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

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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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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. 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. In cases of aggressive disease or clinical symptoms necessitating imminent actions, bridging therapy with cytoreduction may be considered, as long as this does not reduce chances of receiving, and/or postpone, curative treatment and should ideally be investigated in future studies.

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 70-75 years. Median survival in the largest reported series is in the 2 to 3 years range,[1] but is less than 2 years in high-risk patients according to various models of prognostication specifically developed for the disease.[2, 3] To date allogeneic hemopoietic cell transplantation (allo-HCT) remains the only potentially curative treatment strategy for eligible patients.[4] Overall survival for patients with CMML ranges from 30-40% at five years post-allo-HCT, owing to cumulative incidences of relapse of 30-50% and non-relapse mortality rates of 20-40%.[5-12] In the context of allo-HCT the absence of prospective data drags behind many uncertainties not only regarding patient selection, but also possible pre-transplant 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 post-transplant setting.

Given the above, the newly established EBMT Practice and Harmonization & 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 September 25th-26th, 2023. The methodology used is described in supplements., p1.

Workshop Recommendations

1. Patient selection for allo-HCT

Before going into further details as to which classification system, which prognostic scoring system, which other disease-related 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,[6] indicating the need for heightening non-transplant 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,[7-13] indicating the need for better patient selection strategies, more efficacious pre-transplant treatment modalities, faster procedure to transplant, and/or increasing the rates of up-front transplantations. Careful, holistic risk assessment and patient selection is

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

1.1. Classification to CMML

The recently published International Consensus Classification (ICC)[14] and the 2022 World Health Organisation (WHO)[15] Classification have made mostly similar adaptions in CMML (i.e. elimination of CMML-0, lowering of the monocyte threshold to ≥0.5 G/L, 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* (WHO-2022 (no blast count threshold required)[15] and AML with mutated bZIP *CEBPA* (ICC-2022 ((≥10% blasts required)).[14] 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 10-19% blasts, that can be treated either as MDS or as AML.[14] This however, does not affect patients with CMML as yet.

1.2. Patient-related factors

Prospective data have confirmed survival benefits for higher-risk MDS patients aged 60-70, or ≥65[12, 16] years undergoing allo-HCT. Thus, although age alone should not preclude patients from being considered as transplant eligible,[17] 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 (ECOG-PS) or Karnofsky PS scale, Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI),[18, 19] frailty assessment,[20] comprehensive geriatric assessments,[21, 22] and/or combinations thereof.[23-25]

1.3. 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 ≤70 (in select cases ≤75) years
- ECOG-PS <2 or Karnofsky index ≥70%
- HCT-CI <3
- Lack of any comorbidity that the transplant specialist judges to be incompatible with intensive chemotherapy, e.g. as suggested by Ferrara et al.[26]

2. Timing of allo-HCT

Once the decision to proceed to allo-HCT has been made, timing is a crucial consideration, since delaying transplant may result in disease progression and/or acquisition of additional comorbidities, and/or toxicities (if the patient receives pre-transplant 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 pre-transplant treatment in patients candidate for allo-HCT for CMML so far,[27] and 2018 European Hematology Association (EHA)/European LeukemiaNet (ELN) recommendations[28] were largely extrapolated from data obtained in patients with MDS.[28-32]

2.1.1. 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),[33] revised IPSS (IPSS-R),[34]) to CMML-specific scores predicting outcomes (Düsseldorf score,[35] MD-Anderson Prognostic Score (MDAPS),[36] modified Bournemouth score,[37] CMML-specific Prognostic Scoring System (CPSS),[38] Mayo model[39]) or estimating time to first treatment,[40] most of which have been found to be valid and with comparable performance.[1, 2, 41-44] Updated versions of some of these scores have been published incorporating molecular data: IPSS molecular (IPSS-M),[45] Groupe Francophone des Myelodysplasies (GFM) score (*ASXL1*),[46] Mayo Molecular Model (*ASXL1*),[47] CPSS molecular (CPSS-Mol; *ASXL1*, *RUNX1*, *NRAS*, *SETBP1*).[48] ELN and EHA 2018 guidelines recommend five of these scores (MDAPS, CPSS in case of unavailability of molecular data; GFM, Mayo Molecular, CPSS-Mol when molecular data are available).[28] 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 be transplanted. 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, -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.[49-52] These retrospective analyses indicated that allo-HCT improves outcomes for the (very) high IPSS-M risk groups. Very recently the 1102 Study of the Blood and Marrow Transplant Clinical Trials Network was re-analysed after inclusion of molecular data enabling re-stratification of patients according to IPSS-M.[45] This trial identified MDS patients with IPSS-M high-risk to be ideal candidates for early transplantation.[45] In the largest cohorts of transplanted CMML patients with molecular data available (n=313[53] and n=240[54]), the CPSS-Mol was shown to be significantly associated with post-allogeneic disease free survival and/or overall survival.

