



American Society of Hematology
 2021 L Street NW, Suite 900,
 Washington, DC 20036
 Phone: 202-776-0544 | Fax 202-776-0545
 editorial@hematology.org

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

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Francesco Onida (Hematology and BMT Unit, ASST Fatebenefratelli-Sacco, Dept. of Oncology and Hemato-Oncology, University of Milan, Italy, Italy) Nico Gagelmann (University Medical Center Hamburg-Eppendorf, Germany) Yves Chalandon (University Hospital of Geneva, Switzerland) Guido Kobbe (Heinrich Heine University, Medical Faculty, Germany) Marie Robin (Hopital Saint Louis, France) Argiris Symeonidis (Olympion General Hospital & Rehabilitation Center, Department of Hematology, Greece) Theo de Witte (Radboud University Medical Centre, Netherlands) Raphaël Itzykson (Hopital Saint-Louis, France) Madlen Jentzsch (University of Leipzig, Germany) Uwe Platzbecker (University Hospital Leipzig, Department of Hematology and Cell Therapy, Germany) Valeria Santini (MDS Unit, Hematology, AOU Careggi-University of Florence, Italy) Guillermo Sanz (Hospital Universitario y Politécnico La Fe, Valencia, Spain, Health Research Institute La Fe, Valencia, Spain, and CIBERONC, Instituto de Salud Carlos III, Madrid, Spain, Spain) Christoph Scheid (University of Cologne, Germany) Eric Solary (INSERM U1287, France) Peter Valent (Medical University of Vienna, Austria) Raffaella Greco (EBMT Practice Harmonization and Guidelines Committee., Spain) Isabel Sánchez-Ortega (EBMT, Executive Office, Spain) Ibrahim Yakoub-Agha (EBMT Practice Harmonization and Guidelines Committee., Spain) Lisa Pleyer (Salzburg Cancer Research Institute (SCRI) Center for Clinical Cancer and Immunology Trials (CCIT), Salzburg, Austria and Cancer Cluster Salzburg (CCS), Austrian Group of Medical Tumor Therapy (AGMT) Study Group, Vienna, Austria, Austria)

Abstract:

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 as 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 since prospective randomized studies are lacking and retrospective data in the literature is 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 six years ago. Since then, new, CMML-specific data have been published. The European Society for Blood and Marrow Transplantation (EBMT) Practice Harmonization and Guidelines 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, pre-transplant strategies, allo-HCT modality, as well as post-transplant management for patients with CMML were outlined.

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1 Management of adult patients with CMML undergoing allo-HCT: 2 recommendations from the EBMT PH&G Committee

3
4 Francesco Onida^{1,2}, Nico Gagelmann³, Yves Chalandon⁴, Guido Kobbe⁵, Marie Robin⁶, Argiris Symeonidis⁷,
5 Theo de Witte⁸, Raphael Itzykson⁹⁻¹⁰, Madlen Jentzsch¹¹, Uwe Platzbecker¹¹, Valeria Santini¹², Guillermo
6 Sanz^{13,14}, Christof Scheid¹⁵, Eric Solary¹⁶, Peter Valent^{17,18}, Raffaella Greco^{2,19}, Isabel Sanchez-Ortega², Ibrahim
7 Yakoub-Agha^{2,20}, Lisa Pleyer²¹⁻²³

8
9 ¹ Hematology and BMT Unit, ASST Fatebenefratelli-Sacco, Dept. of Oncology and Hemato-Oncology, University of Milan, Italy.

10 ² EBMT Practice Harmonization and Guidelines Committee.

11 ³ University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

12 ⁴ Division of Hematology, University Hospital of Geneva (HUG) and faculty of Medicine, University of Geneva, Geneva, Switzerland.

13 ⁵ Department of Hematology, Oncology and Clinical Immunology, University Hospital Düsseldorf, Heinrich Heine University, Medical
14 Faculty, Düsseldorf, Germany

15 ⁶ Service d'hématologie greffe, Hôpital Saint-Louis, APHP, Université de Paris Cité, France.

16 ⁷ Olympion General Hospital & Rehabilitation Center, Department of Hematology, Patras, Greece.

17 ⁸ Department of Tumor Immunology, Radboud Institute of Molecular Life Sciences, Radboud University Medical Center, Nijmegen,
18 Netherlands.

19 ⁹ Université Paris Cité, Génomes, biologie cellulaire et thérapeutique U944, INSERM, CNRS, F-75010 Paris, France.

20 ¹⁰ Département Hématologie et Immunologie, Hôpital Saint-Louis, Assistance Publique-Hôpitaux de Paris, F-75010 Paris, France.

21 ¹¹ Medical Clinic and Policlinic 1, Hematology and Cellular Therapy, University Hospital Leipzig, Leipzig, Germany.

22 ¹² MDS Unit, Hematology, DMSC, AOUC, University of Florence, Italy.

23 ¹³ University and Polytechnic Hospital La Fe and Health Research Institute La Fe, Valencia, Spain.

24 ¹⁴ CIBERONC, Instituto de Salud Carlos III, Madrid, Spain

25 ¹⁵ Department of Internal Medicine I, University Hospital Cologne, Cologne, Germany.

26 ¹⁶ INSERM UMR1287 and department of hematology, Gustave Roussy Cancer Center, Villejuif, France, and Université Paris Saclay,
27 Faculty of Medicine, Le Kremlin-Bicetre, France.

28 ¹⁷ Department of Internal Medicine I, Division of Hematology and Hemostaseology, Medical University of Vienna, Austria.

29 ¹⁸ Ludwig Boltzmann Institute for Hematology and Oncology, Medical University of Vienna, Austria

30 ¹⁹ Unit of Hematology and Bone Marrow Transplantation, IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy.

31 ²⁰ CHU de Lille, Univ Lille, INSERM U1286, Infinite, 59000, Lille, France.

32 ²¹ Austrian Group of Medical Tumor Therapy (AGMT) Study Group, Vienna, Austria.

33 ²² Salzburg Cancer Research Institute (SCRI) Center for Clinical Cancer and Immunology Trials (CCCIT), Salzburg, Austria and Cancer
34 Cluster Salzburg (CCS), Salzburg, Austria.

35 ²³ 3rd Medical Dept. with Hematology, Medical Oncology, Hemostaseology, Rheumatology and Infectiology, Oncologic Center, Paracelsus
36 Medical University, Salzburg, Austria.

37
38 **Corresponding Author:** Lisa Pleyer

39 Address: Müllnerhauptstraße 48, 5020 Salzburg, Austria

40 E-mail: dr.lisa.pleyer@gmail.com

41 Phone: +43 676 8997 58271

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51 **Abstract**

52 Chronic myelomonocytic leukemia (CMML) is a heterogeneous disease presenting with either
53 myeloproliferative or myelodysplastic features. Allogeneic hematopoietic cell transplantation (allo-HCT)
54 remains the only potentially curative option, but the inherent toxicity of this procedure makes the decision to
55 proceed to allo-HCT challenging, particularly as patients with CMML are mostly older and comorbid. Therefore,
56 the decision between a non-intensive treatment approach and allo-HCT represents a delicate balance, especially
57 since prospective randomized studies are lacking and retrospective data in the literature is conflicting.
58 International consensus on the selection of patients and the ideal timing of allo-HCT specifically in CMML
59 could not be reached in international recommendations published six years ago. Since then, new, CMML-
60 specific data have been published. The European Society for Blood and Marrow Transplantation (EBMT)
61 Practice Harmonization and Guidelines Committee assembled a panel of experts in the field to provide the first
62 best practice recommendations on the role of allo-HCT specifically in CMML. Recommendations were based on
63 the results of an international survey, a comprehensive review of the literature, and expert opinions on the
64 subject, after structured discussion and circulation of recommendations. Algorithms for patient selection, timing
65 of allo-HCT during the course of the disease, pre-transplant strategies, allo-HCT modality, as well as post-
66 transplant management for patients with CMML were outlined. Keynote message is, that once a patient has been
67 identified as a transplant candidate, upfront transplantation without prior disease-modifying treatment is
68 preferred to maximize chances of reaching allo-HCT whenever possible, irrespective of bone marrow blast
69 counts. In cases of aggressive disease or clinical symptoms necessitating imminent actions, bridging therapy
70 with cytoreduction may be considered, as long as this does not reduce chances of receiving, and/or postpone,
71 curative treatment and should ideally be investigated in future studies.

