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Prognostic value of a new clinically-based classification system in patients with CMML undergoing allogeneic HCT: a retrospective analysis of the EBMT-CMWP

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Recently a new three-group clinical classification was reported by an International Consortium to stratify CMML patients with regard to prognosis. The groups were defined as follows: (1) Myelodysplastic (MD)-CMML: WBC ≤ 10×10^9/l, circulating immature myeloid cells (IMC) = 0, no splenomegaly; (2) MD/MP (overlap)–CMML: WBC 10–20×10^9/l or WBC ≤ 10×10^9/l but IMC > 0 and/or splenomegaly; (3) Myeloproliferative (MP)-CMML: WBC > 20×10^9/l. By analysing EBMT Registry patients who underwent allo-HCT for CMML between 1997 and 2016, we aimed to determine the impact of this classification on transplantation outcome and to make a comparison with the conventional WHO classification (CMML-0/CMML-1/CMML-2). Patient grouping was based on the data registered at time of transplantation, with IMC replaced by peripheral blasts. Among 151 patients included in the analysis, 38% were classified as MD-CMML, 42% as MD/MP-CMML and 20% as MP-CMML. With a median survival of 17 months in the whole series, MD-CMML patients were distinguished as a low-risk group with higher CR rate at transplant and a longer post-transplant 2-year progression-free survival in comparison to others (44.5% vs 33.5%, respectively), whereas the WHO classification was superior in identifying high-risk patients (CMML-2) with inferior survival outcomes.

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INTRODUCTION

Extreme heterogeneity of chronic myelomonocytic leukemia (CMML) in terms of clinical characteristics both at presentation and during the disease course has inspired a long-lasting debate with regard to categorization among myelodysplastic syndromes [1–4], finally leading to the disease reclassification within the newly created MDS/MPN entity [5]. According to the last WHO classification of myeloid neoplasms [6], patients with CMML should be subclassified in three stages (CMML-0, CMML-1, and CMML-2) according to the percentage of blasts in marrow and in peripheral blood, with a corresponding decreasing survival. Nonetheless, the distinction between a dysplastic (MD-CMML) and a proliferative (MP-CMML) variant of the disease based on the presence of leukocytosis in the latter (WBC > 13×10^9/l), introduced by the French-American-British Cooperative Leukemia Group in 1994 [2], has also been revived due to the recent discovery of molecular differences among the two phenotypic variants [7–9].

In line with clinical and biological characteristics, life expectancy in patients with CMML is also particularly heterogeneous, with survival ranging from few months to several years. Therefore, identification of disease characteristics independently associated with prognosis in order to build clinically useful algorithms has represented a challenging issue for many authors over the last 20 years [10]. Several models based on hematological and clinical variables have been proposed, with none clearly emerging as superior, being all vulnerable to upstaging (i.e., portions of patients classified as low risk with a specific scoring system would be classified in higher risk categories with others) [11]. In most recent years, newly developed prognostic models incorporating gene mutations shown to be associated with inferior survival in CMML have possibly led to a further improvement in our survival prediction capability [12–15]. Worth mentioning, according to the latest retrospective report from the Fred Hutchinson Cancer Research Center in Seattle, among 52 CMML patients who were

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extensively molecularly characterized by next-generation sequencing (NGS) before transplantation, high overall mutation burden (≥10 mutations) and ≥4 mutated epigenetic regulatory genes associated to highest risk of post-transplant relapse, independent from cytogenetics and blast count [16]. More recently, an international multicenter analysis including 240 patients who were undergoing allo-HCT for CMML, all molecularly characterized by NGS, lead to the generation of a CMML transplant score including ASXL1 and/or NRAS-mutated genotype together with bone marrow blasts higher than 2% and comorbidities [17]. However, it should be highlighted that deep sequencing, still difficult to be implemented in a routine manner, is not available world-wide and that molecular signatures in MD- and MP-CMML patients are significantly different in most cases [18, 19]. Therefore, none of these prognostic tools have been yet universally adopted by the scientific community, as their use in clinical practice and clinical trials appears to be still non-standardized.

By hypothesizing that a subdivision of CMML patients in more homogeneous subclasses not only based on the WBC count but also incorporating other clinically discriminating features may yield a more informative CMML stratification system, in 2016 a new three-group clinical classification schema was proposed [20] and leveraged in a very large CMML database ($n = 1622$ patients) previously established by an International Consortium with the aim of validating prognostic models used in CMML clinical practice [11]. The groups were defined as follows: (1) Myelodysplastic (MD)-CMML: WBC $\leq 10 \times 10^9$/l, circulating immature myeloid cells (IMC) = 0, no splenomegaly; (2) MD/MP (overlap)–CMML: WBC $10–20 \times 10^9$/l or WBC $\leq 10 \times 10^9$/l but IMC > 0 and/or splenomegaly; (3) Myeloproliferative (MP)-CMML: WBC $> 20 \times 10^9$/l. As by definition, IMC included all circulating IMC (from myeloblast to band).