While transplantation of early-stage lower-risk disease offers the lowest rate of non-relapse mortality, it exposes patients who might have had a long period without disease progression to immediate morbidity and mortality. Since life-expectancy of CMML patients with lower-risk disease is >5 years,[48] 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, or R-IPSS) until disease progression to a higher risk category, while HCT should be immediately offered to patients with higher-risk.[29-32] In corroboration thereof, retrospective studies exclusively analysing CMML patients have confirmed the absence of significant survival benefit of allo-HCT for CMML patients with lower-risk disease as categorized by the CPSS.[4, 55] Although allo-HCT provides modest survival benefit as compared to all other treatment modalities including intensive chemotherapy (IC) for patients after having transformed from CMML to AML,[4, 56] most evidence underscores the importance of early transplantation before transformation to AML.[57-59] The latter coincides with disease progression and an increased potential for the acquisition of contraindications for the transplantation. It also needs to be kept in mind, that while high-risk features are indications for allo-HCT in CMML, they also adversely impact allo-HCT outcomes.[5, 55, 60-63]

This panel acknowledges the recent developments in, -and increasing importance of-, molecular data. The CPSS-Mol (Table 1.A.) has been shown to outperform the CPSS in all patients with CMML for both overall survival and cumulative incidence of AML evolution, respectively (Table 1.B.).[48] 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 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.[64] Different from other molecularly integrated CMML-specific prognostic models, only considering nonsense/frameshift ASXL1 mutations as independent adverse factors,[44, 45] 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 patients' risk and to identify the optimal timing of allo-HCT in patients with CMML. Taking the possibility for post-transplant interventions into account, it may be important to dissect those disease features that affect cumulative incidences or relapse from those that can portend higher non-relapse mortality (see also chapter 2.2.2 "Risk-stratification to predict post-HCT outcomes").

2.1.2. Risk-stratification to predict post-HCT outcomes

Although both CPSS risk stratifications,[53, 61] have been significantly associated with post-transplant relapse and/or overall survival, risk stratification by CPSS[5, 55] or CPSS-Mol[5] alone has limitations in predicting post-transplant outcomes.[55] Dynamic use of prognostic scores (IPSS-R[65], CPSS or CPSS-Mol[61, 62]) 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 (e.g. *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 section "2.2.2. 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 for the prediction of post-transplant outcomes on the other hand. For the former, we propose the use of the CPSS-Mol as discussed above. For the latter, transplantation-specific scores to predict transplant outcomes have been developed for CMML patients,[54, 66] or validated in CMML patients,[67] and outperform scores typically used in the non-transplant setting. The CMML transplant score,[54] which incorporates both molecular (*ASXL1* and *NRAS* mutations) and clinical information (bone 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 CMML patients undergoing allo-HCT. Five risk groups were identified with 5-year survival rates ranging from 81-19%, and non-relapse mortality rates ranging

from 5-51% for an increasing transplant score, respectively.[54] 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 non-transplant setting.[54] In addition, the endothelial activation and stress index (EASIX) score might help to predict non-relapse mortality,[67] whereas a more recent score has been criticized because of inclusion of GvHD as a risk factor without adjusting for inherent statistical bias.[66] The inclusion of donor type and source as well as conditioning intensity might further refine transplant specific prognostic scores.

2.1.3. 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.