72

73 Introduction - Current state of the art

74 Chronic myelomonocytic leukemia (CMML) is a hybrid or mixed myelodysplastic/myeloproliferative neoplasm
75 characterized by a large heterogeneity of clinical features with high variability of life expectation. Median age at
76 diagnosis ranges from 70-75 years. Median survival in the largest reported series is in the 2 to 3 years range,¹ but
77 is less than 2 years in high-risk patients according to various models of prognostication specifically developed
78 for the disease.^{2, 3} To date allogeneic hemopoietic cell transplantation (allo-HCT) remains the only potentially
79 curative treatment strategy for eligible patients.⁴ Overall survival for patients with CMML ranges from 30-40%
80 at five years post-allo-HCT, owing to cumulative incidences of relapse of 30-50% and non-relapse mortality
81 rates of 20-40%.⁵⁻¹² In the context of allo-HCT the absence of prospective data drags behind many uncertainties
82 not only regarding patient selection, but also possible pre-transplant treatment strategies, the timing of allo-HCT
83 and the optimal overall transplant policy including donor selection, the choice and intensity of conditioning,
84 graft-versus-host-disease (GvHD) prophylaxis, stem cell source and patient management in the post-transplant
85 setting.

86 Given the above, the newly established EBMT Practice and Harmonization & Guidelines (PH&G)
87 Committee included the best practice recommendation on the management of adult patients with CMML
88 undergoing allo-HCT among the projects to be finalized during the second Annual Workshop, planned in Lille
89 (France) on September 25th-26th, 2023. The methodology used is described in supplements., p1.

90

91 Workshop Recommendations

92 1. Patient selection for allo-HCT

93 Before going into further details as to which classification system, which prognostic scoring system, which other
94 disease-related and patient-related factors define the indication(s) for, -and the most appropriate timing of-, allo-
95 HCT it is critical that patients are at all assessed for their eligibility for allo-HCT. Up to 21% of patients with
96 myelodysplastic neoplasms (MDS) or acute myeloid leukemia (AML) in a large registry-based study were not
97 receiving assessment or consideration for allo-HCT,⁶ indicating the need for heightening non-transplant
98 specialists' awareness in this regard. In addition, there is also a significant proportion (up to one third) of patients
99 failing to reach allo-HCT after the decision to transplant has been made,⁷⁻¹³ indicating the need for better patient
100 selection strategies, more efficacious pre-transplant treatment modalities, faster procedure to transplant, and/or
101 increasing the rates of up-front transplantations. Careful, holistic risk assessment and patient selection is

102 essential to recognize patient eligibility for allo-HCT on the one hand, and to maximize patient benefit while
103 minimizing treatment-related morbidity and mortality on the other.

104

105 1.1. Classification to CMML

106 The recently published International Consensus Classification (ICC)¹⁴ and the 2022 World Health Organisation
107 (WHO)¹⁵ Classification have made mostly similar adaptations in CMML (i.e. elimination of CMML-0, lowering
108 of the monocyte threshold to ≥ 0.5 G/L, reiteration of the myelodysplastic-and myeloproliferative subtype
109 distinction), while retaining the same blast count thresholds, and can thus both be recommended. Neither
110 classification has as yet defined CMML subtypes based on mutational signatures.

111 However, the threshold of blasts required for the definition of AML was lowered or eliminated when
112 certain mutations are present. AML defined by mutations includes AML with mutated *NPM1* (WHO-2022 (no
113 blast count threshold required)¹⁵ and AML with mutated bZIP *CEBPA* (ICC-2022 ($\geq 10\%$ blasts required)).¹⁴ As
114 such, patients with CMML harboring these mutations should be considered and treated as AML.

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

118

119 1.2. Patient-related factors

120 Prospective data have confirmed survival benefits for higher-risk MDS patients aged 60-70, or ≥ 65 ^{12, 16} years
121 undergoing allo-HCT. Thus, although age alone should not preclude patients from being considered as transplant
122 eligible,¹⁷ it must nevertheless be considered. Other patient-related factors that need to be considered for
123 identifying patients eligible for allo-HCT include: Performance status (PS) assessment by the Eastern
124 Cooperative Oncology Group (ECOG-PS) or Karnofsky PS scale, Hematopoietic Cell Transplantation-specific
125 Comorbidity Index (HCT-CI),^{18, 19} frailty assessment,²⁰ comprehensive geriatric assessments,^{21, 22} and/or
126 combinations thereof.²³⁻²⁵

127

128 1.3. Recommendations

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

- 132 • Age ≤ 70 (in select cases ≤ 75) years
- 133 • ECOG-PS < 2 or Karnofsky index $\geq 70\%$
- 134 • HCT-CI < 3
- 135 • Lack of any comorbidity that the transplant specialist judges to be incompatible with intensive
- 136 chemotherapy, e.g. as suggested by Ferrara et al.²⁶

137

138 2. Timing of allo-HCT

139 Once the decision to proceed to allo-HCT has been made, timing is a crucial consideration, since delaying
140 transplant may result in disease progression and/or acquisition of additional comorbidities, and/or toxicities (if
141 the patient receives pre-transplant treatment) that may preclude transplant. To date, no randomized clinical trial
142 has addressed this important question in CMML. Expert panels could not reach a solid consensus regarding the
143 indication for pre-transplant treatment in patients candidate for allo-HCT for CMML so far,²⁷ and 2018 European
144 Hematology Association (EHA)/European LeukemiaNet (ELN) recommendations²⁸ were largely extrapolated
145 from data obtained in patients with MDS.²⁸⁻³²

146

147 2.1.1. Risk-stratification to identify transplant candidates

148 Risk stratification dictates the management of patients with CMML. Allo-HCT is the only treatment that can
149 offer cure in this disease. Identifying those patients that will have the most benefit and the least harm from allo-
150 HCT is thus critical. A myriad of scoring systems used in CMML have evolved from MDS-based models
151 (International Prognostic Scoring System (IPSS),³³ revised IPSS (IPSS-R),³⁴) to CMML-specific scores
152 predicting outcomes (Düsseldorf score,³⁵ MD-Anderson Prognostic Score (MDAPS),³⁶ modified Bournemouth
153 score,³⁷ CMML-specific Prognostic Scoring System (CPSS),³⁸ Mayo model³⁹) or estimating time to first
154 treatment,⁴⁰ most of which have been found to be valid and with comparable performance.^{1, 2, 41-44} Updated
155 versions of some of these scores have been published incorporating molecular data: IPSS molecular (IPSS-M),⁴⁵
156 Groupe Francophone des Myelodysplasies (GFM) score (*ASXLI*),⁴⁶ Mayo Molecular Model (*ASXLI*),⁴⁷ CPSS
157 molecular (CPSS-Mol; *ASXLI*, *RUNXI*, *NRAS*, *SETBP1*).⁴⁸ ELN and EHA 2018 guidelines recommend five of
158 these scores (MDAPS, CPSS in case of unavailability of molecular data; GFM, Mayo Molecular, CPSS-Mol
159 when molecular data are available).²⁸ It needs to be born in mind, that above mentioned prognostic scores were
160 mostly devised in either untreated historic patient cohorts, and/or were not assessed for their predictive capacity
161 on specific treatment outcomes in general, and on allo-HCT outcomes in particular.

162 Risk stratification has been used to identify at which time-point during the course of the disease a
163 patient should be transplanted. Of note, almost all data published to date used older scoring systems (IPSS, IPSS-
164 R or CPSS) that did not incorporate molecular data in attempts to identify the sweet spot at which an allo-HCT
165 bears the most benefit for, -while doing the least potential harm to-, the patient. It remains unclear whether these
166 data can be transferred to newer molecular scores (IPSS-M and CPSS-Mol) in patients with CMML, but the
167 IPSS-M has recently been shown to correlate with allo-HCT outcomes in MDS.⁴⁹⁻⁵² These retrospective analyses
168 indicated that allo-HCT improves outcomes for the (very) high IPSS-M risk groups. Very recently the 1102
169 Study of the Blood and Marrow Transplant Clinical Trials Network was re-analysed after inclusion of molecular
170 data enabling re-stratification of patients according to IPSS-M.⁴⁵ This trial identified MDS patients with IPSS-M
171 high-risk to be ideal candidates for early transplantation.⁴⁵ In the largest cohorts of transplanted CMML patients
172 with molecular data available (n=313⁵³ and n=240⁵⁴), the CPSS-Mol was shown to be significantly associated
173 with post-allogeneic disease free survival and/or overall survival.

