttransplant outcome.<sup>54</sup> *DNMT3A* and *JAK2* mutations had adverse impacts on posttransplant outcomes of patients with CMML, and the CPSS-Mol was shown to be significantly associated with post-allogeneic overall and disease-free survival.<sup>53</sup> Presence of mutated *NPM1* should result in the diagnosis of AML as per new classifications (see "Classification of CMML"). Presence of *FLT3* aberrations in patients with CMML is rare and data is inconclusive regarding prognostic relevance in this disease.<sup>104</sup>

Presence of *TP53* mutations, although very rare in CMML (~1%-2%),<sup>105</sup> had strong multivariate adjusted adverse associations with posttransplant overall survival in patients with MDS<sup>106</sup> and CMML.<sup>53</sup> Very recently, a prospective clinical trial allocated patients with MDS with high-risk genetics to receive either allo-HCT or non-HCT treatment based on donor availability, demonstrated unequivocally, that allo-HCT after reduced intensity conditioning mediates long-term survival for patients bearing *TP53*-mutations, as compared to patients with mutated *TP53* with non-HCT treatment, and this remained independent of *TP53* allelic state and variant allele frequency.<sup>45</sup> Thus, although the absolute survival benefit remains modest, presence of *TP53* mutations alone should not preclude a patient from consideration for allo-HCT based on TP-53 status alone. The prognostic significance of reducing or clearing the burden of mutations associated with adverse outcomes before allo-HCT needs to be further elucidated, because data on molecular clearance of *TP53* mutations with hypomethylating agents (HMAs; azacitidine or decitabine) before allo-HCT in patients with higher-risk MDS are conflicting.<sup>45,107</sup> The evolving field of (molecular) prognostic factors in CMML will continue to play a critical role in identifying those patients for whom allo-HCT portends the highest benefits.

### Pretransplant management of disease symptoms

**Pretransplant management of (hyper)leukocytosis** A recent meta-analysis and several reviews argue against the routine use of leukapheresis for cytoreduction in hyperleukocytotic AML (ie,  $>100\,000$  WBCs/ $\mu$ L).<sup>108-110</sup> There is no formal demonstration that control of leukocytosis (in the absence of symptoms resulting therefrom), or so-called "blood

count cosmetics" has any impact on disease outcome. Neither is there a consensus regarding a target WBC or monocyte count. Hydroxyurea is recommended by the National Comprehensive Cancer Network<sup>111</sup> and the ELN<sup>112</sup> for cytoreduction before IC in AML. Supportive treatment with allopurinol for the prophylaxis/therapy of tumor lysis syndrome, as well as the transfusion of blood products for the management of disseminated intravascular coagulation, should be given if needed.

**Pretransplant management of iron overload** Although high transfusion burden, iron overload, and iron toxicity are known to have an adverse effect on allo-HCT outcomes among patients with MDS (and CMML),<sup>113-125</sup> it remains unresolved whether and when iron chelation treatment should be initiated in transplant eligible patients. Elevated serum ferritin levels in the pretransplant setting usually result from red blood cell transfusion, and in some of these patients, the presence of hemostatic iron regulator (*HFE*) gene mutations may accelerate transfusion-induced iron overload.<sup>126</sup> Non-transferrin bound iron and labile plasma iron are toxic in both the pretransplant and the posttransplant setting, and may be elevated because of macrophage iron recycling from transfused red blood cells and iron-release from dying red blood cells during and after myeloablative chemotherapy. Early posttransplant iron toxicity can impair engraftment, delay recovery of anemia, increase the risk of infections because of iron capability to support microorganism growth and to compromise immune cell functions, increase the risk of veno-occlusive disease and/or renal failure, and may aggravate both acute and chronic GVHD. Late posttransplant iron toxicity can result in typical end-organ damage due to accumulation of iron deposits in the heart, liver, pancreas, and other vital organs (as reviewed elsewhere<sup>123</sup>).

Because retrospective studies in the allo-HCT setting are limited, and prospective studies are lacking, it currently remains unclear whether pretransplant, peritransplant, and/or posttransplant iron chelation therapy is most beneficial for patients. Phlebotomy and deferoxamine are not indicated in CMML because of obvious reasons, and deferasiprone may result in agranulocytosis. Hence, deferasirox remains the only viable option for patients with CMML.

Several prospective and retrospective studies indicate that treatment with deferasirox in transplant recipients is feasible and associated with improved engraftment, hematologic recovery, and potentially also longer relapse-free and/or overall survival.<sup>127-132</sup> A prospective noninterventional study of 222 patients with MDS or CMML indicates that iron reduction therapy (with either iron chelation therapies or phlebotomies) started within 6 months after allo-HCT resulted in significant improvement of relapse-free survival.<sup>116</sup>

**Pretransplant management of splenomegaly** Although splenomegaly is frequently observed in CMML, it is often limited and manageable without specific treatment in CMML. However, some patients do present with massive splenomegaly. In these cases, the need for splenectomy, splenic irradiation, or other means of reducing spleen size before transplant remains debated. Splenomegaly before transplant is a well-recognized risk factor known to adversely affect transplant outcomes in patients with MDS/ myeloproliferative neoplasm,<sup>133</sup> and is also associated with delayed neutrophil

and platelet engraftment as well as higher nonrelapse mortality. In patients with myelofibrosis, splenectomy was shown to improve neutrophil and platelet recovery (but did not result in longer overall survival) when compared with patients who received either splenic irradiation or no treatment for splenomegaly.<sup>134-136</sup> Patients without splenectomy have delayed hematopoietic recovery, but spleen size does recede eventually after transplant in cases of adequate donor engraftment.<sup>137</sup> Thus, perioperative morbidity (43%) and mortality (13%) rates of splenectomy in patients with CMML<sup>138</sup> need to be weighed carefully. Splenic irradiation before transplant may be considered as an alternative<sup>139</sup> but can be associated with severe and protracted pancytopenia. Therefore, if performed, splenic irradiation should possibly be used as an adjunct to conditioning so that ensuing pancytopenia may be rescued by donor engraftment.<sup>140</sup> JAK2 inhibitors may offer an alternative approach.<sup>141-146</sup>

## Recommendations

- All transplant-eligible patients with CMML should be considered for iron chelation therapy pretransplant, peri-transplant, and posttransplant when serum ferritin levels exceed 1000 µg/L; secondary causes of hyperferritinemia have been excluded; and in the absence of contraindications (eg, elevated renal function parameters). In patients receiving upfront transplantations, iron reduction therapy is preferred in the posttransplant setting to avoid potential additional pretransplant toxicity.
- In the absence of clinical sequelae, hydroxyurea-based cytoreduction is only recommended ≤6 weeks before transplant. We suggest an empiric target of <10 000 WBCs/µL, based on experience, rather than evidence.
- For patients with massively enlarged spleen (ie, >20 cm below the costal margin), splenectomy, splenic irradiation, or reduction of spleen size with JAK inhibitors is recommended. A unified coordinated approach needs to be orchestrated between the treating physician and the transplant center.

## Role of pretransplant therapy

**Role of debulking strategies in CMML** It remains unclear whether debulking, that is, reduction of disease burden as typically measured by reduction of bone marrow blasts to <2%,<sup>54</sup> <5% to 10%, and/or complete remission (CR) status is advantageous for allo-HCT outcomes in patients with MDS<sup>7,8,10,27,30,147-164</sup> or CMML.<sup>8,27,59,101,165-170</sup> It remains unknown and unexplored in both MDS and CMML, whether patients who achieved CR without minimal residual disease (MRD) negativity, might benefit from bridging treatment before allo-HCT.<sup>171</sup> Reducing disease burden before transplant may also be more relevant in the reduced-intensity conditioning setting.<sup>152</sup>

Prospective data on the optimal pretransplant strategy for patients with CMML identified as allo-HCT candidates are lacking. Whereas the role of allo-HCT in CMML is established, the sequence of pretransplant treatment, or whether to treat the patient before allo-HCT at all, is not. Several retrospective analyses compared pretransplant treatment with HMAs vs AML induction-type IC in patients with MDS or CMML, showing either no difference,<sup>57,62,155-157,170</sup> or an advantage with HMAs

for all patients,<sup>5,10,113,150,162,172-174</sup> or in subgroups with higher-risk disease,<sup>157</sup> >5% bone marrow blast count at diagnosis,<sup>155</sup> or older patients.<sup>175</sup> Retrospective analyses comparing HMAs vs best supportive care<sup>12,113,149,176-178</sup> before transplant in MDS could not observe a clear beneficial (or adverse) effect for HMAs. Similarly, neither an improvement in relapse-free or overall survival, nor an additional risk of nonrelapse mortality was shown in patients treated with decitabine<sup>10,155,163,177,179</sup> or azacitidine in a pretransplant setting in patients with MDS (as compared with either best supportive care or IC) in single retrospective studies,<sup>10,12,149,150,155-157,162,172,173,176</sup> a prospective phase 2 clinical trial,<sup>8</sup> as well as a meta-analysis published in 2019<sup>175</sup> collating data from 6 retrospective studies.<sup>150,155-157,172,176</sup> It must be kept in mind, that most (but not all, eg, Kroger et al,<sup>7</sup> Voso et al,<sup>8</sup> Lindholm et al,<sup>9</sup> Yahng et al,<sup>10</sup> and Nakamura et al<sup>12</sup>) of these studies captured patients who did not proceed to transplant, which is a relevant caveat, because it remains obscure how many of them failed to proceed to transplant because of disease progression or pre-transplant treatment-related mortality. With regard to patients with CMML, a recent phase 3 trial remains the only evidence of higher rates of death without progression or transformation for decitabine vs hydroxyurea, albeit these data need to be interpreted with caution because most deaths occurred after study exit.<sup>13</sup>

Randomization at the start of pretransplant therapy and the inclusion of a best-supportive-care arm would be needed to identify whether any disease-modifying treatment is required before allo-HCT.

Although prospective randomized data are lacking, the acceptable toxicity of HMAs combined with their potential for cytoreduction and disease stabilization (which may provide time for patients to reach transplant) led several experts to recommend HMAs as pretransplant treatment for patients with MDS<sup>5,8,28,71,162,175,176,180-182</sup> or CMML.<sup>174</sup> However, many transplant specialists, including the American Society for Transplantation and Cellular Therapy Committee on Practice Guidelines,<sup>183</sup> as well as this panel, consider the evidence (with regard to CMML) not to be clear enough to support this conclusion. Thus, the use of HMAs in the pretransplant setting remains controversial.