- **CPSS-Mol high-risk patients** have a median overall survival of 17-18 months and a cumulative incidence of transformation to AML at 48 months of 48-52% (Table 1.B.).[48] 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 section 3 “Role of pre-transplant therapy”).
- **CPSS-Mol intermediate-2 risk patients** have a median overall survival of 30-37 months and a cumulative incidence of transformation to AML at 48 months of 21-24% (Table 1.B.).[48] 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 section 2.2 “Additional disease-related risk factors” and section 3 “Pre-transplant management of disease symptoms”.
- **CPSS-Mol intermediate-2 risk patients without additional risk factors: a watch and wait strategy with dynamic assessment** should be followed whenever possible. Non-transplant treatment strategies, if deemed necessary, should be discussed with the transplant centre. **Dynamic re-assessment** every three 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 re-staging of disease and/or response status, which not only includes bone marrow work-ups (including cytology, histology, flow cytometry, conventional cytogenetics, fluorescence in situ hybridization and next generation sequencing),[68] but also increasingly relies on analyses of the peripheral blood.[69, 70] Re-classification and renewed calculation of CPSS-Mol risk should ensue (**Figure 2**).

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

  For transplant ineligible patients current guidelines[28] and more recent data[13, 71] are applicable.

Prediction of post-transplant outcomes:

- Based on data discussed above, the panel recommends the use of the CMML transplant score[54] to predict post-transplant outcomes for patients that have been previously identified as transplant candidates with the CPSS-Mol.

2.2. Additional disease-related risk factors

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

2.2.1. Clinical symptoms

General symptoms (such as drenching night sweats, unintended weight loss, 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 impacts survival and correlates with higher relapse rates and delayed engraftment in patients with MDS and CMML.[72-79] Extramedullary disease with involvement of the skin,[80, 81] pericardium,[82, 83] pleura,[84-86] kidney[87, 88] and other sites[89] has been associated with disease acceleration or transformation.[90, 91] Transfusion dependence, high transfusion burden, hyperleukocytosis,[5, 92] 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 section 3 “pre-transplant management of disease symptoms”.

2.2.2. Cytogenetics and gene mutations

The genetic landscape and its prognostic relevance have been explored in CMML. Cytogenetic risk stratifications and somatic mutations guide prognosis.[5, 47, 48, 93-100] High-risk aberrations are considered an indication for transplant. Not only the type, but potentially also the mutational burden (i.e. the total number of mutational abnormalities and their variant allele frequency) may be relevant for prognosis. High overall mutation burden (≥10 mutations), and ≥4 mutated epigenetic regulatory genes were linked to increased risk of relapse post-transplant in CMML patients.[101] 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.[102] As such, the impact of somatic aberrations may be less straightforward than in MDS or AML.

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

Presence of *TP53* mutations, although very rare in CMML (~1-2%)[105], had strong multivariate adjusted adverse associations with post-transplant overall survival in patients with MDS[106] and CMML.[53] Very recently, a prospective clinical trial in higher-risk MDS patients allocating patients to allo-HCT vs 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 *TP53*-mutated patients with non-HCT treatment, and this remained independent of *TP53* allelic state and variant allele frequency.[45] 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 prior to allo-HCT needs to be further elucidated, as data on molecular clearance of *TP53* mutations with hypomethylating agents (HMAs; azacitidine or decitabine) prior to allo-HCT in patients with higher-risk MDS are conflicting.[45, 107] 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.

3. Pre-transplant management of disease symptoms

3.1. Pre-transplant management of (hyper)leukocytosis

A recent meta-analysis and several reviews argue against the routine use of leukapheresis for cytoreduction in hyperleukocytotic AML (i.e. >100.000 WBC/ µL).[108-110] 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 Cancer Center Network (NCCN)[111] and the ELN[112] for cytoreduction prior to 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.

3.2. Pre-transplant management of iron overload

While 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),[113-125] it remains unresolved whether and when iron chelation treatment should be initiated in transplant eligible patients. Elevated serum ferritin levels in the pre-transplant 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.[126] Non-transferrin-bound iron and labile plasma iron are toxic in both the pre- and the post-transplant setting, and may be elevated due to macrophage iron recycling from transfused red blood cells and iron-release from dying red blood cells during and after myeloablative chemotherapy. Early post-transplant iron toxicity can impair engraftment, delay recovery of anemia, increase the risk of infections due to iron capability to support micro-organism 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 post-transplant iron toxicity can result in typical end-organ damage due to accumulation of iron deposits in the heart, liver, pancreas, and other vital organs (reviewed in [123]).