174 While transplantation of early-stage lower-risk disease offers the lowest rate of non-relapse mortality, it
175 exposes patients who might have had a long period without disease progression to immediate morbidity and
176 mortality. Since life-expectancy of CMML patients with lower-risk disease is >5 years,⁴⁸ it is generally accepted,
177 that the risks of allo-HCT outweigh the potential benefits. Markov models applied to patients with MDS indicate
178 that allo-HCT should be delayed in patients with lower-risk MDS (according to IPSS, WPSS, or R-IPSS) until
179 disease progression to a higher risk category, while HCT should be immediately offered to patients with higher-
180 risk.²⁹⁻³² In corroboration thereof, retrospective studies exclusively analysing CMML patients have confirmed the
181 absence of significant survival benefit of allo-HCT for CMML patients with lower-risk disease as categorized by
182 the CPSS.^{4, 55} Although allo-HCT provides modest survival benefit as compared to all other treatment modalities
183 including intensive chemotherapy (IC) for patients after having transformed from CMML to AML,^{4, 56} most
184 evidence underscores the importance of early transplantation before transformation to AML.⁵⁷⁻⁵⁹ The latter
185 coincides with disease progression and an increased potential for the acquisition of contraindications for the
186 transplantation. It also needs to be kept in mind, that while high-risk features are indications for allo-HCT in
187 CMML, they also adversely impact allo-HCT outcomes.^{5, 55, 60-63}

188 This panel acknowledges the recent developments in, -and increasing importance of-, molecular data.
189 The CPSS-Mol (Table 1.A.) has been shown to outperform the CPSS in all patients with CMML for both
190 overall survival and cumulative incidence of AML evolution, respectively (Table 1.B.).⁴⁸ The panel
191 acknowledges, that specific data for the use of the CPSS-Mol in patient selection and timing decisions for allo-

192 HCT are lacking. However, very recently, data generated in 8326 MDS with Semi-Markov multistate decision
193 models were presented, showing clinical relevance and statistically significant superiority of using the IPSS-M
194 over the IPSS-R regarding the optimal timing of allo-HCT in the transplant decision making process.⁶⁴ Different
195 from other molecularly integrated CMML-specific prognostic models, only considering nonsense/frameshift
196 ASXL1 mutations as independent adverse factors,^{44, 45} the CPSS-Mol relies on a more comprehensive genetic
197 risk score. In light of these data, and after much internal discussion, the panel ultimately decided to recommend
198 the use of the CPSS-Mol, wherever possible, to stratify patients' risk and to identify the optimal timing of allo-
199 HCT in patients with CMML. Taking the possibility for post-transplant interventions into account, it may be
200 important to dissect those disease features that affect cumulative incidences or relapse from those that can
201 portend higher non-relapse mortality (see also chapter 2.2.2 "Risk-stratification to predict post-HCT
202 outcomes").

203

204 2.1.2. Risk-stratification to predict post-HCT outcomes

205 Although both CPSS risk stratifications,^{53, 61} have been significantly associated with post-transplant relapse
206 and/or overall survival, risk stratification by CPSS^{5, 55} or CPSS-Mol⁵ alone has limitations in predicting post-
207 transplant outcomes.⁵⁵ Dynamic use of prognostic scores (IPSS-R⁶⁵, CPSS or CPSS-Mol^{61, 62}) at the time of
208 transplant (rather than at initial diagnosis) may be more relevant for the prediction of allo-HCT outcome, but this
209 remains to be validated. Of note, aberrations of several genes (e.g. *TP53*), although infrequent in CMML, have
210 also been acknowledged as adverse molecular predictors of outcome, but are not captured by current molecularly
211 integrated prognostic models. These are discussed in section "2.2.2. Cytogenetics and gene mutations".

212 Once the decision to proceed to transplant has been made, it is necessary to differentiate the use of
213 prognostic scores for the identification of transplant eligibility on the one hand, and for the prediction of post-
214 transplant outcomes on the other hand. For the former, we propose the use of the CPSS-Mol as discussed above.
215 For the latter, transplantation-specific scores to predict transplant outcomes have been developed for CMML
216 patients,^{54, 66} or validated in CMML patients,⁶⁷ and outperform scores typically used in the non-transplant setting.
217 The CMML transplant score,⁵⁴ which incorporates both molecular (*ASXL1* and *NRAS* mutations) and clinical
218 information (bone marrow blasts and increasing comorbidity index), was prognostic in patients specifically
219 undergoing transplantation and may facilitate personalized counseling. In particular, the CMML specific
220 transplant score was designed and validated in a cohort of 240 CMML patients undergoing allo-HCT. Five risk
221 groups were identified with 5-year survival rates ranging from 81-19%, and non-relapse mortality rates ranging

222 from 5-51% for an increasing transplant score, respectively.⁵⁴ The score retained performance after validation,
223 and predictions were significant and superior to existing scores incorporating molecular data (including the
224 CPSS-Mol) designed in the non-transplant setting.⁵⁴ In addition, the endothelial activation and stress index
225 (EASIX) score might help to predict non-relapse mortality,⁶⁷ whereas a more recent score has been criticized
226 because of inclusion of GvHD as a risk factor without adjusting for inherent statistical bias.⁶⁶ The inclusion of
227 donor type and source as well as conditioning intensity might further refine transplant specific prognostic scores.

228

229 2.1.3. Recommendations

230 **Choice of transplant candidates and timing of allo-HCT:**

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

- 233 • **CPSS-Mol high-risk patients** have a median overall survival of 17-18 months and a cumulative incidence
234 of transformation to AML at 48 months of 48-52% (Table 1.B.).⁴⁸ The panel recommends that they **should**
235 **proceed to transplant as soon as possible (Figure 2)**, preferably without disease modifying treatment to
236 maximize chances of reaching allo-HCT. (For the discussion on how the recommendation for upfront
237 transplant was reached please see section 3 “Role of pre-transplant therapy”).
- 238 • **CPSS-Mol intermediate-2 risk patients** have a median overall survival of 30-37 months and a cumulative
239 incidence of transformation to AML at 48 months of 21-24% (Table 1.B.).⁴⁸ The panel recommends that
240 patients **with ≥ 1 additional risk factor should proceed to upfront transplant** preferably without disease
241 modifying treatment to maximize chances of reaching allo-HCT (**Figure 2**). Such risk factors include
242 extramedullary involvement, (hyper)leukocytosis, iron overload, splenomegaly, as well as adverse
243 cytogenetics and/or gene mutations. Further details on additional disease-related risk factors are discussed
244 in section 2.2 “Additional disease-related risk factors” and section 3 “Pre-transplant management of disease
245 symptoms”.
- 246 • **CPSS-Mol intermediate-2 risk patients without additional risk factors: a watch and wait strategy**
247 **with dynamic assessment** should be followed whenever possible. Non-transplant treatment strategies, if
248 deemed necessary, should be discussed with the transplant centre. **Dynamic re-assessment** every three
249 months, or sooner in case of suspected disease progression, should occur. In the presence of rapidly
250 increasing white blood cell count (WBC; increases of $>10.000/\mu\text{L}$ within ≤ 3 months) in the absence of
251 signs of active inflammation and or infection, rapidly increasing peripheral blood or bone marrow blasts,

252 and/or worsening of cytopenias, we recommend accurate serial re-staging of disease and/or response status,
 253 which not only includes bone marrow work-ups (including cytology, histology, flow cytometry,
 254 conventional cytogenetics, fluorescence in situ hybridization and next generation sequencing),⁶⁸ but also
 255 increasingly relies on analyses of the peripheral blood.^{69, 70} Re-classification and renewed calculation of
 256 CPSS-Mol risk should ensue (**Figure 2**).