One of the main concerns of this panel regarding pretransplant treatment is that up to 13% to 36% of patients with MDS who started HMAs and for whom a transplant was intended could not proceed to transplant because of disease progression, drug-related adverse events, or new comorbidities.<sup>7-12</sup> Similarly, in patients with CMML, death without progression or transformation was significantly higher with decitabine,<sup>13</sup> underlining that the primary goal should be to bring eligible patients to transplant in a good general condition and that achieving CR before transplant may be of subordinate importance. Thus, pre-HCT debulking strategies (be it with HMAs or IC) may be a double-edged sword,<sup>184</sup> potentially resulting in worsening cytopenias, increased transfusion dependence with ensuing complications such as iron overload or alloimmunization,<sup>185</sup> and/or infections that may preclude proceeding to transplant. Hence, this panel recommends that, once a patient has been identified as an allo-HCT candidate, upfront transplantation without prior disease-modifying treatment is

preferred, in order to maximize chances of reaching allo-HCT whenever possible, irrespective of mere bone marrow blast counts of 10% to 19%. However, in cases of aggressive disease with kinetics indicating rapid disease progression and/or severe clinical symptoms requiring immediate alleviation, bridging therapy with HMA (possibly in combination with off-label use of venetoclax) may be considered, as long as this does not postpone, or reduce the patients' chances of, receiving curative treatment and should ideally be studied within clinical trials.

### Optimal choice of pretransplant treatment in CMML

A large retrospective analysis demonstrated multivariable-adjusted overall survival and time to next treatment to be significantly longer with the use of HMAs as compared with IC in patients with higher-risk CMML (n = 949).<sup>71</sup> We consider the existing evidence to be strong enough to no longer support an indication for conventional IC in any setting in this disease. Patients with newly diagnosed high-risk/secondary AML had significantly longer posttransplant survival and lower early mortality when treated with CPX-351 as opposed to IC with "7 + 3."<sup>186</sup> Data on the CPX-351 (liposomal formulation of cytarabine and daunorubicin) for higher-risk CMML and AML secondary to CMML are available for a handful of patients only from small phase 1/2 clinical trials performed in both the first-line<sup>187</sup> and second-line settings,<sup>188</sup> indicating that the drug may be safe, and it allowed for bridging to allo-HCT in selected (1 of 6<sup>187</sup>) patients with CMML. Five of 5 patients with CMML receiving CPX-351 as first-line treatment responded,<sup>187</sup> whereas only 1 of 6 patients with CMML receiving the drug after HMA failure achieved a response and could proceed to allo-HCT.<sup>188</sup> Given the very small numbers of patients with CMML treated with CPX-351, the efficacy of the drug needs to be further studied in this disease. Novel debulking strategies are needed. Azacitidine plus venetoclax by itself<sup>189-193</sup> or possibly in the future as a backbone for potential triplet combinations incorporating newer substances (eg, CD123 targeting with tagraxofusp or flotetuzumab) may well be the way forward. Data from early phase clinical trials evaluating azacitidine with venetoclax in patients with MDS in the first-line<sup>194</sup> or relapsed/refractory setting<sup>195</sup> are starting to emerge, as are data on the use of the combination as bridging to allo-HCT in patients with high-risk MDS and AML.<sup>196-198</sup> Clinical trials incorporating venetoclax in conditioning regimen (eg, [clinicaltrials.gov](https://clinicaltrials.gov) identifier: NCT05005299, NCT05823714, NCT05807932, and NCT03613532) or as bridging (eg, [clinicaltrials.gov](https://clinicaltrials.gov) identifier: NCT04476199 and NCT04904237) to allo-HCT in patients with MDS and AML are currently underway, and patients with CMML can be included in some of them (eg, [clinicaltrials.gov](https://clinicaltrials.gov) identifier: NCT05807932 and NCT03613532). Because venetoclax in combination with HMA leads to much higher rates of CR (without necessarily translating into longer overall survival),<sup>199</sup> which are achieved more rapidly than with HMA alone, data emerging in patients with CMML who proceeded to allo-HCT will have to be reviewed carefully and may possibly result in a future alteration of this panel's current recommendation. We acknowledge, and perhaps anticipate, that venetoclax with an HMA may be an ideal bridging therapy for patients with CMML (and probably also MDS or AML) with high blast counts and/or proliferative disease and/or other signs of rapid disease kinetics.

### Optimal timing of allo-HCT in patients who are pre-treated

Both retrospective<sup>92,200</sup> and prospective<sup>178</sup> data indicate that it is significantly better to proceed to allo-HCT while patients are responding to HMAs rather than to wait for treatment failure.<sup>165,200</sup> The primary goal may be to bring patients eligible for allo-HCT in a good general condition, or to render patients who were initially transplant ineligible into a transplant-eligible state, whereas achieving CR before transplant may be of subordinate importance. As outcome after HMA-failure is mostly dismal (<6 months), patients should receive transplantation after achieving the best possible response. In patients with CMML treated with azacitidine the median time to first and best response is 4 (interquartile range, 2-5) and 5 (interquartile range, 3-7) cycles, respectively.<sup>70,201,202</sup> Approximately onethird of patients experience further deepening of response after first response, with the median time from first response to best response being 3 to 4 cycles.<sup>201,203</sup> Best outcomes in the HMA-relapsed/refractory setting were observed for patients with MDS able to receive allo-HCT,<sup>204,205</sup> which explains why this procedure should be offered when possible.

### Recommendations

- All patients should be included within clinical trials whenever available and possible.
- Once a patient has been identified to be a transplant candidate, we support an upfront transplantation as soon as a suitable donor is available, without any disease-modifying pretreatment for all patients with CMML, whenever possible, regardless of the bone marrow blast count. Timely referral to a transplant center is essential.
- In the rare cases in which pretransplant treatment is unavoidable (eg, no matching donor available), we recommend the use of HMAs, and no longer see any indication for the use of IC in patients with CMML.<sup>71</sup>
- Upfront transplantation without prior treatment is preferred and recommended whenever possible. In cases in which front-line treatment (most often with HMAs) may have been commenced (because of immediate need of treatment of severe clinical symptoms and/or aggressive disease with kinetics indicating rapid disease progression), allo-HCT should be performed after establishing the best possible response status, which is achieved after  $\leq 7$  cycles of HMAs in 75% of patients with CMML,<sup>70,201,202</sup> provided the patient remains transplant eligible. The patient should not continue the treatment until loss of response, or when disease relapse or progression occur. To this end, we recommend close monitoring and performing of a bone marrow evaluation as soon as response is suspected from amelioration of peripheral blood values, for example, every 2 cycles, with the aim of not subjecting the patient to unnecessary delays in the transplant, and not to lengthen the period at risk for losing, and, most importantly, to avoid loss of, transplant eligibility.
- If relapse after any treatment has already occurred, allo-HCT should nevertheless always be considered for eligible patients, because this remains the best option for these patients.
- Value-based discussions between treating physicians, transplant centers, and patients as to the appropriateness of the procedure are merited in those instances, where the expected benefit from allo-HCT remains modest, eg, when

mutations associated with adverse risk, complex or monosomal karyotype are present and any of the following factors are additionally present: age >70 years, comorbidities, and/or other variables adversely influencing prognosis and transplant outcomes (eg, iron overload, bone marrow fibrosis, therapy-related disease). Possibly, HMAs might be of use (as bridging strategy or instead of allo-HCT) for selected patients aged >60 years,<sup>175</sup> with *TP53* mutations and/or with complex or monosomal karyotypes.<sup>45,206</sup>

### Donor selection

Potential stem cell donors include standard donors (such as HLA-matched siblings and matched unrelated donors), alternative stem cell donors including haploidentical or mismatched unrelated donors, and (less frequently) unrelated umbilical cord donors. Selection of stem cell donors for patients with CMML has improved markedly during the last 2 decades, similar to what has been observed for allo-HCT in other indications. Several studies found differences in absolute survival and relapse rates between HLA-identical sibling and matched unrelated donors, whereas some showed no significant difference after multivariable adjustment.<sup>53,54,165,207</sup> The expert panel agreed to recommend as standard donors (starting with highest preference): HLA-identical siblings, followed by matched unrelated donors (Figure 3). Recent studies in the MDS setting found higher disease-free survival and lower relapse for allo-HCT with younger matched unrelated donors compared with older HLA-identical siblings.<sup>208</sup> Another large EBMT study found an independent effect of cytomegalovirus serostatus of donors (although this study included patients mostly from the pretermovir era).<sup>207</sup> Therefore, the expert panel agreed to take age and cytomegalovirus status of donors into account when balancing the risk for nonrelapse mortality vs relapse during the donor selection process, and to follow the previously formulated donor suitability criteria.<sup>209</sup>

Alternative donor transplants may be considered for patients with higher-risk disease and fit patients, for whom no matched sibling or unrelated donor can be identified within a reasonable search period. Unrelated cord blood transplants showed very poor results in CMML,<sup>103</sup> and should therefore be carefully used, in case no other suitable donor is available.

**Recommendations** Currently, there are no systematic comparative studies between haploidentical transplants and

mismatched unrelated donors, and the panel agreed to use either of them, considering access, timing, and other suitability criteria. For haploidentical donor allo-HCT, based on previous reports in other diseases,<sup>210</sup> posttransplant cyclophosphamide may be the preferred platform.

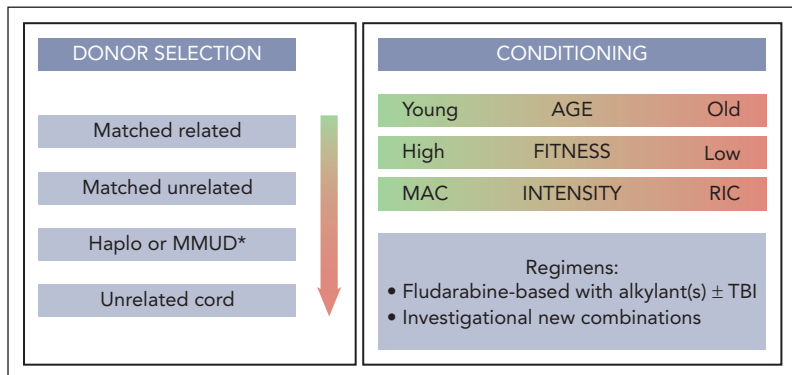
### Stem cell source

Limited data are available on transplant outcomes in CMML according to stem cell source. The panel agreed that peripheral blood is the recommended hematopoietic stem cell source for HLA-matched sibling and unrelated donor transplants. No data exist on the preferred source for haploidentical transplants. Higher doses of CD34<sup>+</sup> cells, if possible, might be targeted for unrelated donor transplants.<sup>211</sup> However, because of lack of data, a preferred stem cell dose cannot be recommended for any transplant modality.

