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Contemporary treatment approaches to CMML – is allogeneic HCT the only cure?

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Abstract

Chronic Myelomonocytic Leukemias are frequently diagnosed in older adults. Their prognosis is heterogeneous, but several prognostic factors can identify patients with an expected survival of a few years only, including among younger patients eligible for allogeneic stem cell transplantation.

Based on the retrospective data available, we discuss how to identify CMML patients for whom curative therapy must be envisaged. We emphasize that, although transplantation remains the only path to cure in CMML, it can be envisaged in only a minority of patients. Despite increased donor availability, its potential remains limited by significant rates of mortality caused both by the procedure and by post-transplantation relapses. We review the options available to bridge patients to transplant, the management of transplantation itself (choice of donor, graft source and condition regimen), and finally the potential for post-transplantation interventions. Our review underscores the need for further prospective studies of allogeneic stem cell transplantation in CMML.

Keywords: Chronic Myelomonocytic Leukemias, Allogeneic Stem Cell Transplantation, Hypomethylating Agents.

Introduction

Chronic myelomonocytic leukemias (CMML) are a heterogeneous group of oligoclonal hematological malignancies characterized by chronic monocytosis (1), and classified by the World Health Organization 2016 (WHO) as overlap myelodysplastic (MDS) /myeloproliferative neoplasms (MPN) (2). CMML is a rare disease with an annual incidence of 1-4 cases per 100,000 in western countries, with a male predominance. It is predominantly diagnosed in elderly patients, with a median age of 75 years at diagnosis (3). The prognosis remains unsatisfactory, with median overall survival ranging 30-36 months in unselected real-life cohorts, with broad inter-patient variability (4-7). Allogeneic hematopoietic stem cell transplantation (HSCT) is the only treatment recognized as potentially curative in CMML. We will review potential alternatives to alter the natural history of CMML, patient selection, timing of transplantation and the expected outcome of CMML patients who undergo transplantation.

It must first be reminded that HSCT is currently restricted to a minority of CMML patients and is associated with a substantial risk of relapse and mortality. Because CMML remains a rare disease, transplantation indications and procedures are largely extrapolated from evidence gathered in more frequent entities such as MDS, or, to a lesser extent, classical MPNs.

Should a cure be sought in all CMML patients?

Patients with CMML may succumb from transformation into acute myeloid leukemia (AML), which occurs in up to 25% of patients and remains difficult to treat (8), but also from complications related to myelodysplastic (MD) features as well as myeloproliferative (MP) features, ie. cytopenias, high white blood cell (WBC) count and splenomegaly respectively. Finally, deaths seemingly unrelated to CMML, such as those from cardio-vascular diseases,

may in fact be indirectly linked to some specific myelomonocytic clones (9, 10). The lack of a clear definition of CMML-attributable mortality is a first methodological hurdle to identify those patients in whom a cure for CMML should be sought.

The 2016 WHO classification acknowledged the existence of MD and MP forms of CMML, reinstating the threshold initially defined by the FAB group of a WBC > 13 x10⁹/L to define MP-CMML. Regardless of the precise cutoff used to define MP-CMML, myeloproliferative traits (high WBC, presence of immature myeloid cells [IMC] and/or splenomegaly) have invariably been shown to worsen CMML prognosis (11).

The WHO classification has also proposed to use the percentage of blasts in the peripheral blood (PB) and bone marrow (BM) to define 3 subgroups with (CMML-0, CMML-1, CMML-2) (2). The prognostic relevance of these cutoffs has been challenged (12), and accurate counting of blasts, which must include promonocytes, remains difficult to standardize (13). Cytogenetics, showing clonal abnormalities in 30% of patients, may also impact prognosis (14, 15). Frequent mutations affecting mostly epigenetic, splicing, and signaling genes are regularly found in CMML patients (4, 16, 17). In order to stratify patients and predict which patients have the higher risk of transformation several scores including clinical (age, splenomegaly, extra-medullary disease) and biological variable (cytopenia, monocytosis, blast, cytogenetics, somatic mutations) have been developed, all of which have been independently validated, with comparable and perfectible predictive power (4-7, 18, 19).

An international consensus has thus yet to emerge (7, 20). However, it is possible to stratify patients into lower risk CMML when survival is expected to extend for several years, and higher risk when expected survival is less than 2 years.

To date, few, if any, treatments have been shown to alter the natural history of CMML.