257 • **CPSS-Mol low and intermediate-1 risk patients** have a median overall survival of 64-68 months and a
 258 cumulative incidence of transformation to AML at 48 months of 3-8% (Table 1.B).⁴⁸ The panel
 259 recommends that these patients **should be managed with non-transplant approaches**. Allo-HCT should
 260 be deferred until progression to higher-risk disease and/or the occurrence of ≥ 1 additional risk factor. To
 261 this end, dynamic re-assessment should be performed as stated above (**Figure 2**).

262 For transplant ineligible patients current guidelines²⁸ and more recent data^{13, 71} are applicable.

263 **Prediction of post-transplant outcomes:**

264 • Based on data discussed above, the panel recommends the use of the CMML transplant score⁵⁴ to predict
 265 post-transplant outcomes for patients that have been previously identified as transplant candidates with the
 266 CPSS-Mol.

268 2.2. Additional disease-related risk factors

269 As mentioned above, the presence or emergence of additional risk factors should result in upfront transplantation
 270 whenever possible in CPSS-Mol intermediate-2 risk patients, and should result in dynamic reassessment in
 271 CPSS-Mol intermediate-1 and low risk patients (**Figure 2** and section 2.1.3 “Choice of transplant candidates and
 272 timing of allo-HCT”).

274 2.2.1. Clinical symptoms

275 General symptoms (such as drenching night sweats, unintended weight loss, unexplained fever) are
 276 acknowledged signs of higher disease activity and potentially pending/imminent disease progression in many
 277 cancer types and may be early signs of transformation to AML. Bone marrow fibrosis adversely impacts survival
 278 and correlates with higher relapse rates and delayed engraftment in patients with MDS and CMML.⁷²⁻⁷⁹
 279 Extramedullary disease with involvement of the skin,^{80, 81} pericardium,^{82, 83} pleura,⁸⁴⁻⁸⁶ kidney^{87, 88} and other
 280 sites⁸⁹ has been associated with disease acceleration or transformation.^{90, 91} Transfusion dependence, high
 281 transfusion burden, hyperleukocytosis,^{5, 92} splenomegaly, and iron overload (which may be confounded by

282 prolonged anemia and complications resulting therefrom) are acknowledged adverse risk factors in CMML and
283 are discussed in section 3 “pre-transplant management of disease symptoms”.

284

285 2.2.2. Cytogenetics and gene mutations

286 The genetic landscape and its prognostic relevance have been explored in CMML. Cytogenetic risk
287 stratifications and somatic mutations guide prognosis.^{5, 47, 48, 93-100} High-risk aberrations are considered an
288 indication for transplant. Not only the type, but potentially also the mutational burden (i.e. the total number of
289 mutational abnormalities and their variant allele frequency) may be relevant for prognosis. High overall mutation
290 burden (≥ 10 mutations), and ≥ 4 mutated epigenetic regulatory genes were linked to increased risk of relapse
291 post-transplant in CMML patients.¹⁰¹ However, the spectrum of molecular aberrations in CMML seems to be
292 more restricted than in MDS or AML and the clinical heterogeneity of the disease is thought to exceed genetic
293 heterogeneity.¹⁰² As such, the impact of somatic aberrations may be less straightforward than in MDS or AML.

294 While several mutations have already been incorporated into molecular scores (*ASXL1*, *RUNX1*, *NRAS*,
295 *SETBP1*),⁴⁸ their prognostic impact in the transplant setting remains less clear. For example, mutations typically
296 associated with altered risk in the non-transplant setting could not predict post-HCT survival in several studies:
297 *ASXL1*,^{5, 57, 101} *RUNX1*,^{5, 101} *SRSF2*,⁵⁷ *SETBP1*,¹⁰¹ with conflicting results for *TET2*.^{5, 57, 101} In contrast, abnormal
298 karyotype or adverse cytogenetics had an adverse impact on outcomes of transplanted CMML patients in most,^{57,}
299 ^{63, 101, 103} but not all⁵ studies. However, a recent multicenter cohort identified *ASXL1* and *NRAS* as potential strong
300 molecular predictors of post-transplant outcome.⁵⁴ *DNMT3A* and *JAK2* mutations had adverse impacts on post-
301 transplant outcomes of CMML patients, and the CPSS-Mol was shown to be significantly associated with post-
302 allogeneic overall and disease free survival.⁵³ Presence of mutated *NPM1* should result in the diagnosis of AML
303 as per new classifications (see section 1.1 “Classification of CMML”). Presence of *FLT3* aberrations in patients
304 with CMML is rare and data is inconclusive regarding prognostic relevance in this disease.¹⁰⁴

305 Presence of *TP53* mutations, although very rare in CMML ($\sim 1-2\%$)¹⁰⁵, had strong multivariate adjusted
306 adverse associations with post-transplant overall survival in patients with MDS¹⁰⁶ and CMML.⁵³ Very recently, a
307 prospective clinical trial in higher-risk MDS patients allocating patients to allo-HCT vs non-HCT treatment
308 based on donor availability, demonstrated unequivocally, that allo-HCT after reduced intensity conditioning
309 mediates long-term survival for patients bearing *TP53*-mutations, as compared to *TP53*-mutated patients with
310 non-HCT treatment, and this remained independent of *TP53* allelic state and variant allele frequency.⁴⁵ Thus,
311 although the absolute survival benefit remains modest, presence of *TP53* mutations alone should not preclude a

312 patient from consideration for allo-HCT based on TP-53 status alone. The prognostic significance of reducing or
313 clearing the burden of mutations associated with adverse outcomes prior to allo-HCT needs to be further
314 elucidated, as data on molecular clearance of *TP53* mutations with hypomethylating agents (HMAs; azacitidine
315 or decitabine) prior to allo-HCT in patients with higher-risk MDS are conflicting.^{45, 107} The evolving field of
316 (molecular) prognostic factors in CMML will continue to play a critical role in identifying those patients for
317 whom allo-HCT portends the highest benefits.

318

319 3. Pre-transplant management of disease symptoms

320 3.1. Pre-transplant management of (hyper)leukocytosis

321 A recent meta-analysis and several reviews argue against the routine use of leukapheresis for cytoreduction in
322 hyperleukocytotic AML (i.e. >100.000 WBC/ μ L).¹⁰⁸⁻¹¹⁰ There is no formal demonstration that control of
323 leukocytosis (in the absence of symptoms resulting therefrom), or so-called “blood count cosmetics” has any
324 impact on disease outcome. Neither is there a consensus regarding a target WBC or monocyte count.
325 Hydroxyurea is recommended by the National Cancer Center Network (NCCN)¹¹¹ and the ELN¹¹² for
326 cytoreduction prior to IC in AML. Supportive treatment with allopurinol for the prophylaxis/therapy of tumor
327 lysis syndrome, as well as the transfusion of blood products for the management of disseminated intravascular
328 coagulation, should be given if needed.

329

330 3.2. Pre-transplant management of iron overload

331 While high transfusion burden, iron overload and iron toxicity are known to have an adverse effect on allo-HCT
332 outcomes among patients with MDS (and CMML),¹¹³⁻¹²⁵ it remains unresolved whether and when iron chelation
333 treatment should be initiated in transplant eligible patients. Elevated serum ferritin levels in the pre-transplant
334 setting usually result from red blood cell transfusion, and in some of these patients, the presence of hemostatic
335 iron regulator (*HFE*) gene mutations may accelerate transfusion-induced iron overload.¹²⁶ Non-transferrin-bound
336 iron and labile plasma iron are toxic in both the pre- and the post-transplant setting, and may be elevated due to
337 macrophage iron recycling from transfused red blood cells and iron-release from dying red blood cells during
338 and after myeloablative chemotherapy. Early post-transplant iron toxicity can impair engraftment, delay
339 recovery of anemia, increase the risk of infections due to iron capability to support micro-organism growth and
340 to compromise immune cell functions, increase the risk of veno-occlusive disease and/or renal failure, and may

341 aggravate both acute and chronic GvHD. Late post-transplant iron toxicity can result in typical end-organ
342 damage due to accumulation of iron deposits in the heart, liver, pancreas, and other vital organs (reviewed in ¹²³).