### Conditioning intensity

Choosing the right conditioning intensity and regimen is a cornerstone of allo-HCT, balancing the risk of increased non-relapse mortality when choosing more intensive treatment compared with increased risk for relapse when choosing less intensive regimens. The expert panel defined the various preparatory intensities according to the classification used by several previous studies (mostly in the setting of MDS).<sup>212</sup> Most retrospective studies in patients with CMML and MDS report equivocal outcome after commonly used myeloablative or reduced intensity conditioning regimens.<sup>52,165,213,214</sup> Therefore, the panel agreed that there is currently no superiority of 1 intensity over another. However, it can be extrapolated from clinical practice that posttransplant relapse in CMML appears to be more frequent than in MDS (with the largest retrospective series reporting relapse rates in the 27%-to-52% range<sup>57,62</sup> and ~80% of patients experience relapse within the first year from allo-HCT). Thus, if patients are fit enough to undergo more intensive treatment, myeloablative conditioning should be preferred (Figure 3).

If myeloablative conditioning is not feasible, combination of fludarabine and busulfan appeared to be associated with best outcomes across diseases in MDS and myeloproliferative neoplasm and can therefore also be considered in CMML, with or without total-body irradiation.<sup>214-217</sup> Recent increased adoption of treosulfan-based regimens within a reduced-toxicity approach showed promising results in other indication.<sup>166,218</sup> However, there is no direct evidence to favor a particular



**Figure 3. Transplant modalities.** \*According to center preference. MAC, myeloablative conditioning; MMUD, mismatched unrelated donor; RIC, reduced intensity conditioning; TBI, total body irradiation.

regimen over another. There is currently no evidence for the association of disease and mutation burden or the threshold of MRD with the choice for conditioning intensity or regimen.

**Recommendations** The expert panel recommended not to adopt pretreatment decisions based on intensity of planned conditioning but to focus on posttransplant strategies, including chimerism and/or MRD monitoring, as well as to prevent relapse (see “Posttransplant management” in supplemental pp2-5).

## Acknowledgments

The European Society for Blood and Marrow Transplantation (EBMT) is a not-for-profit medical and scientific organization. The EBMT performed administrative and legal management, as well as funding acquisition. No pharmaceutical company and no other funding source were involved in any way or had a role in the study design, data collection, data analysis, data interpretation, or writing of the report. No medical writer or editor was involved.

## Authorship

Contribution: F.O., N.G., Y.C., G.K., M.R., A.S., I.Y.-A., and L.P. were responsible for literature research, and interpretation of data, conceived and designed the manuscript topics to be covered as well as the recommendations to be made, and conception of figures; F.O. was responsible for writing of the “Introduction” and “Unanswered questions”; L.P. was responsible for writing sections “Patient selection for allo-HCT,” “Timing of allo-HCT,” “Pretransplant management of disease symptoms,” and “Role of pretransplant therapy” and design of figures and tables; N.G. was responsible for writing “Donor selection,” “Stem cell source,” “Conditioning intensity,” and the supplemental Data; I.Y.-A. was responsible for defining the EBMT Practice Harmonization and Guidelines according to which this manuscript was written; all authors played an important role in interpreting results, revised the manuscript, approved the final version, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; and F.O., N.G., Y.C., G.K., M.R., A.S., I.Y.-A., and L.P. accept final responsibility for the decision to submit for publication.

Conflict-of-interest disclosure: F.O. received honoraria from Takeda, MEDAC Pharma, and Kyowa Kirin; and received travel support from Takeda, Jazz Pharma, and Kyowa Kirin. Y.C. received honoraria from AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Gilead, Incyte, Jazz, Merck Sharp & Dohme (MSD), Novartis, Pfizer, Roche, Servier, and Takeda; and received travel support from AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Gilead, Incyte, Jazz, MSD, Novartis, Pfizer, Roche, and Sanofi. G.K. received research support from Bristol Myers Squibb/Celgene, Amgen, AbbVie, Medac, and Eurocept; received honoraria from Novartis, MSD, Pfizer, Amgen, Gilead, Bristol Myers Squibb/Celgene, AbbVie, Biotest, Takeda, and Eurocept; and received travel

support from Medac, Gilead, and Neovii. M.R. received research support from AbbVie, Astex, Medac, Neovii, and Novartis; and received travel support from Medac and Jazz. A.S. received honoraria from AbbVie, Amgen, Bristol Myers Squibb, Incyte/Genesis, Gilead, Sanofi, and Servier; and received travel support from AbbVie, Bristol Myers Squibb, Roche, Servier, and Takeda. R.I. received research support from AbbVie; received honoraria from AbbVie, Bristol Myers Squibb/Celgene, CTI Biopharma, Gilead, Jazz, Novartis, and Servier; and received travel support from AbbVie and Gilead/Kite. M.J. received honoraria from AbbVie, Bristol Myers Squibb/Celgene, Novartis, JAZZ Pharmaceuticals, and Pfizer; and received travel support from AbbVie, Bristol Myers Squibb/Celgene, and Pfizer. U.P. received research support from Bristol Myers Squibb, Curis, Jazz, Amgen, Bergenbio, Janssen, and Novartis; and received honoraria from Bristol Myers Squibb, Curis, Jazz, Amgen, Bergenbio, Janssen, and Novartis. V.S. received honoraria from AbbVie, Bristol Myers Squibb/Celgene, CTI Biopharma, Curis, Geron, Gilead, Novartis, Otsuka Pharmaceutical Co, Servier, and Syros; and received travel support from Janssen. G.S. received research funding from Celgene; received honoraria from AbbVie, Bristol Myers Squibb/Celgene, ExCellThera, Novartis, Roche, and Takeda; and received travel support from BeiGene and Celgene. C.S. received research support from Janssen, Novartis, and Takeda; received honoraria from AbbVie, Amgen, Bristol Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Novartis, Roche, Sanofi, and Takeda; and received travel support from GlaxoSmithKline, Janssen, and Sanofi. E.S. received research support from Fondation Amgen; and received honoraria from Blueprint and Novartis. P.V. received research support from AOP Orphan and Pfizer; and received honoraria from Blueprint, Bristol Myers Squibb/Celgene, Cogent, Incyte, Novartis, Pfizer, Servier, and Stemline. R.G. received honoraria from Biotest, Pfizer, Medac, and Magenta. I.Y.-A. received honoraria from Bristol Myers Squibb, Novartis, Janssen, Kite/Gilead, and Biotest. L.P. received honoraria from AbbVie, Bristol Myers Squibb/Celgene, Novartis, and Otsuka Pharmaceutical Co; and received travel support from AbbVie, AstraZeneca, BeiGene, and Takeda. The remaining authors declare no competing financial interests.

ORCID profiles: N.G., [0000-0002-0891-1744](https://orcid.org/0000-0002-0891-1744); Y.C., [0000-0001-9341-8104](https://orcid.org/0000-0001-9341-8104); M.R., [0000-0003-1388-9876](https://orcid.org/0000-0003-1388-9876); A.S., [0000-0002-3685-3473](https://orcid.org/0000-0002-3685-3473); R.I., [0000-0003-2139-6262](https://orcid.org/0000-0003-2139-6262); U.P., [0000-0003-1863-3239](https://orcid.org/0000-0003-1863-3239); G.S., [0000-0002-2767-8191](https://orcid.org/0000-0002-2767-8191); E.S., [0000-0002-8629-1341](https://orcid.org/0000-0002-8629-1341); P.V., [0000-0003-0456-5095](https://orcid.org/0000-0003-0456-5095); R.G., [0000-0002-6117-5328](https://orcid.org/0000-0002-6117-5328); I.S.-O., [0009-0005-5519-9154](https://orcid.org/0009-0005-5519-9154); I.Y.-A., [0000-0003-4524-8782](https://orcid.org/0000-0003-4524-8782).

Correspondence: Lisa Pleyer, 3rd Medical Department, Paracelsus Medical University Hospital, Müllnerhauptstr 48, 5020 Salzburg, Austria; email: [dr.lisa.pleyer@gmail.com](mailto:dr.lisa.pleyer@gmail.com).

## Footnotes

Submitted 6 December 2023; accepted 23 February 2024; prepublished online on *Blood* First Edition 17 March 2024. <https://doi.org/10.1182/blood.2023023476>.

The online version of this article contains a data supplement.

## REFERENCES

1. Padron E, Garcia-Manero G, Patnaik MM, et al. An international data set for CMML validates prognostic scoring systems and demonstrates a need for novel prognostication strategies. *Blood Cancer J*. 2015;5(7):e333.
2. Onida F. Models of prognostication in chronic myelomonocytic leukemia. *Curr Hematol Malig Rep*. 2017;12(6):513-521.
3. Patnaik MM. How I diagnose and treat chronic myelomonocytic leukemia. *Haematologica*. 2022;107(7):1503-1517.
4. Robin M, de Wreede LC, Padron E, et al. Role of allogeneic transplantation in chronic myelomonocytic leukemia: an international collaborative analysis. *Blood*. 2022;140(12):1408-1418.
5. Wedge E, Hansen JW, Dybedal I, et al. Allogeneic hematopoietic stem cell transplantation for chronic myelomonocytic leukemia: clinical and molecular genetic prognostic factors in a Nordic population. *Transplant Cell Ther*. 2021;27(12):991.e1-991.e9.
6. Tomlinson B, de Lima M, Cogle CR, et al. Transplantation referral patterns for patients with newly diagnosed higher-risk myelodysplastic syndromes and acute myeloid leukemia at academic and community sites in the Connect(R) Myeloid Disease Registry: potential barriers to care. *Transplant Cell Ther*. 2023;29(7):460.e1-460.e9.
7. Kroger N, Sockel K, Wolschke C, et al. Comparison between 5-azacytidine treatment and allogeneic stem-cell transplantation in elderly patients with advanced MDS according to donor availability (VidazaAllo Study). *J Clin Oncol*. 2021;39(30):3318-3327.
8. Voso MT, Leone G, Picicchi A, et al. Feasibility of allogeneic stem-cell transplantation after azacitidine bridge in