Though this is likely to be related to the intrinsic biology of the disease and the frequent

frailty of older patients, the almost complete lack of randomized studies dedicated to CMML also contribute to this fact. In the only randomized study published so far, management of myeloproliferation with hydroxurea (HY) rather than with oral etoposide was shown to prolong survival in MP-CMML with adverse risk disease (21). A randomized trial of the hypomethylating agent (HMA) decitabine compared to HY has recently completed accrual in this patient population (EudraCT 2014-000200-10). However, neither cytoreductive agents nor HMAs are curative in CMML (21-24), notably because neither treatment eradicates the founding leukemic clones (17, 25). Thus, HSCT remains the only curative option for CMML.

Who is eligible for transplantation?

Half of CMML patients are older than 75 years and are usually not considered eligible for transplantation due to their age. However, the age limit of HSCT eligibility is a moving frontier, as depicted in the series reported in **Table 1**. Non-relapse mortality (NRM) has been evaluated as acceptable in several series of patients older than 60 or 70 years. Recently, Heidenreich et al have reported on behalf of the European Bone Marrow Transplantation (EBMT) organization a cohort of 313 MDS patients older than 70 years (maximum 78 years) who have received HSCT. There were no CMML patients in this series. NRM was 32% at one year and overall survival (OS) was 34% at 3 years. OS was significantly better in patients with a good performance status and seronegative for cytomegalovirus (26). Aside from assessment of comorbidities (27), performance status estimation by the Karnofsky score and comprehensive geriatric assessment are largely underused in this population while they have shown prognostic impact in across a broad spectrum of cancers, and can guide treatment decision (28). The increasing feasibility of HSCT in older or frail patients results from new conditioning regimens with reduced toxicity and improvements in peri-transplant supportive care, notably anti-infectious therapies. It may further be extended by the development of

familial haplo-identical HSCT using new GVHD prophylaxes, in particular post-transplant cyclophosphamide (PTC) (29). In MDS, haplo-identical donors have been reported as acceptable graft sources by the EBMT group (30). Outcomes of haplo-identical transplants seem at least equivalent to those of transplants from other sources of HLA mismatched donors (unrelated or cord blood) (31). In a single center cohort of 94 AML patients older than 60 years, outcomes of patients transplanted from an haplo-identical donor were not only similar to those from an unrelated donor (UD), but also to those from matched related donors (MRD) (32). The MD Anderson Cancer Center also reported a series of 43 patients with AML or MDS older than 55 years who underwent an haploidentical HSCT followed by PTC. The low incidence of grade 3-4 acute graft-versus-host disease (GVHD, 5%) and of chronic GVHD (9%) further suggests the feasibility of haplo-identical HSCT in older patients with myeloid malignancies, who may be less prone to recover from GVHD (33). However, all of these studies include very few, if any, CMML patients. CMML-specific studies are thus needed to investigate the safety and efficacy of haplo-identical transplantation in this specific patient population. However, increased donor availability will not overcome the ineligibility of many older CMML patients owing to comorbid conditions, patient or physician preferences. Moreover, the timing of transplant must be defined to avoid transplantation in uncontrolled disease or, conversely, in stable CMML not requiring treatment.

When should transplant be indicated?

Transplantation indication should always be envisaged considering alternative treatments which may decrease the risk of transformation to AML transformation and prolong survival, as previously discussed (11). Patnaik et al reported the outcome of a large cohort of 261 CMML patients younger than 65 years, who represent the population most likely to be transplanted. Depending on the prognostic scoring system used, lower and higher risk groups

could be identified, with median overall survivals ranging from more than 5 years in lower risk patients to 24-36 months in the higher risk groups (34). In this cohort accrued in tertiary centers, 20% of patients underwent HSCT, but there was no comparative study examining the potential benefit of HSCT. No study has investigated the benefit of HSCT in CMML, eg. by time-dependent analyses (Mantel-Byar method) (35-37). Thus, recommendations regarding the timing of transplantation in CMML have been extrapolated from MDS data (20, 38).