343 Since retrospective studies in the allo-HCT setting are limited, and prospective ones are lacking, it
344 currently remains unclear whether pre-, peri-, and/or post-transplant iron chelation therapy is most beneficial for
345 patients. Phlebotomy and deferoxamine are not indicated in CMML due to obvious reasons, and deferiprone may
346 result in agranulocytosis. Hence, deferasirox remains the only viable option for CMML patients.

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

352

353 3.3. Pre-transplant management of splenomegaly

354 While splenomegaly is frequently observed in CMML, it is often limited and manageable without specific
355 treatment in CMML. However, some patients do present with massive splenomegaly. In these cases, the need for
356 splenectomy, splenic irradiation, or other means of reducing spleen size pre-transplant remains debated.

357 Splenomegaly prior to transplant is a well-recognized risk factor known to adversely affect transplant outcomes
358 in patients with MDS/MPN,¹³³ and is also associated with delayed neutrophil and platelet engraftment as well as
359 higher non-relapse mortality. In patients with myelofibrosis, splenectomy was shown to improve neutrophil and
360 platelet recovery (but did not result in longer overall survival) when compared to patients who received either
361 splenic irradiation or no treatment for splenomegaly.¹³⁴⁻¹³⁶ Patients without splenectomy have delayed
362 hematopoietic recovery, but spleen size does recede eventually post-transplant in cases of adequate donor
363 engraftment.¹³⁷ Thus, perioperative morbidity (43%) and mortality (13%) rates of splenectomy in CMML
364 patients¹³⁸ need to be weighed carefully. Splenic irradiation prior to transplant may be considered as an
365 alternative,¹³⁹ but can be associated with severe and protracted pancytopenia. Therefore, if performed, splenic
366 irradiation should possibly be used as an adjunct to conditioning, so that ensuing pancytopenia may be rescued
367 by donor engraftment.¹⁴⁰ *JAK2* inhibitors may offer an alternative approach.¹⁴¹⁻¹⁴⁶

368

369 3.4. Recommendations

- 370 • All transplant-eligible CMML patients should be considered for iron chelation therapy pre-, peri-, post-
 371 transplant when serum ferritin levels exceed 1000 µg/L, secondary causes of hyperferritinemia have been
 372 excluded, and in the absence of contraindications (e.g. elevated renal function parameters). In patients
 373 receiving upfront transplantations, iron reduction therapy is preferred in the post-transplant setting to avoid
 374 potential additional pre-transplant toxicity.
- 375 • In the absence of clinical sequelae, hydroxyurea-based cytoreduction is only recommended ≤6 weeks prior
 376 to transplant. We suggest an empiric target of <10.000 WBC/ µL, based on experience, rather than
 377 evidence.
- 378 • For patients with massively enlarged spleen (i.e. >20 cm below the costal margin), splenectomy, splenic
 379 irradiation, or reduction of spleen size with *JAK* inhibitors is recommended. A unified coordinated
 380 approach needs to be orchestrated between the treating physician and the transplant center.

381

382 4. Role of pre-transplant therapy

383 4.1. Role of de-bulking strategies in CMML

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

390 Prospective data on the optimal pre-transplant strategy for CMML patients identified as allo-HCT
 391 candidates is lacking. Whereas the role of allo-HCT in CMML is established, the sequence of pre-transplant
 392 treatment, or whether to treat the patient prior to allo-HCT at all, is not. Several retrospective analyses compared
 393 pre-transplant treatment with HMAs versus AML induction-type IC in patients with MDS or CMML, showing
 394 either no difference,^{57, 62, 155-157, 170} or an advantage for HMAs for all patients,^{5, 10, 113, 150, 162, 172-174} or in subgroups
 395 with higher-risk disease,¹⁵⁷ >5% bone marrow blast count at diagnosis,¹⁵⁵ or older patients.¹⁷⁵ Retrospective
 396 analyses comparing HMAs versus best supportive care^{12, 113, 149, 176-178} prior to transplant in MDS could not
 397 observe a clear beneficial (or adverse) effect for HMAs. Similarly, neither an improvement in relapse-free or
 398 overall survival, nor an additional risk of non-relapse mortality was shown in patients treated with decitabine¹⁰.

399 ^{155, 163, 177, 179} or azacitidine in a pre-transplant setting in patients with MDS (as compared to either best supportive
400 care or IC) in single retrospective studies,^{10, 12, 149, 150, 155-157, 162, 172, 173, 176} a prospective phase-II clinical trial,⁸ as
401 well as a meta-analysis published in 2019¹⁷⁵ collating data from 6 retrospective studies.^{150, 155-157, 172, 176} It must be
402 kept in mind, that most (but not all, e.g.^{7-10, 12}) of these studies captured patients who did not proceed to
403 transplant, which is a relevant caveat, as it remains obscure how many of them failed to proceed to transplant due
404 to disease progression or pre-transplant treatment-related mortality. With regards to CMML patients, a recent
405 phase-3 trial remains the only evidence of higher rates of death without progression or transformation for
406 decitabine versus hydroxyurea, albeit these data need to be interpreted with caution most deaths occurred after
407 study exit.¹³

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

410 Although prospective randomised data are lacking, the acceptable toxicity of HMAs combined with
411 their potential for cytoreduction and disease stabilisation (which may provide time for patients to reach
412 transplant) led several experts to recommend HMAs as pre-transplant treatment for patients with MDS^{5, 8, 28, 71,}
413 ^{162, 175, 176, 180-182} or CMML.¹⁷⁴ However, many transplant specialists, including the American Society for
414 Transplantation and Cellular Therapy Committee on Practice Guidelines,¹⁸³ as well as this panel, consider the
415 evidence (with regard to CMML) not to be clear enough to support this conclusion. Thus, the use of HMAs in
416 the pre-transplant setting remains controversial.

417 One of the main concerns of this panel regarding pre-transplant treatment, is that up to 13-36% of MDS
418 patients who started HMAs and for whom a transplant was intended could not proceed to transplant due to
419 disease progression, drug-related adverse events, or new comorbidities.⁷⁻¹² Similarly, in CMML patients death
420 without progression or transformation was significantly higher with decitabine,¹³ underlining that the primary
421 goal should be to bring eligible patients to transplant in a good general condition and that achieving CR before
422 transplant may be of subordinate importance. Thus, pre-HCT debulking strategies (be it with HMAs or IC) may
423 be a double-edged sword,¹⁸⁴ potentially resulting in worsening cytopenias, increased transfusion dependence
424 with ensuing complications such as iron overload or alloimmunization¹⁸⁵ and/or infections that may preclude
425 proceeding to transplant. Hence, this panel recommends, that once a patient has been identified as an allo-HCT
426 candidate, upfront transplantation without prior disease-modifying treatment is preferred, in order to maximize
427 chances of reaching allo-HCT whenever possible, irrespective of mere bone marrow blast counts of 10-19%.
428 However, in cases of aggressive disease with kinetics indicating rapid disease progression and/or severe clinical

429 symptoms requiring immediate alleviation, bridging therapy with HMA (possibly in combination with off-label
430 use of venetoclax) may be considered, as long as this does not postpone, or reduce the patients' chances of,
431 receiving curative treatment and should ideally be studied within clinical trials.

432

433 4.2. Optimal choice of pre-transplant treatment in CMML

434 A large retrospective analysis demonstrated multivariable-adjusted overall survival and time to next treatment to
435 be significantly longer with the use of HMAs as compared to IC in patients with higher-risk CMML (n=949).⁷¹

436 We consider the existing evidence to be strong enough to no longer support an indication for conventional IC in
437 any setting in this disease. Patients with newly diagnosed high-risk/secondary AML had significantly longer
438 post-transplant survival and lower early mortality when treated with CPX-351 as opposed to IC with 7 + 3.¹⁸⁶

439 Data on the CPX-351 (liposomal formulation of cytarabine and daunorubicin) for higher-risk CMML and AML
440 secondary to CMML are available for a handful of patients only from small phase I/II clinical trials performed in
441 both the first line¹⁸⁷ and second line settings,¹⁸⁸ indicating that the drug may be safe and it allowed for bridging

442 to allo-HCT in selected (1 of 6¹⁸⁷) CMML patients. Five of five CMML patients receiving CPX-351 first line
443 responded,¹⁸⁷ whereas only one of 6 CMML patients receiving the drug after HMA-failure achieved a response
444 and could proceed to allo-HCT.¹⁸⁸ Given the very small numbers of patients with CMML treated with CPX-351,

445 the efficacy of the drug needs to be further studied in this disease. Novel debulking strategies are needed.