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

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.[127-132] A prospective non-interventional study of 222 MDS and CMML patients 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.[116]

3.3. Pre-transplant management of splenomegaly

While 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 pre-transplant remains debated. Splenomegaly prior to transplant is a well-recognized risk factor known to adversely affect transplant outcomes in patients with MDS/MPN,[133] and is also associated with delayed neutrophil and platelet engraftment as well as higher non-relapse mortality. In patients with myelofibrosis, splenectomy was shown to improve neutrophil and platelet recovery (but did not result in longer overall survival) when compared to patients who received either splenic irradiation or no treatment for splenomegaly.[134-136] Patients without splenectomy have delayed hematopoietic recovery, but spleen size does recede eventually post-transplant in cases of adequate donor engraftment.[137] Thus, perioperative morbidity (43%) and mortality (13%) rates of splenectomy in CMML patients[138] need to be weighed carefully. Splenic irradiation prior to transplant may be considered as an alternative,[139] 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.[140] *JAK2* inhibitors may offer an alternative approach.[141-146]

3.4. Recommendations

- All transplant-eligible CMML patients should be considered for iron chelation therapy pre-, peri-, post-transplant when serum ferritin levels exceed 1000 µg/L, secondary causes of hyperferritinemia have been excluded, and in the absence of contraindications (e.g. elevated renal function parameters). In patients receiving upfront transplantations, iron reduction therapy is preferred in the post-transplant setting to avoid potential additional pre-transplant toxicity.
- In the absence of clinical sequelae, hydroxyurea-based cytoreduction is only recommended ≤6 weeks prior to transplant. We suggest an empiric target of <10.000 WBC/ µL, based on experience, rather than evidence.
- For patients with massively enlarged spleen (i.e. >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.

4. Role of pre-transplant therapy

4.1. Role of de-bulking strategies in CMML

It remains unclear whether debulking, i.e. reduction of disease burden as typically measured by reduction of bone marrow blasts to <2%,[54] <5-10% and/or complete remission (CR) status is advantageous for allo-HCT 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 in both MDS and CMML, whether patients who achieved CR without minimal residual disease (MRD) negativity, might benefit from bridging treatment before allo-HCT.[171] Reducing disease burden prior to transplant may also be more relevant in the reduced intensity conditioning setting.[152]

Prospective data on the optimal pre-transplant strategy for CMML patients identified as allo-HCT candidates is lacking. Whereas the role of allo-HCT in CMML is established, the sequence of pre-transplant treatment, or whether to treat the patient prior to allo-HCT at all, is not. Several retrospective analyses compared pre-transplant treatment with HMAs versus AML induction-type IC in patients with MDS or CMML, showing 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 with higher-risk disease,[157] >5% bone marrow blast count at diagnosis,[155] or older patients.[175] Retrospective analyses comparing HMAs versus best supportive care[12, 113, 149, 176-178] prior to 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 non-relapse mortality was shown in patients treated with decitabine[10,

[155, 163, 177, 179] or azacitidine in a pre-transplant setting in patients with MDS (as compared to either best supportive 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 well as a meta-analysis published in 2019[175] collating data from 6 retrospective studies.[150, 155-157, 172, 176] It must be kept in mind, that most (but not all, e.g.[7-10, 12]) of these studies captured patients who did not proceed to transplant, which is a relevant caveat, as it remains obscure how many of them failed to proceed to transplant due to disease progression or pre-transplant treatment-related mortality. With regards to CMML patients, a recent phase-3 trial remains the only evidence of higher rates of death without progression or transformation for decitabine versus hydroxyurea, albeit these data need to be interpreted with caution most deaths occurred after study exit.[13]

Randomisation at the start of pre-transplant 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 randomised data are lacking, the acceptable toxicity of HMAs combined with their potential for cytoreduction and disease stabilisation (which may provide time for patients to reach transplant) led several experts to recommend HMAs as pre-transplant treatment for patients with MDS[5, 8, 28, 71, 162, 175, 176, 180-182] or CMML.[174] However, many transplant specialists, including the American Society for Transplantation and Cellular Therapy Committee on Practice Guidelines,[183] 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 pre-transplant setting remains controversial.