Decision analyses based on multistate models with various designs, all derived from retrospective cohorts of transplanted and non-transplanted patients, have indeed shown that HSCT induces a gain of survival on in MDS patients with higher risk (intermediate-2 and high) disease according to the MDS International Prognostic Scoring System (IPSS) (35-37, 39). We have reported results from a prospective study showing the significant advantage of HSCT over non-transplant strategies in higher-risk MDS patients. This cohort included 13% of patients with CMML (40). Based on these results, an international expert panel has recommended to apply these rules in CMML, though CMML-specific data is missing (38). This panel thus recommends to transplant CMML patients who are IPSS intermediate-2 or high while transplantation should be delayed in IPSS low/intermediate-1 patients until progression during their disease course. During follow-up, transplant is often discussed in case of hematological worsening, which can be captured by changes CMML-specific prognostic scores including GFM score (4), CMML-specific Prognostic Score (CPSS) (18), its molecular variant CPSS-mol (5), or the Mayo Molecular Model (41) among others, though the dynamic application of either of these scores, ie. beyond diagnosis, has yet to be validated. These scores may prove especially relevant in MP-CMML where IPSS is less reliable. By extension, an expected survival less than 24-36 months estimated by any of published and validated scores may be an indication of HSCT. For practicality purposes, the recently published EHA/ELN guidelines rely on CPSS, which is based on WBC count, blast

percentage, cytogenetics and anemia, thus not requiring molecular data, and defines patients who should be considered for transplant as those with a CPSS risk intermediate-2 or high (20). Decision analyses with transplanted and non-transplanted CMML cohorts will be instrumental in validated this expert consensus (42).

Due to lower non-relapse mortality in younger patients, it may be tempting to consider transplant earlier in these patients. This should be done with caution, as younger patients may have less aggressive disease (4, 34). CMML patients with refractory thrombocytopenia (or less frequently, neutropenia) or those harboring poor risk somatic mutations (eg *ASXL1*, *RUNX1*, *SETBP1* or *NRAS*) may also be considered for transplantation, though evidence supporting the latter remains low (43, 44). Finally, due to their poor prognosis, the rare cases of therapy-related CMML should be considered for HSCT, again with limited evidence to support the benefit of transplantation in these high-risk patients (45).

How to perform HSCT?

The curative potential of HSCT in CMML could theoretically be attributed to clonal replacement, or to an immune graft-versus-leukemia effect (GVL). Itonaga et al, on behalf of the Japan Society for Hematopoietic Cell Transplantation, have elegantly provided evidence for the latter. They reported that chronic GVHD, evaluated in 108 patients in a landmark study, was significantly associated with prolonged survival and lower relapse risk compared with the absence of chronic GVHD in CMML patients not in CR at the time of transplantation (46). However, the development of chronic extensive GVHD was associated with higher risk of NRM. Indeed, the downside of GVL remains the morbidity and mortality related to GVHD. Several groups have reported outcome after HSCT in CMML patients (**Table 1**). The general trend of these studies over the past decades is the transplantation of increasingly older

patients (more than one decade from ~45 years of age in 2015 to >55 years in 2015), the more frequent use of reduced intensity conditioning regimens, of peripheral blood stem cells over bone marrow, and the increasing use of donors other than HLA-matched related donors. Post-transplantation outcomes reported in these cohorts have also improved over time, and is confirmed in one retrospective study spanning over several decades (47). Though it is difficult to demonstrate it, this improvement is unlikely to reflect more stringent patient selection, as the number of transplantations performed for CMML have increased in the same period (48). Collectively, these retrospective series report long-term Relapse-free (RFS) and Overall (OS) survivals between 18 and 50%, with little difference between RFS and OS owing to the dismal prognosis of CMML relapse after transplantation. Relapse and non-relapse causes of mortality (GVHD, infections) equally contribute to this prognosis, with cumulative incidences of relapse and NRM both in the 20-40% range. Both patient (age, comorbidity index and karnofsky score) and disease-related factors (CPSS score and disease status at time of HSCT) predict post-transplant survival, mostly through increased risk of NRM and relapse respectively.

Following a report from the Japanese Bone Marrow Transplantation Registry pointing to the poor prognosis of transplanted MDS/MPN patients harboring RAS pathway mutations (43), Woo et al recently reported a single center study highlighting the impact of CMML molecular features on transplantation outcome. This report stressed the adverse prognostic role of the total mutation burden, notably mutations in epigenetic regulators (44). Specifically, *NRAS* mutations were found to augment the risk of relapse, while less frequent mutations, such as those in *ATRX* or *WT1* were associated with both increased risk relapse and mortality.