- higher-risk myelodysplastic syndromes and low blast count acute myeloid leukemia: results of the BMT-AZA prospective study. *Ann Oncol.* 2017;28(7):1547-1553.
9. Lindholm C, Olofsson E, Creignou M, et al. Failure to reach hematopoietic allogeneic stem cell transplantation in patients with myelodysplastic syndromes planned for transplantation: a population-based study. *Bone Marrow Transplant.* 2022;57(4):598-606.
  10. Yahng SA, Kim M, Kim TM, et al. Better transplant outcome with pre-transplant marrow response after hypomethylating treatment in higher-risk MDS with excess blasts. *Oncotarget.* 2017;8(7):12342-12354.
  11. Getta BM, Kishtagari A, Hilden P, et al. Allogeneic hematopoietic stem cell transplantation is underutilized in older patients with myelodysplastic syndromes. *Biol Blood Marrow Transplant.* 2017;23(7):1078-1086.
  12. Nakamura R, Saber W, Martens MJ, et al. Biologic assignment trial of reduced-intensity hematopoietic cell transplantation based on donor availability in patients 50-75 years of age with advanced myelodysplastic syndrome. *J Clin Oncol.* 2021;39(30):3328-3339.
  13. Itzykson R, Santini V, Thepot S, et al. Decitabine versus hydroxyurea for advanced proliferative chronic myelomonocytic leukemia: results of a randomized phase III trial within the EMSCO Network. *J Clin Oncol.* 2023;41(10):1888-1897.
  14. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of myeloid neoplasms and acute Leukemias: integrating morphologic, clinical, and genomic data. *Blood.* 2022;140(11):1200-1228.
  15. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. *Leukemia.* 2022;36(7):1703-1719.
  16. Atallah E, Logan B, Chen M, et al. Comparison of patient age groups in transplantation for myelodysplastic syndrome: the Medicare Coverage With Evidence Development Study. *JAMA Oncol.* 2020;6(4):486-493.
  17. Platzbecker U, Schetelig J, Finke J, et al. Allogeneic hematopoietic cell transplantation in patients age 60-70 years with de novo high-risk myelodysplastic syndrome or secondary acute myelogenous leukemia: comparison with patients lacking donors who received azacitidine. *Biol Blood Marrow Transplant.* 2012;18(9):1415-1421.
  18. Carre M, Porcher R, Finke J, et al. Role of age and hematopoietic cell transplantation-specific comorbidity index in myelodysplastic patients undergoing an allotransplant: a retrospective study from the Chronic Malignancies Working Party of the European Group for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant.* 2020;26(3):451-457.
  19. Sorror ML, Storb RF, Sandmaier BM, et al. Comorbidity-age index: a clinical measure of biologic age before allogeneic hematopoietic cell transplantation. *J Clin Oncol.* 2014;32(29):3249-3256.
  20. Arora M, Sun CL, Ness KK, et al. Physiologic frailty in nonelderly hematopoietic cell transplantation patients: results from the Bone Marrow Transplant Survivor Study. *JAMA Oncol.* 2016;2(10):1277-1286.
  21. Muffy LS, Kocherginsky M, Stock W, et al. Geriatric assessment to predict survival in older allogeneic hematopoietic cell transplantation recipients. *Haematologica.* 2014;99(8):1373-1379.
  22. Rodrigues M, de Souza PMR, de Oliveira Muniz Koch L, Hamerschlag N. The use of comprehensive geriatric assessment in older patients before allogeneic hematopoietic stem cell transplantation: a cross-sectional study. *J Geriatr Oncol.* 2020;11(1):100-106.
  23. Aydin S, Passera R, Cerrano M, et al. Combining the HCT-CI, G8, and AML-score for fitness evaluation of elderly patients with acute myeloid leukemia: a single center analysis. *Cancers (Basel).* 2023;15(4):1002.
  24. Sorror ML. The use of prognostic models in allogeneic transplants: a perspective guide for clinicians and investigators. *Blood.* 2023;141(18):2173-2186.
  25. Fernandez-Caballero M, Jimenez Lorenzo MJ, Morgades de la Fe M, et al. Impact of risk scores in outcome of patients with myeloid neoplasms after allogeneic stem cell transplant. *Med Clin (Barc).* 2022;158(10):451-457.
  26. Ferrara F, Barosi G, Venditti A, et al. Consensus-based definition of unfit to intensive and non-intensive chemotherapy in acute myeloid leukemia: a project of SIE, SIES and GITMO group on a new tool for therapy decision making. *Leukemia.* 2013;27(5):997-999.
  27. de Witte T, Bowen D, Robin M, et al. Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel. *Blood.* 2017;129(13):1753-1762.
  28. Itzykson R, Fenaux P, Bowen D, et al. Diagnosis and treatment of chronic myelomonocytic leukemias in adults: recommendations from the European Hematology Association and the European LeukemiaNet. *Hemasphere.* 2018;2(6):e150.
  29. Alessandrino EP, Porta MG, Malcovati L, et al. Optimal timing of allogeneic hematopoietic stem cell transplantation in patients with myelodysplastic syndrome. *Am J Hematol.* 2013;88(7):581-588.
  30. Della Porta MG, Jackson CH, Alessandrino EP, et al. Decision analysis of allogeneic hematopoietic stem cell transplantation for patients with myelodysplastic syndrome stratified according to the revised International Prognostic Scoring System. *Leukemia.* 2017;31(11):2449-2457.
  31. Cutler CS, Lee SJ, Greenberg P, et al. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: delayed transplantation for low-risk myelodysplasia is associated with improved outcome. *Blood.* 2004;104(2):579-585.
  32. Koreth J, Pidala J, Perez WS, et al. Role of reduced-intensity conditioning allogeneic hematopoietic stem-cell transplantation in older patients with de novo myelodysplastic syndromes: an international collaborative decision analysis. *J Clin Oncol.* 2013;31(21):2662-2670.
  33. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood.* 1997;89(6):2079-2088.
  34. Greenberg PL, Tuechler H, Schanz J, et al. Revised International Prognostic Scoring System for myelodysplastic syndromes. *Blood.* 2012;120(12):2454-2465.
  35. Aul C, Gattermann N, Heyll A, Germing U, Derigs G, Schneider W. Primary myelodysplastic syndromes: analysis of prognostic factors in 235 patients and proposals for an improved scoring system. *Leukemia.* 1992;6(1):52-59.
  36. Onida F, Kantarjian HM, Smith TL, et al. Prognostic factors and scoring systems in chronic myelomonocytic leukemia: a retrospective analysis of 213 patients. *Blood.* 2002;99(3):840-849.
  37. Worsley A, Oscier DG, Stevens J, et al. Prognostic features of chronic myelomonocytic leukaemia: a modified Bournemouth score gives the best prediction of survival. *Br J Haematol.* 1988;68(1):17-21.
  38. Such E, Germing U, Malcovati L, et al. Development and validation of a prognostic scoring system for patients with chronic myelomonocytic leukemia. *Blood.* 2013;121(15):3005-3015.
  39. Patnaik MM, Padron E, LaBorde RR, et al. Mayo prognostic model for WHO-defined chronic myelomonocytic leukemia: ASXL1 and spliceosome component mutations and outcomes. *Leukemia.* 2013;27(7):1504-1510.
  40. Huemer F, Weiss L, Faber V, et al. Establishment and validation of a novel risk model for estimating time to first treatment in 120 patients with chronic myelomonocytic leukaemia. *Wien Klin Wochenschr.* 2018;130(3-4):115-125.
  41. Beran M, Wen S, Shen Y, et al. Prognostic factors and risk assessment in chronic myelomonocytic leukemia: validation study of the M.D. Anderson Prognostic Scoring