One of the main concerns of this panel regarding pre-transplant treatment, is that up to 13-36% of MDS patients who started HMAs and for whom a transplant was intended could not proceed to transplant due to disease progression, drug-related adverse events, or new comorbidities.[7-12] Similarly, in CMML patients death without progression or transformation was significantly higher with decitabine,[13] 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,[184] potentially resulting in worsening cytopenias, increased transfusion dependence with ensuing complications such as iron overload or alloimmunization[185] 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 10-19%. 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.

4.2. Optimal choice of pre-transplant 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 to IC in patients with higher-risk CMML (n=949).[71] 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 post-transplant survival and lower early mortality when treated with CPX-351 as opposed to IC with 7 + 3.[186] Data on the CPX-351 (liposomal formulation of cytarabine and daunoribicin) for higher-risk CMML and AML secondary to CMML are available for a handful of patients only from small phase I/II clinical trials performed in both the first line[187] and second line settings,[188] indicating that the drug may be safe and it allowed for bridging to allo-HCT in selected (1 of 6[187]) CMML patients. Five of five CMML patients receiving CPX-351 first line responded,[187] whereas only one of 6 CMML patients receiving the drug after HMA-failure achieved a response and could proceed to allo-HCT.[188] 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[189-193] or possibly in the future as a backbone for potential triplet combinations incorporating newer substances (e.g. CD123 targeting with tagraxofusp or flotetuzumab) may well be the way forward. Data from early phase clinical trials evaluating azacytidine with venetoclax in patients with MDS in the first line[194] or relapsed refractory setting[195] 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.[196-198] Clinical trials incorporating venetoclax in conditioning regimen (e.g. NCT05005299, NCT05823714, NCT05807932, NCT03613532) or as bridging (e.g. NCT04476199, NCT04904237) to allo-HCT in patients with MDS and AML are currently underway, , and CMML patients can be included in some of them (e.g. NCT05807932, NCT03613532). As venetoclax in combination with HMA leads to much higher rates of CR (without necessarily translating into longer overall survival),[199] which are achieved more rapidly than with HMA alone, data emerging in patients with CMML that proceeded to allo-HCT will have to be reviewed carefully and may possibly result in a future alteration of this panels 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.

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

Both retrospective[92, 200] and prospective[178] 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.[165, 200] 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 be transplanted after achieving the best possible response. In azacitidine-treated CMML patients median time to first and best response is 4 (IQR 2-5) and 5 (IQR 3-7) cycles, respectively.[70, 201, 202] Approximately one third of patients experience further deepening of response after first response, with the median time from first response to best response being 3-4 cycles.[201, 203] Best outcomes in the HMA-relapsed/refractory setting were observed for MDS patients able to receive allo-HCT,[204, 205] which explains why this procedure should be offered when possible.

4.4. 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 pre-treatment for all CMML patients, whenever possible, regardless of the bone marrow blast count. Timely referral to a transplant center is essential.
- In the rare cases where pre-transplant treatment is unavoidable (e.g. 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.[71]
- Upfront transplantation without prior treatment is preferred and recommended whenever possible. In cases where front line treatment (most often with HMAs) may have been commenced (due to 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 ≤7 cycles of HMAs in 75% of CMML patients,[70, 201, 202] 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, e.g. every two 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, as this remains the best option for these patients.
- In those instances, where the expected benefit from allo-HCT remains modest (e.g. mutations associated with adverse risk, complex or monosomal karyotype, combined with age >70, comorbidities, and other variables adversely influencing prognosis and transplant outcomes e.g. iron overload, bone marrow fibrosis, therapy-related disease), value-based discussions between treating physicians, transplant centers and patients as to the appropriateness of the procedure are merited. Possibly, HMAs might be of use (as bridging strategy or instead of allo-HCT) for selected patients >60 years,[175] with *TP53* mutations and/or with complex or monosomal karyotoypes.[45, 206]

5. Donor selection

Potential stem cell donors include standard donors, such as human leukocyte antigen (HLA) matched siblings and matched unrelated donors, and 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 two 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, while some showed no significant difference after multivariable adjustment.[53, 54, 165, 207] 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.[208] Another large EBMT study found an independent effect of cytomegalovirus serostatus of donors (although this study included patients mostly from the pre-letermovir era).[207] Therefore, the expert panel agreed to take age and cytomegalovirus status of donors into account when balancing the risk for non-relapse mortality versus relapse during the donor selection process and to follow the previously formulated donor suitability criteria.[209]

Alternative donor transplants may be considered for higher-risk 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,[103] and should therefore be carefully used, in case no other suitable donor is available.