None of the published retrospective studies found a significant impact of conditioning intensity on overall survival, variations in NRM being counterbalanced by relapse incidence (**Table 1**). Total body irradiation (TBI) containing conditioning regimens have not been

compared to TBI-free regimen and TBI is not recommended outside of prospective trials. However, a recent phase 2 study with 2 different doses of TBI (300 Gy or 450 Gy) reported minimal toxicity in MDS/MPN patients receiving HSCT after a RIC (49). Most events occurred the first 2 years post-transplant and long-term outcome appears encouraging. These findings are in keeping with long-term follow-up data of 85 CMML patients from a single institution reporting 10-year OS and NRM of 40% and 34%, respectively, with few events beyond the second year post-transplant (44, 50).

Who and how to bridge to transplant?

There is no prospective study on whether and how to lower disease burden prior to transplant in CMML. Therefore, ‘bridging’ therapies are still controversial and recommendations are extrapolated from MDS, where debulking therapies before HSCT are thought necessary in patients with > 10% marrow blast, in order to limit relapse risk (38). CMML data from the EBMT registry may indirectly support this contention, as the only risk factor associated with survival in this series was achievement of CR before transplantation (51). However, 95 patients of the 210 CMML patients in that study had progressed to AML before transplantation, and this conclusion must be taken with caution in non-transformed patients. Kongtim et al have reported a retrospective study including 37 patients who received hypomethylating agents (HMA) and 41 intensive chemotherapy before HSCT. Patients who received HMA had a significantly lower relapse incidence than others (22% vs 35%), translating into higher DFS (43% vs 27%) without significant change in NRM (52). These retrospective results have yet to be confirmed. Indeed, Liu et al, reporting CIBMTR data, showed that transplantation outcome was comparable in treated and untreated CMML patients, regardless of bridging therapy (HMA or IC) (53). It is nevertheless generally admitted that HMAs can be started while transplant procedure is elaborated because single-

agent HMAs are overall well-tolerated in CMML patients, and induce a response in approximately 40-50% of patients, including complete responses in ~25% of cases (22-24, 52-55). Data regarding other bridging therapies in CMML remain scant (56). In patients who are transformed into AML, HSCT without any pre-graft treatment is followed by a dismal outcome and these patients are usually not transplanted without treatment. A recent study from EBMT has reported 4214 patients with MPN or MDS transformed into AML, including 251 patients with previous CMML. Outcome was worse in CMML transformed patients (as compared to MDS) and influenced by remission status at transplantation (57).

How to prevent post-transplant relapse

Hematological relapse after transplantation is often intractable in CMML, because of poor patient's condition and resistant disease. There is almost no data regarding the use of donor lymphocyte infusions in CMML (58, 59). In other myeloid malignancies (MDS and AML), preventive (ie. maintenance) and pre-emptive options have been studied, mostly relying on hypomethylating agents (60). These must often be used in reduced regimens to limit toxicity. Pre-emptive therapy could be guided by longitudinal sensitive monitoring of chimerism on sorted CD34+ cells (61), or by the persistence of detectable clones after transplantation, a finding present in up to two thirds of patients in MDS (62), whose frequency remains unknown in CMML. Currently, no data is available regarding the use of post-transplant HMAs in CMML.

Conclusion

HSCT is commonly proposed in younger patients and appears able to cure approximately one third of patients. Unfortunately, relapse and mortality remain high and efforts should be sustained to improve outcome of these patients. These include pre-transplant and post-

transplant strategies aimed to decrease deleterious GVHD, mortality and relapse in these specific patients. Timing to transplant should also be investigated, hypothesizing that lower risk patients may have less mortality and relapse after HSCT.

Conflicts of interest

RI has received research funding from Novartis, Janssen and Oncoethix (now MSD) and consulting fees from Abbvie, Jazz Pharmaceuticals, Karyopharm, Stemline and Otsuka Pharma. MR has received research funding from Novartis and Neovii.

Authors contribution

MR and RI conceived and wrote the manuscript.