- System. *Leuk Lymphoma*. 2007;48(6):1150-1160.
42. Calvo X, Nomdedeu M, Santacruz R, et al. Comparison of three prognostic scoring systems in a series of 146 cases of chronic myelomonocytic leukemia (CMML): MD Anderson prognostic score (MDAPS), CMML-specific Prognostic Scoring System (CPSS) and Mayo prognostic model. A detailed review of prognostic factors in CMML. *Leuk Res*. 2015;39(11):1146-1153.
  43. Moreno Berggren D, Kjellander M, Backlund E, et al. Prognostic scoring systems and comorbidities in chronic myelomonocytic leukaemia: a nationwide population-based study. *Br J Haematol*. 2021;192(3):474-483.
  44. Germing U, Kundgen A, Gattermann N. Risk assessment in chronic myelomonocytic leukemia (CMML). *Leuk Lymphoma*. 2004;45(7):1311-1318.
  45. Versluis J, Saber W, Tsai HK, et al. Allogeneic hematopoietic cell transplantation improves outcome in myelodysplastic syndrome across high-risk genetic subgroups: genetic analysis of the Blood and Marrow Transplant Clinical Trials Network 1102 Study. *J Clin Oncol*. 2023;41(28):4497-4510.
  46. Itzykson R, Kosmider O, Renneville A, et al. Prognostic score including gene mutations in chronic myelomonocytic leukemia. *J Clin Oncol*. 2013;31(19):2428-2436.
  47. Patnaik MM, Itzykson R, Lasho TL, et al. ASXL1 and SETBP1 mutations and their prognostic contribution in chronic myelomonocytic leukemia: a two-center study of 466 patients. *Leukemia*. 2014;28(11):2206-2212.
  48. Elena C, Galli A, Such E, et al. Integrating clinical features and genetic lesions in the risk assessment of patients with chronic myelomonocytic leukemia. *Blood*. 2016;128(10):1408-1417.
  49. Sauta E, Robin M, Bersanelli M, et al. Real-world validation of molecular International Prognostic Scoring System for myelodysplastic syndromes. *J Clin Oncol*. 2023;41(15):2827-2842.
  50. Lee WH, Tsai MT, Tsai CH, et al. Validation of the molecular International Prognostic Scoring System in patients with myelodysplastic syndromes defined by International Consensus Classification. *Blood Cancer J*. 2023;13(1):120.
  51. Ma J, Gu Y, Wei Y, et al. Evaluation of new IPSS-Molecular model and comparison of different prognostic systems in patients with myelodysplastic syndrome. *Blood Sci*. 2023;5(3):187-195.
  52. Gurnari C, Gagelmann N, Badbaran A, et al. Outcome prediction in myelodysplastic neoplasm undergoing hematopoietic cell transplant in the molecular era of IPSS-M. *Leukemia*. 2023;37(3):717-719.
  53. Mei M, Pillai R, Kim S, et al. The mutational landscape in chronic myelomonocytic leukemia and its impact on allogeneic hematopoietic cell transplantation outcomes: a Center for Blood and Marrow Transplantation Research (CIBMTR) analysis. *Haematologica*. 2023;108(1):150-160.
  54. Gagelmann N, Badbaran A, Beelen DW, et al. A prognostic score including mutation profile and clinical features for patients with CMML undergoing stem cell transplantation. *Blood Adv*. 2021;5(6):1760-1769.
  55. Gagelmann N, Bogdanov R, Stolz F, et al. Long-term survival benefit after allogeneic hematopoietic cell transplantation for chronic myelomonocytic leukemia. *Transplant Cell Ther*. 2021;27(1):95.e1-95.e4.
  56. Patnaik MM, Pierola AA, Vallapureddy R, et al. Blast phase chronic myelomonocytic leukemia: Mayo-MDACC collaborative study of 171 cases. *Leukemia*. 2018;32(11):2512-2518.
  57. Pophali P, Matin A, Mangaonkar AA, et al. Prognostic impact and timing considerations for allogeneic hematopoietic stem cell transplantation in chronic myelomonocytic leukemia. *Blood Cancer J*. 2020;10(11):121.
  58. Ruggiu M, Cassinat B, Kiladjian JJ, et al. Should transplantation still be considered for Ph1-negative myeloproliferative neoplasms in transformation? *Biol Blood Marrow Transplant*. 2020;26(6):1160-1170.
  59. Kroger N, Eikema DJ, Koster L, et al. Impact of primary disease on outcome after allogeneic stem cell transplantation for transformed secondary acute leukaemia. *Br J Haematol*. 2019;185(4):725-732.
  60. Della Porta MG, Alessandrino EP, Bacigalupo A, et al. Predictive factors for the outcome of allogeneic transplantation in patients with MDS stratified according to the revised IPSS-R. *Blood*. 2014;123(15):2333-2342.
  61. Koenecke C, Eikema DJ, Hazelaar S, et al. Prognostic value of CPSS cytogenetic risk classification in patients with CMML after allogeneic hematopoietic cell transplantation: a retrospective multicenter study of the Chronic Malignancies Working Party of the EBMT. *Bone Marrow Transplant*. 2022;57(10):1607-1611.
  62. Liu HD, Ahn KW, Hu ZH, et al. Allogeneic hematopoietic cell transplantation for adult chronic myelomonocytic leukemia. *Biol Blood Marrow Transplant*. 2017;23(5):767-775.
  63. Eissa H, Gooley TA, Sorror ML, et al. Allogeneic hematopoietic cell transplantation for chronic myelomonocytic leukemia: relapse-free survival is determined by karyotype and comorbidities. *Biol Blood Marrow Transplant*. 2011;17(6):908-915.
  64. Tentori CA, Gregorio C, Robin M, et al. Clinical and genomic-based decision support system to define the optimal timing of allogeneic hematopoietic stem cell transplantation in patients with myelodysplastic syndromes (MDS) [abstract]. *Blood*. 2023;142(suppl 1):197.
  65. Scheid C, de Wreede L, van Biezen A, et al. Validation of the revised IPSS at transplant in patients with myelodysplastic syndrome/transformed acute myelogenous leukemia receiving allogeneic stem cell transplantation: a retrospective analysis of the EBMT chronic malignancies working party. *Bone Marrow Transplant*. 2017;52(11):1519-1525.
  66. Zhou JY, Wang S, Yuan HL, et al. Impact of a novel prognostic model on allogeneic hematopoietic stem cell transplantation outcomes in patients with CMML. *Am J Hematol*. 2023;98(9):1394-1406.
  67. Baranwal A, Mangaonkar A, Shah MV, et al. High EASIX score is an independent predictor of non-relapse mortality in patients with CMML undergoing allogeneic stem cell transplant. *Bone Marrow Transplant*. 2022;57(12):1842-1844.
  68. Valent P, Orazi A, Savona MR, et al. Proposed diagnostic criteria for classical chronic myelomonocytic leukemia (CMML), CMML variants and pre-CMML conditions. *Haematologica*. 2019;104(10):1935-1949.
  69. Jansko-Gadermeir B, Leisch M, Gassner FJ, et al. Myeloid NGS analyses of paired samples from bone marrow and peripheral blood yield concordant results: a prospective cohort analysis of the AGMT Study Group. *Cancers (Basel)*. 2023;15(8):2305.
  70. Pleyer L, Vaisband M, Drost M, et al. Cox proportional hazards deep neural network identifies peripheral blood complete remission to be at least equivalent to morphologic complete remission in predicting outcomes of patients treated with azacitidine-a prospective cohort study by the AGMT. *Am J Hematol*. 2023;98(11):1685-1698.
  71. Pleyer L, Leisch M, Kourakli A, et al. Outcomes of patients with chronic myelomonocytic leukaemia treated with non-curative therapies: a retrospective cohort study. *Lancet Haematol*. 2021;8(2):e135-e148.
  72. Della Porta MG, Malcovati L. Myelodysplastic syndromes with bone marrow fibrosis. *Haematologica*. 2011;96(2):180-183.
  73. Kroger N, Zabelina T, van Biezen A, et al. Allogeneic stem cell transplantation for myelodysplastic syndromes with bone marrow fibrosis. *Haematologica*. 2011;96(2):291-297.
  74. Wang J, Wang Q, Zhang H, et al. Moderate to severe marrow fibrosis as a more advanced risk factor for MDS receiving allogeneic hematopoietic stem cell transplantation. *Transplant Cell Ther*. 2021;27(8):666.e1-666.e9.

75. Scott BL, Storer BE, Greene JE, Hackman RC, Appelbaum FR, Deeg HJ. Marrow fibrosis as a risk factor for posttransplantation outcome in patients with advanced myelodysplastic syndrome or acute myeloid leukemia with multilineage dysplasia. *Biol Blood Marrow Transplant.* 2007;13(3):345-354.
76. Jain AG, Zhang L, Bennett JM, Komrokji R. Myelodysplastic Syndromes with bone marrow fibrosis: an update. *Ann Lab Med.* 2022;42(3):299-305.
77. Gur HD, Loghavi S, Garcia-Manero G, et al. Chronic myelomonocytic leukemia with fibrosis is a distinct disease subset with myeloproliferative features and frequent JAK2 p.V617F mutations. *Am J Surg Pathol.* 2018;42(6):799-806.
78. Khan M, Muzzafar T, Kantarjian H, et al. Association of bone marrow fibrosis with inferior survival outcomes in chronic myelomonocytic leukemia. *Ann Hematol.* 2018;97(7):1183-1191.
79. Petrova-Drus K, Chiu A, Margolskee E, et al. Bone marrow fibrosis in chronic myelomonocytic leukemia is associated with increased megakaryopoiesis, splenomegaly and with a shorter median time to disease progression. *Oncotarget.* 2017;8(61):103274-103282.
80. Mathew RA, Bennett JM, Liu JJ, et al. Cutaneous manifestations in CMML: indication of disease acceleration or transformation to AML and review of the literature. *Leuk Res.* 2012;36(1):72-80.
81. Bonometti A. Cutaneous involvement in Ph-negative myeloproliferative neoplasms: from extramedullary hematopoiesis to myeloid metastasis with histiocytic differentiation. A systematic review of the literature. *Int J Dermatol.* 2023;62(10):1228-1236.
82. Bradford CR, Smith SR, Wallis JP. Pericardial extramedullary haemopoiesis in chronic myelomonocytic leukaemia. *J Clin Pathol.* 1993;46(7):674-675.
83. Mani S, Duffy TP. Pericardial tamponade in chronic myelomonocytic leukemia. *Chest.* 1994;106(3):967-970.
84. Bourantas KL, Tsiara S, Panteli A, Milionis C, Christou L. Pleural effusion in chronic myelomonocytic leukemia. *Acta Haematol.* 1998;99(1):34-37.
85. Hu L, Zheng B, Fu L, Hu M. Chronic myelomonocytic leukemia (CMML)-0 with pleural effusion as first manifestation: a case report. *Medicine (Baltimore).* 2020;99(44):e23030.
86. Imataki O, Watanabe N, Matsumoto K, Uemura M. Chronic myelomonocytic leukemia presenting with polyserositis due to an immune-mediated monocyte activation. *Clin Case Rep.* 2014;2(2):42-44.
87. Hyams ES, Gupta R, Melamed J, Taneja SS, Shah O. Renal involvement by chronic myelomonocytic leukemia requiring nephroureterectomy. *Rev Urol.* 2009;11(1):33-37.
88. Person F, Meyer SC, Hopfer H, Menter T. Renal post-mortem findings in myeloproliferative and myelodysplastic/myeloproliferative neoplasms. *Virchows Arch.* 2021;479(5):1013-1020.
89. Vural F, Ozcan MA, Ozsan GH, et al. Gingival involvement in a patient with CD56+ chronic myelomonocytic leukemia. *Leuk Lymphoma.* 2004;45(2):415-418.
90. Faria C, Tzankov A. Progression in myeloid neoplasms: beyond the myeloblast. *Pathobiology.* 2024;91:55-75.
91. Pudasainee P, Pyakuryal B, Subedi Y, Upadhyay J, Adhikari S. Extramedullary manifestations of chronic myelomonocytic leukemia: do we treat like an acute myeloid leukemia? *Case Rep Hematol.* 2019;2019:8360454.
92. Onida F, Sbianchi G, Radujkovic A, et al. Prognostic value of a new clinically-based classification system in patients with CMML undergoing allogeneic HCT: a retrospective analysis of the EBMT-CMWP. *Bone Marrow Transplant.* 2022;57(6):896-902.
93. Tang G, Zhang L, Fu B, et al. Cytogenetic risk stratification of 417 patients with chronic myelomonocytic leukemia from a single institution. *Am J Hematol.* 2014;89(8):813-818.
94. Carr RM, Vorobyev D, Lasho T, et al. RAS mutations drive proliferative chronic myelomonocytic leukemia via a KMT2A-PLK1 axis. *Nat Commun.* 2021;12(1):2901.
95. Patnaik MM, Tefferi A. Cytogenetic and molecular abnormalities in chronic myelomonocytic leukemia. *Blood Cancer J.* 2016;6(2):e393.
96. Laborde RR, Patnaik MM, Lasho TL, et al. SETBP1 mutations in 415 patients with primary myelofibrosis or chronic myelomonocytic leukemia: independent prognostic impact in CMML. *Leukemia.* 2013;27(10):2100-2102.
97. Coltro G, Mangaonkar AA, Lasho TL, et al. Clinical, molecular, and prognostic correlates of number, type, and functional localization of TET2 mutations in chronic myelomonocytic leukemia (CMML)-a study of 1084 patients. *Leukemia.* 2020;34(5):1407-1421.
98. Duchmann M, Yalniz FF, Sanna A, et al. Prognostic role of gene mutations in chronic myelomonocytic leukemia patients treated with hypomethylating agents. *EBioMedicine.* 2018;31:174-181.
99. Nomdedeu M, Calvo X, Pereira A, et al. Prognostic impact of chromosomal translocations in myelodysplastic syndromes and chronic myelomonocytic leukemia patients. A study by the Spanish Group of Myelodysplastic Syndromes. *Genes Chromosomes Cancer.* 2016;55(4):322-327.
100. Such E, Cervera J, Costa D, et al. Cytogenetic risk stratification in chronic myelomonocytic leukemia. *Haematologica.* 2011;96(3):375-383.
101. Woo J, Choi DR, Storer BE, et al. Impact of clinical, cytogenetic, and molecular profiles on long-term survival after transplantation in patients with chronic myelomonocytic leukemia. *Haematologica.* 2020;105(3):652-660.
102. Ball M, List AF, Padron E. When clinical heterogeneity exceeds genetic heterogeneity: thinking outside the genomic box in chronic myelomonocytic leukemia. *Blood.* 2016;128(20):2381-2387.
103. Itonaga H, Aoki K, Aoki J, et al. Prognostic impact of donor source on allogeneic hematopoietic stem cell transplantation outcomes in adults with chronic myelomonocytic leukemia: a nationwide retrospective analysis in Japan. *Biol Blood Marrow Transplant.* 2018;24(4):840-848.
104. Daver N, Strati P, Jabbour E, et al. FLT3 mutations in myelodysplastic syndrome and chronic myelomonocytic leukemia. *Am J Hematol.* 2013;88(1):56-59.
105. Gurney M, Mangaonkar AA, Lasho T, et al. Somatic TP53 single nucleotide variants, indels and copy number alterations in chronic myelomonocytic leukemia (CMML). *Leukemia.* 2023;37(8):1753-1756.
106. Zhang T, Auer P, Dong J, et al. Whole-genome sequencing identifies novel predictors for hematopoietic cell transplant outcomes for patients with myelodysplastic syndrome: a CIBMTR study. *J Hematol Oncol.* 2023;16(1):37.
107. Hunter AM, Komrokji RS, Yun S, et al. Baseline and serial molecular profiling predicts outcomes with hypomethylating agents in myelodysplastic syndromes. *Blood Adv.* 2021;5(4):1017-1028.
108. Bewersdorf JP, Zeidan AM. Hyperleukocytosis and leukostasis in acute myeloid leukemia: can a better understanding of the underlying molecular pathophysiology lead to novel treatments? *Cells.* 2020;9(10):2310.
109. Shallis RM, Stahl M, Bewersdorf JP, Hendrickson JE, Zeidan AM. Leukocytapheresis for patients with acute myeloid leukemia presenting with hyperleukocytosis and leukostasis: a contemporary appraisal of outcomes and benefits. *Expert Rev Hematol.* 2020;13(5):489-499.
110. Oberoi S, Lehrnbecher T, Phillips B, et al. Leukapheresis and low-dose chemotherapy do not reduce early mortality in acute myeloid leukemia hyperleukocytosis: a systematic review and meta-analysis. *Leuk Res.* 2014;38(4):460-468.
111. Tallman MS, Wang ES, Altman JK, et al. Acute myeloid leukemia, version 3.2019, NCCN Clinical Practice Guidelines in oncology. *J Natl Compr Canc Netw.* 2019;17(6):721-749.
112. Dohner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an