5.1. 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,[210] post-transplant cyclophosphamide may be the preferred platform.

6. 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 human leukocyte antigen (HLA) matched sibling and unrelated donor transplants. No data exist on the preferred source for haploidentical transplants. Higher doses of CD34+ cells, if possible, might be targeted for unrelated donor transplants.[211] However, due to lack of data, a preferred stem cell dose cannot be recommended for any transplant modality.

7. 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).[212] Most retrospective studies in patients with CMML and MDS report equivocal outcome after commonly used myeloablative or reduced intensity conditioning regimens.[52, 165, 213, 214] Therefore, the panel agreed that there is currently no superiority of one intensity over another. However, it can be extrapolated from clinical practice that, post-transplant relapse in CMML appears to be more frequent than in MDS (with the largest retrospective series reporting relapse rates in the 27-52% range[57, 62] and about 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**).

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

Figure legends

Figure 1. Patient selection for allo-HCT.

Figure 2. Timing of allo-HCT.

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

Figure 3. Transplant modalities.

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

*According to center preference.

Author Contributions

FO, NG, YC, GK, MR, AS, IY-A and LP: literature research, interpretation of data, conceived and designed the manuscript topics to be covered as well as the recommendations to be made, and conception of figures; **FO**: writing of the "Introduction" and "Unanswered questions" sections. **LP**: writing of sections 1-4, design of figures and coauthor correspondence. **NG**: writing of the methodology and sections 5-8. **IY-A**: Writing of the abstract. **FO, RG, IS, IY-A**: defined the EBMT Practice and Harmonization & Guidelines (PH&G) according to which this manuscript was written. **All co-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. **FO, NG, YC, GK, MR, AS, IY-A and LP**: accept final responsibility for the decision to submit for publication.

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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	-

Genetic risk group category:

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

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%	$<13 \times 10^9$/L	No
1	Intermediate-1	≥5%	$\geq 13 \times 10^9$/L	Yes
2	Intermediate-2	-	-	-
3	High	-	-	-

*As reported in Table 1.A.

CPSS-Mol risk group category:

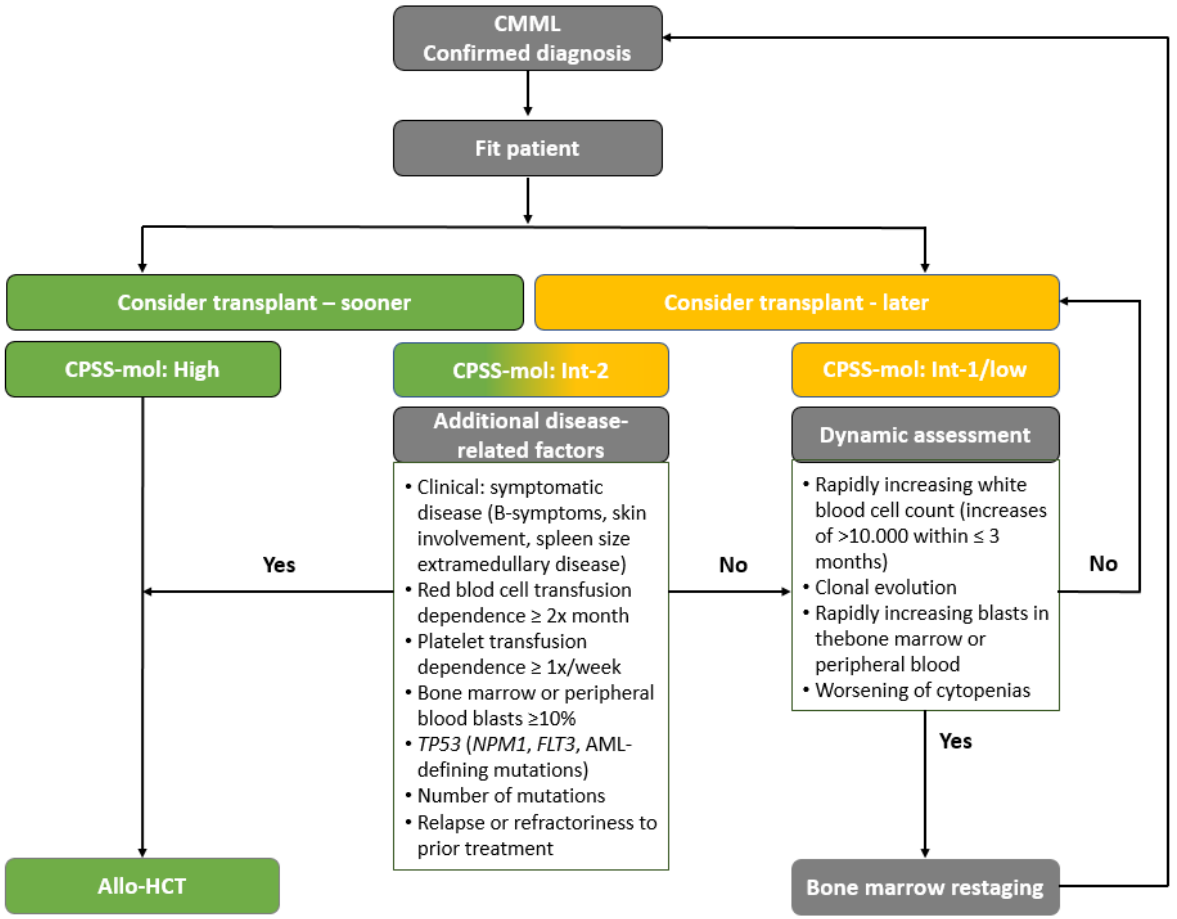
Total score points	CPSS-Mol risk group	Median overall survival*, months	Cumulative incidence of transformation to AML at 48 months*, %
0	Low	Not reached	0
1	Intermediate-1	64-68	3-8
2-3	Intermediate-2	30-37	21-24
≥4	High	17-18	48-52

*In the training and validation cohorts, respectively.

Visual Abstract

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

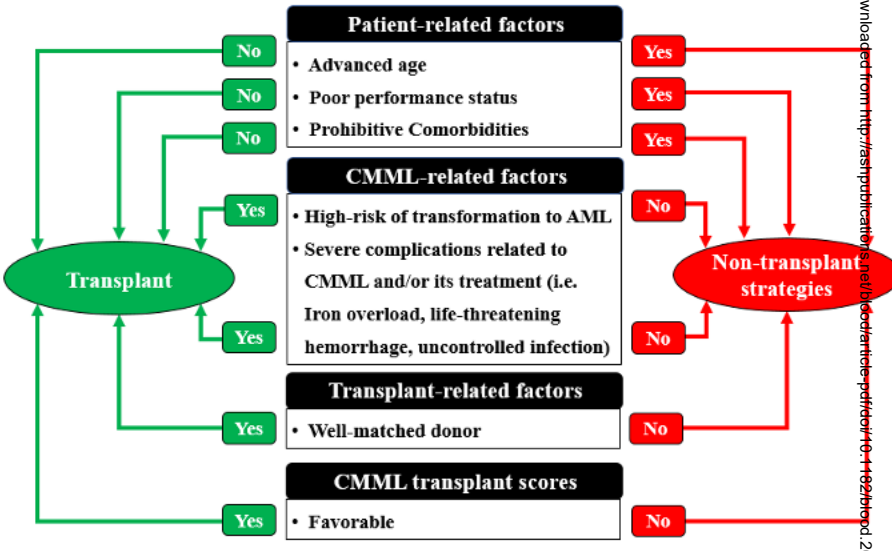
Transplant timing algorithm for patients with CMML



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
  - ➞ developement of chemo-resistance
- Azacitidine not approved for MP-CMML in Europe
- Decitabine not approved for CMML in Europe
- No cure ➞ certain death