Summary

Though heterogeneous, the prognosis of CMML remains overall poor, with a survival shorter than 5 years in most patients. Even in patients with seemingly ‘low risk’ disease, comparative cause-specific mortality studies are required to study the potential increase of the risk of fatal cardiovascular disease caused by myelomonocytic clones. Though hypomethylating agents are active in CMML, they are not curative. Thus, allogeneic stem cell transplantation should be envisaged in all eligible patients. Eligibility should not rely on a fixed age limit but rather include assessment of frailty, comorbidities, and overall performance status. In the absence of prospective data, current guidelines recommend to transplant patients with higher-risk disease. Decision model analyses are requested to clarify the best timing of transplantation. In patients with significant excess of blasts (>10%), hypomethylating agents can be envisaged to

bridge patients to transplantation. The use of related haplo-identical donors is increasing in myeloid neoplasms, but little data is available in the context of CMML. Data from published registries indicate that, regardless of conditioning regimen intensity, the risk of relapse and of non-relapse mortality remain highly unsatisfactory. Whether the former can be reduced by preventive or pre-emptive strategies, notably using low-dose hypomethylating agents, is one of the many questions that remain to be addressed in prospective trials or registries to improve the cure rate of CMML.

Practice Points.

- Though heterogeneous, the prognosis of CMML remains overall poor, with a survival shorter than 5 years in most patients.
- Even in patients with seemingly ‘low risk’ disease, comparative cause-specific mortality studies are required to study the potential increase of the risk of fatal cardiovascular disease caused by myelomonocytic clones.
- Though hypomethylating agents are active in CMML, they are not curative. Thus, allogeneic stem cell transplantation should be envisaged in all eligible patients.
- Eligibility should not rely on a fixed age limit but rather include assessment of frailty, comorbidities, and overall performance status. In the absence of prospective data, current guidelines recommend to transplant patients with higher-risk disease.

Research Agenda

Decision model analyses are requested to clarify the best timing of transplantation. In patients with significant excess of blasts (>10%), hypomethylating agents can be envisaged to bridge patients to transplantation. The use of related haplo-identical donors is increasing in myeloid

neoplasms, but little data is available in the context of CMML. Data from published registries indicate that, regardless of conditioning regimen intensity, the risk of relapse and of non-relapse mortality remain highly unsatisfactory. Whether the former can be reduced by preventive or pre-emptive strategies, notably using low-dose hypomethylating agents, is one of the many questions that remain to be addressed in prospective trials or registries to improve the cure rate of CMML.

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Table 1. Results of series including 40 patients or more transplanted patients

Reference	Number Period	Median age, years	Donor % MRD	Regimen % MAC	RFS/OS	NRM/RI	Risk factors for mortality (multivariate only)
Kroger 2002 EBMT (63)	50 1988-2000	44	43%	86%	21%/18% At 5-y	55% at 1 y/42% at 2 y	None
Kerbauy 2005 FHRC (64)	43 1990-2004	48	42%	98%	41% 4y/41%	/23% 4y	HCT-CI
Eissa 2011 FHRC (50)	85 1984-2008	52	37%	86%	40%/38% 10y	33%/24% 2y	HCT-CI Hematocrit Age
Park 2013 SFGMTC (47)	73 1992-2009	53	56%	41%	29%/32% at 3y	36%/35% at 3y	HSCT<2004 Splénomegaly
Itonaga 2016 JSHCT (46)	141 1987-2010	49	71%				
Symeonidis 2015 EBMT (51)	513 <2010	53	54%	48%	27%/33%	41%/32% 4y	Disease status at HSCT (CR)
Kongtim 2016 MDACC(52)	83 1991-2013	57			34%/35% at 3y	31% 1y/33% at 3y	Blast count HMA exposure
Liu 2017 CIBMTR (53)	209 2001-2012	57	35%	24%	20%/30% 5y	28%/52% 5y	CPSS KPS BM graft (poor)
Itonaga 2018 JSHCT(65)	159 2001-2012	54	32%	58%	/MRD:50% U-BM: 31% U-CB: 15%	18% 24.5% 38% 42% At 3-y	No MRD

					MismRD: 17% At 3-y		
Woo 2019 FHRC (44)	129 1986-2017	55	29.5%	81%	/38% at 3 years	/28% at 3 years	High risk cytogenetics Gene mutations MDAPS

CIBMTR: Center for International Blood and Marrow Transplant Research; FHRC: Fred Hutchinson Cancer Research Center; EBMT: European European Group for Blood and Marrow Transplantation; HCT-CI: Hematopoietic cell transplantation - comorbidity index (ref (27)); MDACC : MD Anderson Cancer Center; MDAPS: MD Anderson prognostic score, MRD: minima residual disease, JSHCR: the Japan Society for Hematopoietic Cell Transplantation; SFGM-TC: Société Française de greffe de moelle et de thérapie cellulaire. RI Relapse Incidence.