- international expert panel on behalf of the ELN. *Blood*. 2022;140(12):1345-1377.
113. Oran B, Kongtim P, Popat U, et al. Cytogenetics, donor type, and use of hypomethylating agents in myelodysplastic syndrome with allogeneic stem cell transplantation. *Biol Blood Marrow Transplant*. 2014;20(10):1618-1625.
  114. Cremers EM, van Biezen A, de Wreede LC, et al. Prognostic pre-transplant factors in myelodysplastic syndromes primarily treated by high dose allogeneic hematopoietic stem cell transplantation: a retrospective study of the MDS subcommittee of the CMWP of the EBMT. *Ann Hematol*. 2016;95(12):1971-1978.
  115. Penack O, Peczynski C, van der Werf S, et al. Association of serum ferritin levels before start of conditioning with mortality after alloSCT - a prospective, non-interventional study of the EBMT Transplant Complications Working Party. *Front Immunol*. 2020;11:586.
  116. Cremers EMP, de Witte T, de Wreede L, et al. A prospective non-interventional study on the impact of transfusion burden and related iron toxicity on outcome in myelodysplastic syndromes undergoing allogeneic hematopoietic cell transplantation. *Leuk Lymphoma*. 2019;60(10):2404-2414.
  117. Alessandrino EP, Della Porta MG, Bacigalupo A, et al. Prognostic impact of pre-transplantation transfusion history and secondary iron overload in patients with myelodysplastic syndrome undergoing allogeneic stem cell transplantation: a GITMO study. *Haematologica*. 2010;95(3):476-484.
  118. Kim YR, Kim JS, Cheong JW, Song JW, Min YH. Transfusion-associated iron overload as an adverse risk factor for transplantation outcome in patients undergoing reduced-intensity stem cell transplantation for myeloid malignancies. *Acta Haematol*. 2008;120(3):182-189.
  119. Lim ZY, Fiaccadori V, Gandhi S, et al. Impact of pre-transplant serum ferritin on outcomes of patients with myelodysplastic syndromes or secondary acute myeloid leukaemia receiving reduced intensity conditioning allogeneic haematopoietic stem cell transplantation. *Leuk Res*. 2010;34(6):723-727.
  120. Armand P, Kim HT, Cutler CS, et al. Prognostic impact of elevated pretransplantation serum ferritin in patients undergoing myeloablative stem cell transplantation. *Blood*. 2007;109(10):4586-4588.
  121. Pullarkat V, Blanchard S, Tegtmeyer B, et al. Iron overload adversely affects outcome of allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant*. 2008;42(12):799-805.
  122. Platzbecker U, Bornhauser M, Germing U, et al. Red blood cell transfusion dependence and outcome after allogeneic peripheral blood stem cell transplantation in patients with de novo myelodysplastic syndrome (MDS). *Biol Blood Marrow Transplant*. 2008;14(11):1217-1225.
  123. Isidori A, Loscocco F, Visani G, et al. Iron toxicity and chelation therapy in hematopoietic stem cell transplant. *Transplant Cell Ther*. 2021;27(5):371-379.
  124. Wang C, Zhao M, Nie Y, et al. Impact of iron overload on poor graft function after allo-HSCT in a patient with transfusion-dependent low-risk MDS: a case report and literature review. *Medicine (Baltimore)*. 2022;101(51):e32012.
  125. Wermke M, Eckoldt J, Gotze KS, et al. Enhanced labile plasma iron and outcome in acute myeloid leukaemia and myelodysplastic syndrome after allogeneic haematopoietic cell transplantation (ALLIVE): a prospective, multicentre, observational trial. *Lancet Haematol*. 2018;5(5):e201-e210.
  126. Schneeweiss-Gleixner M, Greiner G, Herndlhofer S, et al. Impact of HFE gene variants on iron overload, overall survival and leukemia-free survival in myelodysplastic syndromes. *Am J Cancer Res*. 2021;11(3):955-967.
  127. Cho BS, Jeon YW, Hahn AR, et al. Improved survival outcomes and restoration of graft-vs-leukemia effect by deferasirox after allogeneic stem cell transplantation in acute myeloid leukemia. *Cancer Med*. 2019;8(2):501-514.
  128. Shapira S, Raanani P, Samara A, et al. Deferasirox selectively induces cell death in the clinically relevant population of leukemic CD34(+)CD38(-) cells through iron chelation, induction of ROS, and inhibition of HIF1alpha expression. *Exp Hematol*. 2019;70:55-69.e4.
  129. Michallet M, Sobh M, Labussiere H, et al. Potential anti-leukemic activity of iron chelation after allogeneic hematopoietic stem cell transplantation in patients with acute myeloid leukemia. *Leuk Lymphoma*. 2017;58(1):237-240.
  130. Sivgin S, Baldane S, Akyol G, et al. The oral iron chelator deferasirox might improve survival in allogeneic hematopoietic cell transplant (alloHSCT) recipients with transfusional iron overload. *Transfus Apher Sci*. 2013;49(2):295-301.
  131. Armand P, Sainvil MM, Kim HT, et al. Pre-transplantation iron chelation in patients with MDS or acute leukemia and iron overload undergoing myeloablative allo-SCT. *Bone Marrow Transplant*. 2013;48(1):146-147.
  132. Vallejo C, Battle M, Vazquez L, et al. Phase IV open-label study of the efficacy and safety of deferasirox after allogeneic stem cell transplantation. *Haematologica*. 2014;99(10):1632-1637.
  133. Jain T, Tsai HL, Elmariah H, et al. Haploidentical donor hematopoietic cell transplantation for myelodysplastic/myeloproliferative overlap neoplasms: results from a North American collaboration. *Haematologica*. 2023;108(12):3321-3332.
  134. Kroger N, Holler E, Kobbe G, et al. Allogeneic stem cell transplantation after reduced-intensity conditioning in patients with myelofibrosis: a prospective, multicenter study of the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Blood*. 2009;114(26):5264-5270.
  135. Robin M, Tabrizi R, Mohty M, et al. Allogeneic haematopoietic stem cell transplantation for myelofibrosis: a report of the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire (SFGM-TC). *Br J Haematol*. 2011;152(3):331-339.
  136. Akpek G, Pasquini MC, Logan B, et al. Effects of spleen status on early outcomes after hematopoietic cell transplantation. *Bone Marrow Transplant*. 2013;48(6):825-831.
  137. Ciurea SO, Sadegi B, Wilbur A, et al. Effects of extensive splenomegaly in patients with myelofibrosis undergoing a reduced intensity allogeneic stem cell transplantation. *Br J Haematol*. 2008;141(1):80-83.
  138. Pophali P, Horna P, Lasho TL, et al. Splenectomy in patients with chronic myelomonocytic leukemia: indications, histopathological findings and clinical outcomes in a single institutional series of thirty-nine patients. *Am J Hematol*. 2018;93(11):1347-1357.
  139. Ito T, Akagi K, Kondo T, Kawabata H, Ichinohe T, Takaori-Kondo A. Splenic irradiation as a component of a reduced-intensity conditioning regimen for hematopoietic stem cell transplantation in myelofibrosis with massive splenomegaly. *Tohoku J Exp Med*. 2012;228(4):295-299.
  140. Kekre N, Ho VT. Allogeneic hematopoietic stem cell transplantation for myelofibrosis and chronic myelomonocytic leukemia. *Am J Hematol*. 2016;91(1):123-130.
  141. Geissler K, Jager E, Barna A, et al. In vitro and in vivo effects of JAK2 inhibition in chronic myelomonocytic leukemia. *Eur J Haematol*. 2016;97(6):562-567.
  142. Francke S, Mies A, Meggendorfer M, et al. Disease-modifying activity of ruxolitinib in a patient with JAK2-negative CMML-2. *Leuk Lymphoma*. 2017;58(5):1271-1272.
  143. Hunter AM, Newman H, Dezern AE, et al. Integrated human and murine clinical study establishes clinical efficacy of ruxolitinib in chronic myelomonocytic leukemia. *Clin Cancer Res*. 2021;27(22):6095-6105.
  144. Shastri A, Adrianzen-Herrera DA. Ruxolitinib in CMML: a case study of innovative trial design in a rare cancer. *Clin Cancer Res*. 2021;27(22):6069-6071.
  145. Assi R, Kantarjian HM, Garcia-Manero G, et al. A phase II trial of ruxolitinib in combination with azacitidine in myelodysplastic syndrome/myeloproliferative neoplasms. *Am J Hematol*. 2018;93(2):277-285.
  146. Padron E, Dezern A, Andrade-Campos M, et al. A multi-institution phase I trial of