446 Azacitidine plus venetoclax by itself¹⁸⁹⁻¹⁹³ or possibly in the future as a backbone for potential triplet
447 combinations incorporating newer substances (e.g. CD123 targeting with tagraxofusp or flotetuzumab) may well
448 be the way forward. Data from early phase clinical trials evaluating azacytidine with venetoclax in patients with

449 MDS in the first line¹⁹⁴ or relapsed refractory setting¹⁹⁵ are starting to emerge, as are data on the use of the
450 combination as bridging to allo-HCT in patients with high-risk MDS and AML.¹⁹⁶⁻¹⁹⁸ Clinical trials

451 incorporating venetoclax in conditioning regimen (e.g. NCT05005299, NCT05823714, NCT05807932,
452 NCT03613532) or as bridging (e.g. NCT04476199, NCT04904237) to allo-HCT in patients with MDS and AML
453 are currently underway, , and CMML patients can be included in some of them (e.g. NCT05807932,

454 NCT03613532). As venetoclax in combination with HMA leads to much higher rates of CR (without necessarily
455 translating into longer overall survival),¹⁹⁹ which are achieved more rapidly than with HMA alone, data

456 emerging in patients with CMML that proceeded to allo-HCT will have to be reviewed carefully and may
457 possibly result in a future alteration of this panels current recommendation. We acknowledge, and perhaps

458 anticipate, that venetoclax with an HMA may be an ideal bridging therapy for patients with CMML (and

459 probably also MDS or AML) with high blast counts and/or proliferative disease and/or other signs of rapid
460 disease kinetics.

461

462 4.3. Optimal timing of allo-HCT in pre-treated patients

463 Both retrospective^{92, 200} and prospective¹⁷⁸ data indicate that it is significantly better to proceed to allo-HCT
464 while patients are responding to HMAs rather than to wait for treatment failure.^{165, 200} The primary goal may be
465 to bring patients eligible for allo-HCT in a good general condition, or to render patients who were initially
466 transplant ineligible into a transplant-eligible state, whereas achieving CR before transplant may be of
467 subordinate importance. As outcome after HMA-failure is mostly dismal (<6 months), patients should be
468 transplanted after achieving the best possible response. In azacitidine-treated CMML patients median time to
469 first and best response is 4 (IQR 2-5) and 5 (IQR 3-7) cycles, respectively.^{70, 201, 202} Approximately one third of
470 patients experience further deepening of response after first response, with the median time from first response to
471 best response being 3-4 cycles.^{201, 203} Best outcomes in the HMA-relapsed/refractory setting were observed for
472 MDS patients able to receive allo-HCT,^{204, 205} which explains why this procedure should be offered when
473 possible.

474

475 4.4. Recommendations

- 476 • All patients should be included within clinical trials whenever available and possible.
- 477 • Once a patient has been identified to be a transplant candidate, we support an upfront transplantation as
478 soon as a suitable donor is available, without any disease-modifying pre-treatment for all CMML patients,
479 whenever possible, regardless of the bone marrow blast count. Timely referral to a transplant center is
480 essential.
- 481 • In the rare cases where pre-transplant treatment is unavoidable (e.g. no matching donor available), we
482 recommend the use of HMAs, and no longer see any indication for the use of IC in patients with CMML.⁷¹
- 483 • Upfront transplantation without prior treatment is preferred and recommended whenever possible. In cases
484 where front line treatment (most often with HMAs) may have been commenced (due to immediate need of
485 treatment of severe clinical symptoms and/or aggressive disease with kinetics indicating rapid disease
486 progression), allo-HCT should be performed after establishing the best possible response status, which is
487 achieved after ≤ 7 cycles of HMAs in 75% of CMML patients,^{70, 201, 202} provided the patient remains
488 transplant eligible. The patient should not continue the treatment until loss of response, or when disease

489 relapse or progression occur. To this end, we recommend close monitoring and performing of a bone
490 marrow evaluation as soon as response is suspected from amelioration of peripheral blood values, e.g.
491 every two cycles, with the aim of not subjecting the patient to unnecessary delays in the transplant, and not
492 to lengthen the period at risk for losing, -and most importantly to avoid loss of-, transplant eligibility.

- 493 • If relapse after any treatment has already occurred, allo-HCT should nevertheless always be considered for
494 eligible patients, as this remains the best option for these patients.
- 495 • In those instances, where the expected benefit from allo-HCT remains modest (e.g. mutations associated
496 with adverse risk, complex or monosomal karyotype, combined with age >70, comorbidities, and other
497 variables adversely influencing prognosis and transplant outcomes e.g. iron overload, bone marrow fibrosis,
498 therapy-related disease), value-based discussions between treating physicians, transplant centers and
499 patients as to the appropriateness of the procedure are merited. Possibly, HMAs might be of use (as
500 bridging strategy or instead of allo-HCT) for selected patients >60 years,¹⁷⁵ with *TP53* mutations and/or
501 with complex or monosomal karyotypes.^{45, 206}

502

503 5. Donor selection

504 Potential stem cell donors include standard donors, such as human leukocyte antigen (HLA) matched siblings
505 and matched unrelated donors, and alternative stem cell donors, including haploidentical or mismatched
506 unrelated donors, and (less frequently) unrelated umbilical cord donors. Selection of stem cell donors for patients
507 with CMML has improved markedly during the last two decades, similar to what has been observed for allo-
508 HCT in other indications. Several studies found differences in absolute survival and relapse rates between HLA-
509 identical sibling and matched unrelated donors, while some showed no significant difference after multivariable
510 adjustment.^{53, 54, 165, 207} The expert panel agreed to recommend as standard donors (starting with highest
511 preference): HLA-identical siblings, followed by matched unrelated donors (**Figure 3**). Recent studies in the
512 MDS setting found higher disease-free survival and lower relapse for allo-HCT with younger matched unrelated
513 donors compared with older HLA-identical siblings.²⁰⁸ Another large EBMT study found an independent effect
514 of cytomegalovirus serostatus of donors (although this study included patients mostly from the pre-letermovir
515 era).²⁰⁷ Therefore, the expert panel agreed to take age and cytomegalovirus status of donors into account when
516 balancing the risk for non-relapse mortality versus relapse during the donor selection process and to follow the
517 previously formulated donor suitability criteria.²⁰⁹

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

522

523 5.1. Recommendations

524 Currently, there are no systematic comparative studies between haploidentical transplants and mismatched
525 unrelated donors, and the panel agreed to use either of them, considering access, timing, and other suitability
526 criteria. For haploidentical donor allo-HCT, based on previous reports in other diseases,²¹⁰ post-transplant
527 cyclophosphamide may be the preferred platform.

528

529 6. Stem cell source

530 Limited data are available on transplant outcomes in CMML according to stem cell source. The panel agreed that
531 peripheral blood is the recommended hematopoietic stem cell source for human leukocyte antigen (HLA)
532 matched sibling and unrelated donor transplants. No data exist on the preferred source for haploidentical
533 transplants. Higher doses of CD34+ cells, if possible, might be targeted for unrelated donor transplants.²¹¹
534 However, due to lack of data, a preferred stem cell dose cannot be recommended for any transplant modality.

535

536 7. Conditioning intensity

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

548 If MAC is not feasible, combination of fludarabine and busulfan appeared to be associated with best
549 outcomes across diseases in MDS and MPN and can therefore also be considered in CMML, with or without
550 total-body irradiation.²¹⁴⁻²¹⁷ Recent increased adoption of treosulfan-based regimens within a reduced-toxicity
551 approach showed promising results in other indication.^{166, 218} However, there is no direct evidence to favor one
552 particular regimen over another. There is currently no evidence for the association of disease and mutation
553 burden or the threshold of MRD with the choice for conditioning intensity or regimen.