With a median overall survival (OS) of 54 (CI 44.8–70.3), 32.3 (CI 29.1–36.8), and 20.2 (CI 17.6–23.3) months, in the MD-, MD/MP- and MP-CMML subgroup of patients, respectively, the new subclassification was indeed shown to independently stratify CMML patients with regard to prognosis by the International Consortium [20] (with MD/MP-CMML as reference, HR were 0.60, 95% CI 0.49–0.73, in MD-CMML, and 1.57, 95% CI 1.36–1.81, in MP-CMML, respectively) and subsequently validated by the MDS Düsseldorf Registry [21].

The aim of this study was to determine the impact of this new classification schema on the outcome of patients undergoing allogeneic hematopoietic cell transplantation (allo-HCT), still representing the only curative option for eligible patients with CMML, and reported to the EBMT Registry. A comparison with the conventional marrow and blood blast percentage-based WHO subclassification system (CMML-0, -1 -2) was also planned. Since time from diagnosis to transplant is highly variable with clinical data being highly dependent both on the disease natural history and on pretransplant treatments, in this study the group classification was based on the data registered at time of transplantation.

PATIENTS AND METHODS

This study, conducted on behalf of the Chronic Malignancies Working Party of the EBMT, was based on registry data from patients who had received a first allo-HCT for the treatment of CMML between 1997 and 2016. Patients transformed into AML at the time of transplantation were excluded. In total, 1614 patients were initially included. With regard to available clinical data, IMC was replaced by peripheral blasts (PB). Since information on marrow blast percentage and spleen assessment was reported only in 27% and 16% of patients (with splenomegaly in 22.5% of them), respectively, the final number of patients with all the required information available and included in the analysis was 151. Survival of this group of patients and the remaining 1463 for whom spleen and PB data were not reported were nearly superimposable (3-year OS 44% and 42%, respectively), therefore validating the assumption that the subpopulation of patients included in the analysis can be considered representative of the whole study population with respect to survival. Informed consent for the data collection was obtained from the patients or legal guardians. All the date were managed according to European regulation on privacy.

Impact of the new classification and WHO classification was analyzed regarding OS and progression-free survival (PFS), which were estimated by the Kaplan–Meier method. Cumulative incidence of relapse (REL) and non-relapse mortality (NRM) after allo-HCT were analyzed by proper methods, considering these outcomes as competing event. The log-rank test was used to compare survival curves and Gray test was used to compare REL and NRM between groups.

Patients' characteristics between the three groups were compared using the χ^2 test for categorical information and the Kruskal-Wallis test for continuous variables.

To assess whether any pretransplant chemotherapy treatment given to achieve CR had an impact on survival outcomes according to the new classification and WHO classification, a multivariate analysis was performed by Cox proportional hazard regression model.

RESULTS

Out of the 151 patients included in the study, the new subclassification schema was able to generate a three groups partition, with a similar allocation in the MD- and MD/MP-CMML (38% and 42%, respectively) and a minority within the MP-CMML group (20%) (Table 1).

Together with patient and transplant characteristics in the whole series and in the three patient groups according to the new subclassification schema—including the p value deriving from the comparison of the three groups, Table 1 displays the distribution of the subclassification-related variables (upper rows).

Median age at transplant was 60 years (range 20–75). With regard to the disease status at transplant (information missing in 2 cases), 39 (26%) were in complete remission, whereas 110 (74%) had active disease. Even though treatment given prior to transplantation were highly heterogeneous (missing in 39 cases), patients who were reported as having received any type of therapy aiming for CR (i.e., intensive AML-like chemotherapy or hypomethylating agents) and those reported as not having been treated or having received only disease-controlling treatments (i.e., oral cytoreductive or low-dose i.v. CT) were precisely shared in equal groups (56 patients each). Concerning the donor type, allo-HCT was performed by an HLA-identical sibling in 30% of the patients, mismatched related in 3%, and unrelated in 67% (fully matched in 61%, mismatched in 6%). Stem cell source was peripheral blood in 90%, bone marrow in 8%, and cord blood in 2%. Reduced-intensity regimens were given to 69.5% of patients, whereas a myeloablative preparative regimen was used in the remaining part.

At transplantation, the three CMML groups differed only by the median BM blast percentage, that increased by shifting from the MD- to the MD/MP, to the MP-CMML group, and, most important, by disease status at transplant, with a proportion of patients being in CR decreasing from 41% in the MD-group, to 23% in the MD/MP, to only 3.4% in the MP group ($p = 0.001$). Even though it was reported only in 112 patients (74%), a significant difference was also located in the pretransplant treatment strategy. Indeed, the proportion of untreated patients was significantly lower in the MD-group than in MD/MP- or MP-groups ($p = 0.05$) and treatments aiming to achieve CR (i.e., intensive AML-like CT or HMAs) were more often administered to MD-CMML patients in comparison to other groups ($p = 0.035$). Differently, percentage of cases getting treatment only to control the disease (mainly oral cytoreductive or low-dose CT) was higher in the MP-CMML group, but the comparison failed to reach the significance, probably due to the low numbers ($p = 0.57$) [Table 1].