- ruxolitinib in patients with chronic myelomonocytic leukemia (CMML). *Clin Cancer Res.* 2016;22(15):3746-3754.
147. 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(1):30-38.
  148. Alzahrani M, Power M, Abou Mourad Y, et al. Improving revised International Prognostic Scoring System pre-allogeneic stem cell transplantation does not translate into better post-transplantation outcomes for patients with myelodysplastic syndromes: a single-center experience. *Biol Blood Marrow Transplant.* 2018;24(6):1209-1215.
  149. Robin M, Porcher R, Ades L, et al. HLA-matched allogeneic stem cell transplantation improves outcome of higher risk myelodysplastic syndrome A prospective study on behalf of SFGM-TC and GFM. *Leukemia.* 2015;29(7):1496-1501.
  150. Potter VT, Iacobelli S, van Biezen A, et al. Comparison of intensive chemotherapy and hypomethylating agents before allogeneic stem cell transplantation for advanced myelodysplastic syndromes: a study of the Myelodysplastic Syndrome Subcommittee of the Chronic Malignancies Working Party of the European Society for Blood and Marrow Transplant Research. *Biol Blood Marrow Transplant.* 2016;22(9):1615-1620.
  151. Robin M, Porcher R, Zinke-Cerwenka W, et al. Allogeneic haematopoietic stem cell transplant in patients with lower risk myelodysplastic syndrome: a retrospective analysis on behalf of the Chronic Malignancy Working Party of the EBMT. *Bone Marrow Transplant.* 2017;52(7):1081.
  152. Festuccia M, Deeg HJ, Gooley TA, et al. Minimal identifiable disease and the role of conditioning intensity in hematopoietic cell transplantation for myelodysplastic syndrome and acute myelogenous leukemia evolving from myelodysplastic syndrome. *Biol Blood Marrow Transplant.* 2016;22(7):1227-1233.
  153. Jain AG, Elmariah H. BMT for myelodysplastic syndrome: when and where and how. *Front Oncol.* 2021;11:771614.
  154. Castro-Malaspina H, Jabubowski AA, Papadopoulos EB, et al. Transplantation in remission improves the disease-free survival of patients with advanced myelodysplastic syndromes treated with myeloablative T cell-depleted stem cell transplants from HLA-identical siblings. *Biol Blood Marrow Transplant.* 2008;14(4):458-468.
  155. Kim Y, Kim IH, Kim HJ, et al. Multicenter study evaluating the impact of hypomethylating agents as bridging therapy to hematopoietic stem cell transplantation in myelodysplastic syndromes. *Int J Hematol.* 2014;99(5):635-643.
  156. Damaj G, Duhamel A, Robin M, et al. Impact of azacitidine before allogeneic stem-cell transplantation for myelodysplastic syndromes: a study by the Societe Francaise de Greffe de Moelle et de Therapie-Cellulaire and the Groupe-Francophone des Myelodysplasies. *J Clin Oncol.* 2012;30(36):4533-4540.
  157. Oshikawa G, Yoshioka K, Takahashi Y, et al. Impact of prior azacitidine on the outcome of allogeneic hematopoietic transplantation for myelodysplastic syndrome. *Pathol Oncol Res.* 2015;21(4):1037-1043.
  158. Brierley CK, Steensma DP. Allogeneic stem cell transplantation in myelodysplastic syndromes: does pretransplant clonal burden matter? *Curr Opin Hematol.* 2016;23(2):167-174.
  159. Schroeder T, Wegener N, Lauseker M, et al. Comparison between upfront transplantation and different pretransplant cytoreductive treatment approaches in patients with high-risk myelodysplastic syndrome and secondary acute myelogenous leukemia. *Biol Blood Marrow Transplant.* 2019;25(8):1550-1559.
  160. Rautenberg C, Germing U, Stepanow S, et al. Influence of somatic mutations and pretransplant strategies in patients allografted for myelodysplastic syndrome or secondary acute myeloid leukemia. *Am J Hematol.* 2021;96(1):E15-E17.
  161. Yoshizato T, Nannya Y, Atsuta Y, et al. Genetic abnormalities in myelodysplasia and secondary acute myeloid leukemia: impact on outcome of stem cell transplantation. *Blood.* 2017;129(17):2347-2358.
  162. Wang H, Wang Q, Qi J, et al. Appropriate pre-transplant strategy for patients with myelodysplastic syndromes receiving allogeneic haematopoietic stem cell transplantation after myeloablative conditioning. *Front Immunol.* 2023;14:1146619.
  163. Zheng H, Wang J, Zhou J, et al. Retrospective efficacy analysis of decitabine bridging allogeneic hematopoietic stem cell transplantation on the treatment of myelodysplastic syndrome [in Chinese]. *Zhonghua Xue Ye Xue Za Zhi.* 2015;36(2):121-124.
  164. Park S, Baek DW, Sohn SK, et al. Favorable outcomes with tumor burden reduction following administration of hypomethylating agents before allogeneic hematopoietic cell transplantation in patients with higher risk myelodysplastic syndrome. *Clin Lymphoma Myeloma Leuk.* 2019;19(7):e367-e373.
  165. Symeonidis A, van Biezen A, de Wreede L, 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):239-246.
  166. Wedge E, Sengeløv H, Hansen JW, et al. Improved outcomes after allogeneic hematopoietic stem cell transplantation with fludarabine/treosulfan for patients with myelodysplastic syndromes. *Biol Blood Marrow Transplant.* 2020;26(6):1091-1098.
  167. Sun YQ, Zhao C, Wang Y, et al. Haploidentical stem cell transplantation in patients with chronic myelomonocytic leukemia. *Sci China Life Sci.* 2020;63(8):1261-1264.
  168. Bewersdorf JP, Zeidan AM. Risk-adapted, individualized treatment strategies of myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML). *Cancers (Basel).* 2021;13(7):1610.
  169. Chan O, Renneville A, Padron E. Chronic myelomonocytic leukemia diagnosis and management. *Leukemia.* 2021;35(6):1552-1562.
  170. Sekeres MA, Othus M, List AF, et al. Randomized phase II study of azacitidine alone or in combination with lenalidomide or with vorinostat in higher-risk myelodysplastic syndromes and chronic myelomonocytic leukemia: North American Intergroup Study SWOG S1117. *J Clin Oncol.* 2017;35(24):2745-2753.
  171. Yang G, Wang X, Huang S, et al. Generalist in allogeneic hematopoietic stem cell transplantation for MDS or AML: epigenetic therapy. *Front Immunol.* 2022;13:1034438.
  172. Gerds AT, Gooley TA, Estey EH, Appelbaum FR, Deeg HJ, Scott BL. Pretransplantation therapy with azacitidine vs induction chemotherapy and posttransplantation outcome in patients with MDS. *Biol Blood Marrow Transplant.* 2012;18(8):1211-1218.
  173. Kako S, Kanda Y, Kato J, et al. The bridge treatment selected at the decision for transplantation did not affect the outcomes in patients with MDS. *Hematol Oncol.* 2017;35(3):341-349.
  174. Kongtim P, Popat U, Jimenez A, 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.
  175. Qin Y, Kuang P, Zeng Q, Wu Y, Liu T. Hypomethylating agents for patients with myelodysplastic syndromes prior to hematopoietic stem cell transplantation: a systematic review and meta-analysis. *Ann Hematol.* 2019;98(11):2523-2531.
  176. Field T, Perkins J, Huang Y, et al. 5-azacitidine for myelodysplasia before allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant.* 2010;45(2):255-260.
  177. Lubbert M, Bertz H, Ruter B, et al. Non-intensive treatment with low-dose 5-aza-2'-deoxycytidine (DAC) prior to allogeneic blood SCT of older MDS/AML patients. *Bone Marrow Transplant.* 2009;44(9):585-588.
  178. Modi D, Kim S, Singh V, et al. Pre-transplant hypomethylating agents do not influence