554

555 7.1. Recommendations

556 The expert panel recommended not to adopt pre-treatment decisions based on intensity of planned conditioning,
557 but to focus on post-transplant strategies, including chimerism and/or MRD monitoring, as well as to prevent
558 relapse (see “Post-transplant management” in supplements pp2-5).

559

560 Figure legends

561 **Figure 1. Patient selection for allo-HCT.**

562

563 **Figure 2. Timing of allo-HCT.**

564 CMML indicates chronic myelomonocytic leukemia; CPSS, CMML-specific Prognostic Scoring System; CPSS-
565 mol, CPSS molecular; Int, intermediate; AML, acute myeloid leukemia; Allo-HCT, allogeneic hematopoietic
566 cell transplantation.

567

568 **Figure 3. Transplant modalities.**

569 MMUD indicates mismatched unrelated donor; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; TBI, total body
570 irradiation.

571 *According to center preference.

572

573 Author Contributions

574 **FO, NG, YC, GK, MR, AS, IY-A and LP:** literature research, interpretation of data, conceived and designed
575 the manuscript topics to be covered as well as the recommendations to be made, and conception of figures; **FO:**
576 writing of the “Introduction” and “Unanswered questions” sections. **LP:** writing of sections 1-4, design of
577 figures and coauthor correspondence. **NG:** writing of the methodology and sections 5-8. **IY-A:** Writing of the
578 abstract. **FO, RG, IS, IY-A:** defined the EBMT Practice and Harmonization & Guidelines (PH&G) according to
579 which this manuscript was written. **All co-authors:** played an important role in interpreting results, revised the
580 manuscript, approved the final version, and agreed to be accountable for all aspects of the work in ensuring that
581 questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
582 **FO, NG, YC, GK, MR, AS, IY-A and LP:** accept final responsibility for the decision to submit for publication.

583 Competing Interests

584 **FO:** Honoraria: Takeda, MEDAC Pharma, Kyowa Kirin; Travel support: Takeda, Jazz Pharma, Kyowa Kirin;
585 **NG:** none reported; **YC:** Honoraria: Abbvie, Amgen, Astra-Zeneca, BMS, Gilead, Incyte, Jazz, MSD, Novartis,
586 Pfizer, Roche, Servier, Takeda; Travel support: Abbvie, Amgen, Astra-Zeneca, BMS, Gilead, Incyte, Jazz,
587 MSD, Novartis, Pfizer, Roche, Sanofi; **GK:** Research support: BMS-Celgene, Amgen, Abbvie, Medac,
588 Eurocept; Honoraria: Novartis, MSD, Pfizer, Amgen, Gilead, BMS-Celgene, Abbvie, Biotest, Takeda, Eurocept;
589 Travel support: Medac, Gilead; Neovii; **MR:** Research support: AbbVie, Astex, Medac, Neovii, Novartis; Travel

590 support: Medac, Jazz. **AS**: Honoraria: AbVie, Amgen, BMS, Incyte/Genesis, Gilead, Sanofi, Servier; Travel
591 support: AbbVie, BMS, Roche, Servier, Takeda; **TdW**: none reported; **RI**: Research support: AbbVie;
592 Honoraria: AbbVie, BMS/Celgene, CTI Biosciences, Gilead, Jazz, Novartis, Servier; Travel support: AbbVie,
593 Gilead/Kite; **MJ**: Honoraria: AbbVie, BMS/Celgene, Novartis, JAZZ Pharmaceuticals, Pfizer; Travel support:
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612

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1631 Table 1.A. CPSS genetic risk group (adapted from ⁴⁸).

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	-

1632

1633 Genetic risk group category:

Total score points	CPSS genetic risk group
0	Low
1	Intermediate-1
2	Intermediate-2
≥ 3	High

1634

1635

1636 Table 1.B. CPSS-Mol score (adapted from ⁴⁸).

Score points	Genetic risk group*	Bone marrow blasts	White blood cell count	Red blood cell transfusion dependency
0	Low	<5%	<13 x 10 ⁹ /L	No
1	Intermediate-1	$\geq 5\%$	$\geq 13 \times 10^9$ /L	Yes
2	Intermediate-2	-	-	-
3	High	-	-	-

1637 *As reported in Table 1.A.

1638

1639 CPSS-Mol risk group category:

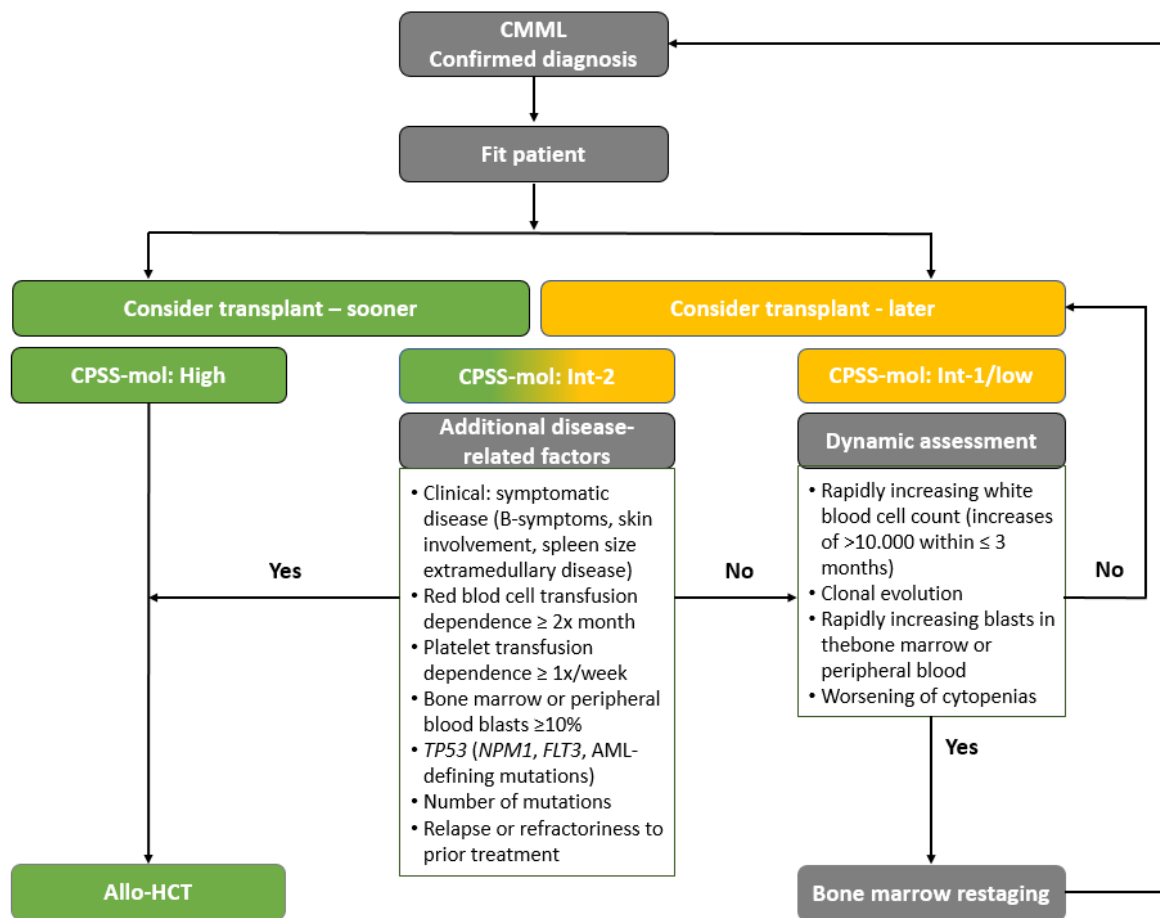
Total score points	CPSS-Mol risk group	Median overall survival*, months	Cumulative incidence of transformation to AML at 48 months*, %
0	Low	Not reached	0
1	Intermediate-1	64-68	3-8
2-3	Intermediate-2	30-37	21-24
≥ 4	High	17-18	48-52

1640 *In the training and validation cohorts, respectively.