- post-transplant survival in myelodysplastic syndrome. *Leuk Lymphoma*. 2019;60(11):2762-2770.
179. Liu J, Cao YG, Zhang RL, et al. Effect and safety of 10-day decitabine-containing conditioning regimen for allogeneic hematopoietic stem cell transplantation in 31 patients with acute myeloid leukemia/myelodysplastic syndrome [in Chinese]. *Zhonghua Xue Ye Xue Za Zhi*. 2023;44(6):472-478.
  180. Cutler C. Timing of allogeneic stem cell transplantation for myelodysplastic syndromes and aplastic anemia. *Hematology Am Soc Hematol Educ Program*. 2014;2014(1):77-81.
  181. Symeonidis A, Chondropoulos S, Verigou E, Lazaris V, Kourakli A, Tsigiotis P. Allogeneic hematopoietic stem cell transplantation for mixed or overlap myelodysplastic/myeloproliferative disorders. *Front Oncol*. 2022;12:884723.
  182. Tremblay D, Rippel N, Feld J, El Jamal SM, Mascarenhas J. Contemporary risk stratification and treatment of chronic myelomonocytic leukemia. *Oncologist*. 2021;26(5):406-421.
  183. DeFilipp Z, Ciurea SO, Cutler C, et al. Hematopoietic cell transplantation in the management of myelodysplastic syndrome: an evidence-based review from the American Society for Transplantation and Cellular Therapy Committee on Practice Guidelines. *Transplant Cell Ther*. 2023;29(2):71-81.
  184. Patnaik MM, Tefferi A. Chronic myelomonocytic leukemia: 2022 update on diagnosis, risk stratification, and management. *Am J Hematol*. 2022;97(3):352-372.
  185. Leisch M, Weiss L, Lindlbauer N, et al. Red blood cell alloimmunization in 184 patients with myeloid neoplasms treated with azacitidine - a retrospective single center experience. *Leuk Res*. 2017;59:12-19.
  186. Cortes JE, Lin TL, Asubonteng K, Faderl S, Lancet JE, Prebet T. Efficacy and safety of CPX-351 versus 7 + 3 chemotherapy by European LeukemiaNet 2017 risk subgroups in older adults with newly diagnosed, high-risk/secondary AML: post hoc analysis of a randomized, phase 3 trial. *J Hematol Oncol*. 2022;15(1):155.
  187. Peterlin P, Le Bris Y, Turlure P, et al. CPX-351 in higher risk myelodysplastic syndrome and chronic myelomonocytic leukaemia: a multicentre, single-arm, phase 2 study. *Lancet Haematol*. 2023;10(7):e521-e529.
  188. Montalban-Bravo G, Jabbour E, Borthakur G, et al. Phase 1/2 study of CPX-351 for patients with Int-2 or high risk International Prognostic Scoring System myelodysplastic syndromes and chronic myelomonocytic leukaemia after failure to hypomethylating agents. *Br J Haematol*. 2024;204(3):898-909.
  189. Montalban-Bravo G, Hammond D, DiNardo CD, et al. Activity of venetoclax-based therapy in chronic myelomonocytic leukemia. *Leukemia*. 2021;35(5):1494-1499.
  190. Ball S, Jain AG, Aguirre LE, et al. Hypomethylating agent and venetoclax in patients with chronic myelomonocytic leukemia: is the combination indeed better? *Am J Hematol*. 2022;97(5):E185-E188.
  191. Saliba AN, Litzow MR, Gangat N, et al. Outcomes of venetoclax-based therapy in chronic phase and blast transformed chronic myelomonocytic leukemia. *Am J Hematol*. 2021;96(11):E433-E436.
  192. Garcia-Horton A, Maze D, McNamara CJ, Sibai H, Gupta V, Murphy T. Azacitidine and venetoclax for the treatment of accelerated and blast phase myeloproliferative neoplasms and chronic myelomonocytic leukemia: a case series. *Leuk Lymphoma*. 2021;62(6):1525-1527.
  193. Li C, Deng C, Wu P, et al. Outcomes of intermediate or high-risk CMML patients treated with hypomethylating agents combined with venetoclax: a single center experience. *Clin Transl Sci*. 2024;17(1):e13711.
  194. Bazinet A, Darbaniyan F, Jabbour E, et al. Azacitidine plus venetoclax in patients with high-risk myelodysplastic syndromes or chronic myelomonocytic leukaemia: phase 1 results of a single-centre, dose-escalation, dose-expansion, phase 1-2 study. *Lancet Haematol*. 2022;9(10):e756-e765.
  195. Zeidan AM, Borate U, Pollyea DA, et al. A phase 1b study of venetoclax and azacitidine combination in patients with relapsed or refractory myelodysplastic syndromes. *Am J Hematol*. 2023;98(2):272-281.
  196. Bewersdorf JP, Derkach A, Gowda L, et al. Venetoclax-based combinations in AML and high-risk MDS prior to and following allogeneic hematopoietic cell transplant. *Leuk Lymphoma*. 2021;62(14):3394-3401.
  197. Bang SY, Park S, Kwag D, et al. A successful bridge therapy combining hypomethylating agents with venetoclax for adult patients with newly diagnosed or relapsed/refractory acute myeloid leukemia. *Cancers (Basel)*. 2023;15(6):1666.
  198. Pleyer L, Sekeres MA. An early glimpse at azacitidine plus venetoclax for myelodysplastic syndromes. *Lancet Haematol*. 2022;9(10):e714-e716.
  199. Tremblay D, Csizmar CM, DiNardo CD, et al. Venetoclax (VEN) improves response rates but not survival in patients with chronic myelomonocytic leukemia (CMML) treated with hypomethylating agents (HMA): a multicenter, propensity score analysis [abstract]. *Blood*. 2023;142(suppl 1):321.
  200. Festuccia M, Baker K, Gooley TA, Sandmaier BM, Deeg HJ, Scott BL. Hematopoietic cell transplantation in myelodysplastic syndromes after treatment with hypomethylating agents. *Biol Blood Marrow Transplant*. 2017;23(9):1509-1514.
  201. Pleyer L, Germing U, Sperr WR, et al. Azacitidine in CMML: matched-pair analyses of daily-life patients reveal modest effects on clinical course and survival. *Leuk Res*. 2014;38(4):475-483.
  202. Pleyer L, Heibl S, Tinchon C, et al. Health-related quality of life as assessed by the EQ-5D-5L predicts outcomes of patients treated with azacitidine-a prospective cohort study by the AGMT. *Cancers (Basel)*. 2023;15(5):1388.
  203. Pleyer L, Burgstaller S, Girschikofsky M, et al. Azacitidine in 302 patients with WHO-defined acute myeloid leukemia: results from the Austrian Azacitidine Registry of the AGMT-Study Group. *Ann Hematol*. 2014;93(11):1825-1838.
  204. Prebet T, Gore SD, Esterni B, et al. Outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure. *J Clin Oncol*. 2011;29(24):3322-3327.
  205. Jabbour E, Garcia-Manero G, Batty N, et al. Outcome of patients with myelodysplastic syndrome after failure of decitabine therapy. *Cancer*. 2010;116(16):3830-3834.
  206. Welch JS, Petti AA, Miller CA, et al. TP53 and decitabine in acute myeloid leukemia and myelodysplastic syndromes. *N Engl J Med*. 2016;375(21):2023-2036.
  207. Gagelmann N, Eikema DJ, Stelljes M, et al. Optimized EBMT transplant-specific risk score in myelodysplastic syndromes after allogeneic stem-cell transplantation. *Haematologica*. 2019;104(5):929-936.
  208. Guru Murthy GS, Kim S, Hu ZH, et al. Relapse and disease-free survival in patients with myelodysplastic syndrome undergoing allogeneic hematopoietic cell transplantation using older matched sibling donors vs younger matched unrelated donors. *JAMA Oncol*. 2022;8(3):404-411.
  209. Worel N, Buser A, Greinix HT, et al. Suitability criteria for adult related donors: a consensus statement from the worldwide network for Blood and Marrow Transplantation Standing Committee on Donor Issues. *Biol Blood Marrow Transplant*. 2015;21(12):2052-2060.
  210. Gagelmann N, Bacigalupo A, Rambaldi A, et al. Haploidentical stem cell transplantation with posttransplant cyclophosphamide therapy vs other donor transplantations in adults with hematologic cancers: a systematic review and meta-analysis. *JAMA Oncol*. 2019;5(12):1739-1748.
  211. Pereira MP, Remberger M, Chen C, et al. Choosing between older matched sibling donor and younger matched unrelated donor in allogeneic hematopoietic cell transplantation: comparison of clinical outcomes in acute myeloid leukemia and myelodysplastic syndrome. *Transplant Cell Ther*. 2023;29(11):697.e1-697.e10.
  212. Gagelmann N, Kroger N. Dose intensity for conditioning in allogeneic hematopoietic cell transplantation: can we recommend

"when and for whom" in 2021?

*Haematologica*. 2021;106(7):1794-1804.

213. Kurosawa S, Shimomura Y, Itonaga H, et al. Myeloablative versus reduced-intensity conditioning with fludarabine/busulfan for myelodysplastic syndrome: a propensity score-matched analysis. *Transplant Cell Ther*. 2022;28(6):323.e1-323.e9.
214. Kroger N, Iacobelli S, Franke GN, et al. Dose-reduced versus standard conditioning followed by allogeneic stem-cell transplantation for patients with myelodysplastic syndrome: a prospective randomized phase III study of the EBMT (RICMAC Trial). *J Clin Oncol*. 2017;35(19):2157-2164.
215. Scott B, Deeg HJ, Storer B, et al. Targeted busulfan and cyclophosphamide as compared to busulfan and TBI as preparative regimens for transplantation in patients with advanced MDS or transformation to AML. *Leuk Lymphoma*. 2004;45(12):2409-2417.
216. Kroger N, Wolschke C, Gagelmann N. How I treat transplant-eligible patients with myelofibrosis. *Blood*. 2023;142(20):1683-1696.
217. Radujkovic A, Hegenbart U, Muller-Tidow C, Herfarth K, Dreger P, Luft T. High leukemia-free survival after TBI-based conditioning and mycophenolate mofetil-containing immunosuppression in patients allografted for chronic myelomonocytic leukemia: a single-center experience. *Ann Hematol*. 2020;99(4):855-866.
218. Beelen DW, Trensche R, Stelljes M, et al. Treosulfan or busulfan plus fludarabine as conditioning treatment before allogeneic haemopoietic stem cell transplantation for older patients with acute myeloid leukaemia or myelodysplastic syndrome (MC-FludT.14/L): a randomised, non-inferiority, phase 3 trial. *Lancet Haematol*. 2020;7(1):e28-e39.

© 2024 American Society of Hematology. Published by Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.