1641

Allogeneic Hematopoietic Cell Transplantation in Chronic Myelomonocytic Leukemia (CMML) - Best Practice Recommendations of the EBMT

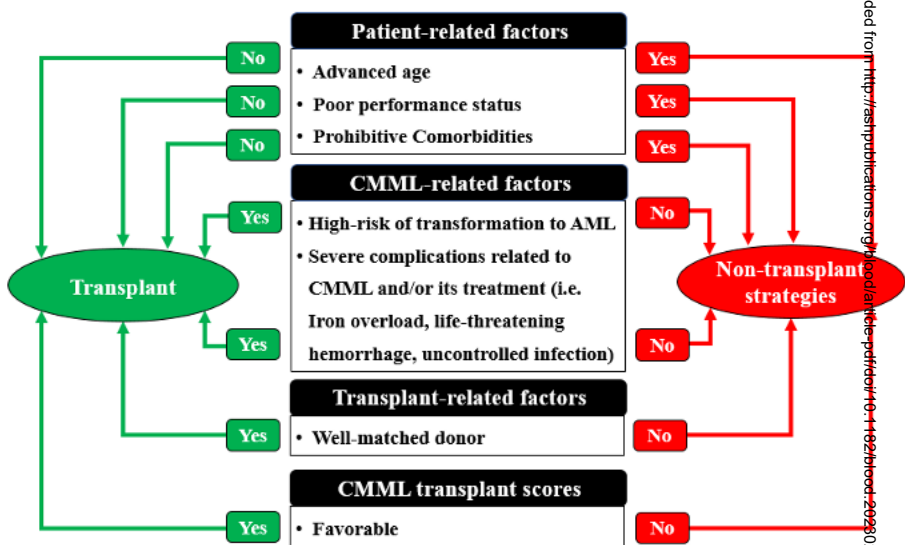
Transplant timing algorithm for patients with CMML



Conclusions: Upfront transplantation without prior disease-modifying treatment is preferred to maximize chances of being transplanted whenever possible, irrespective of bone marrow blast counts.

Onida et al. DOI: 10.xxxx/*blood*.2024xxxxxx

**Blood
Visual
Abstract**



ALLOGENEIC TRANSPLANT

PROs:

- Potential cure

CONs:

- High non-relapse mortality
- Worse quality of life
- Risk of Complications
- Acute graft versus host disease (GvHD)
- Chronic GvHD

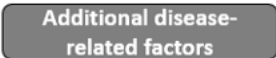
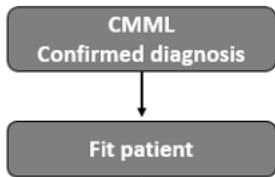
NON-TRANSPLANT STRATEGY

PROs:

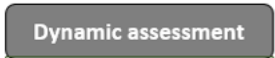
- Potential long watch and wait period
- Hypomethylating agents (HMAs) well tolerated
- Better quality of life

CONs:

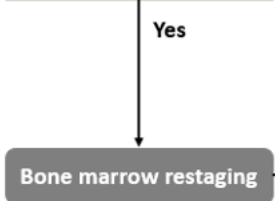
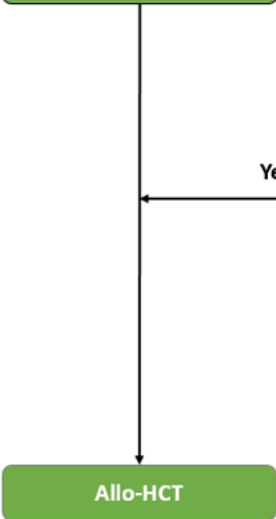
- Initial worsening of cytopenias:
 - risk of infections and other adverse events
 - risk of loss of allo-HCT eligibility
- Risk of missing best time-point for allo-HCT:
 - disease progression to AML
 - development of chemo-resistance
- Azacitidine not approved for MP-CMML in Europe
- Decitabine not approved for CMML in Europe
- No cure → certain death



- Clinical: symptomatic disease (B-symptoms, skin involvement, spleen size extramedullary disease)
- Red blood cell transfusion dependence $\geq 2x$ month
- Platelet transfusion dependence $\geq 1x/week$
- Bone marrow or peripheral blood blasts $\geq 10\%$
- *TP53* (*NPM1*, *FLT3*, AML-defining mutations)
- Number of mutations
- Relapse or refractoriness to prior treatment



- Rapidly increasing white blood cell count (increases of $>10,000$ within ≤ 3 months)
- Clonal evolution
- Rapidly increasing blasts in the bone marrow or peripheral blood
- Worsening of cytopenias

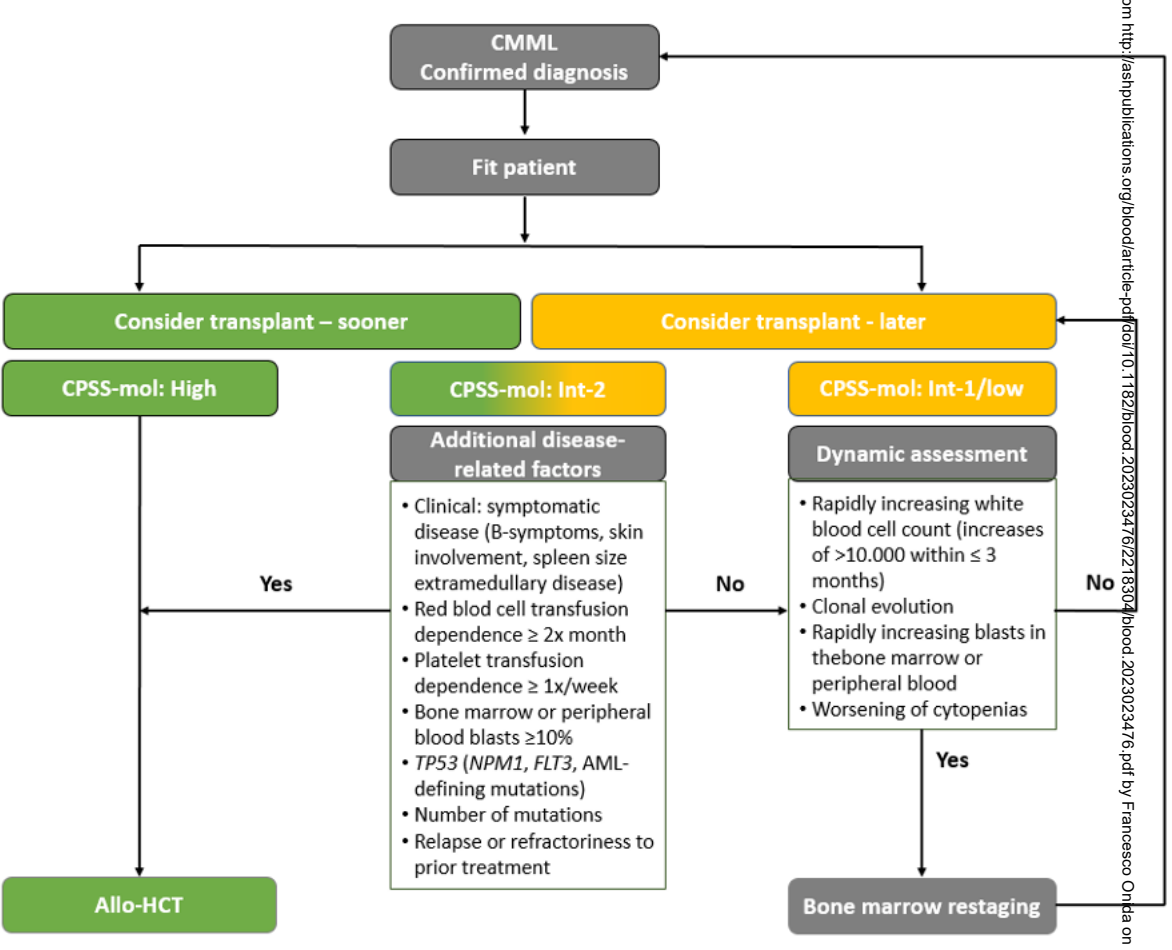


Yes

No

No

Yes



DONOR SELECTION

Matched related

Matched unrelated

Haplo or MMUD*

Unrelated cord



CONDITIONING

Young

AGE

Old

High

FITNESS

Low

MAC

INTENSITY

RIC

Regimens:

- Fludarabine-based with alkylant(s) \pm TB
- Investigational new combinations