Median OS of the entire patient population was 17 months (95% CI 13–38).

Table 1. Patient characteristics at transplant and transplantation modalities according to the new subclassification scheme.

Variable	Overall	MD-CMML	MD/MP-CMML	MP-CMML	*p* value
Total pt number (%)	151 (100%)	57 (38%)	64 (42%)	30 (20%)	–
Total WBC count	Median 7.4×10^9/l (range 1.10–181)				
$<10 \times 10^9$/l	90 (59.5%)	57 (63 %)	33 (34 %)	0	<0.001
$10–20 \times 10^9$/l	31 (20.5%)	0	31 (100%)	0	–
$>20 \times 10^9$/l	30 (20%)	0	0	30 (100%)	–
Splenomegaly	34 (22.5%)	0	25 (73.5 %)	9 (26.5 %)	<0.001
PB-Blasts >0% Median 0 (range 0–18)	51 (33.8%)	0	30 (59%)	21 (41%)	
Male gender	98 (64.9%)	34 (59.6%)	42 (65.6%)	22 (73.3%)	NS
Median age (years)	60 (20–75)	58.8 (20–71)	60.1 (30–73)	62.4 (33.6–75)	NS
Median Hb (g/dl)	10.4 (5.3–15.2)	10.6 (8.0–14.9)	10.2 (6.9–15.0)	10.4 (5.3–15.2)	NS
Median PLT ($\times 10^9$/l)	88 (3–900)	97 (5–553)	84 (3–900)	85.5 (13–403)	NS
Median BM blasts%	4 (0–19)	3 (0–19)	4 (0–19)	5 (0–19)	**0.05**
Interval Dx-Tx (months)	8.3 (1–94)	9.6 (1–83)	8.7 (2.5–94)	6.9 (2–50)	NS
Pre-TX treatment[a]					
None	38 (33.9%)	8 (20.5%)	16 (32%)	14 (60.9%)	**0.005**
Aimed for CR	56 (50%)	25 (64.1%)	24 (48%)	7 (34.4%)	**0.035**
For disease control	33 (21.9%)	10 (25.6%)	14 (28%)	9 (39.1%)	NS
Stage at TX					
CR	39 (26%)	23 (41%)	15 (23%)	1 (3%)	**0.001**
Not in CR	110 (74%)	33 (59%)	49 (77%)	28 (97)	
Median follow-up (months)	42.2 (3.3-241)	47.7 (3.3-241)	40.0 (3.3-229)	46.7 (15-141)	NS
SC source					
BM	12 (8%)	2 (4%)	6 (9%)	4 (13%)	NS
PB	135 (90%)	51 (91%)	58 (91%)	26 (87%)	
CB	3 (2%)	3 (5%)	0	0	
Donor type					
Matched Id Sib	45 (30%)	17 (30%)	20 (31%)	8 (27%)	NS
Unrelated	101 (67%)	37 (65%)	43 (67%)	21 (70%)	
Other	5 (3%)	3 (5%)	1 (2%)	1 (3%)	
Sex donor/recipient					
Female/Male	27 (18%)	9 (16%)	10 (16%)	8 (27%)	NS
Others	124 (82%)	48 (84%)	54 (84%)	22 (73%)	
Donor CMV status					
Positive	76 (51%)	25 (45.5%)	34 (54%)	17 (57%)	NS
Negative	72 (49%)	30 (54.5%)	29 (46%)	13 (43%)	
T-cell depletion[b]					
Yes	81 (56.6%)	29 (52%)	35 (54%)	17 (65%)	NS
No	62 (43.4%)	27 (48%)	26 (43%)	9 (35%)	
Conditioning					
RIC	105 (69.5%)	37 (65%)	48 (75%)	20 (67%)	NS
MAC	46 (30.5%)	20 (35%)	16 (25%)	10 (33%)	
TBI-based cond.					
Yes	48 (32%)	21 (37%)	21 (33%)	6 (20%)	NS
No	101 (68%)	35 (63%	42 (67%)	24 (80%)	

Bold values indicate statistical significance $p < 0.05$. All non significant values were reported as NS.
Hb hemoglobin, *PLT* platelets, *BM* bone marrow, *Dx* diagnosis, *Tx* transplantation, *CR* complete remission, *SC* stem cells, *PB* peripheral blood, *CB* cord blood, *Id Sib* identical sibling, *CMV* cytomegalovirus, *RIC* reduced-intensity conditioning, *MAC* myeloablative conditioning, *TBI* total body irradiation.
[a]Data reported in 112 pts.
[b]In vivo/ex vivo (data reported in 143 pts).

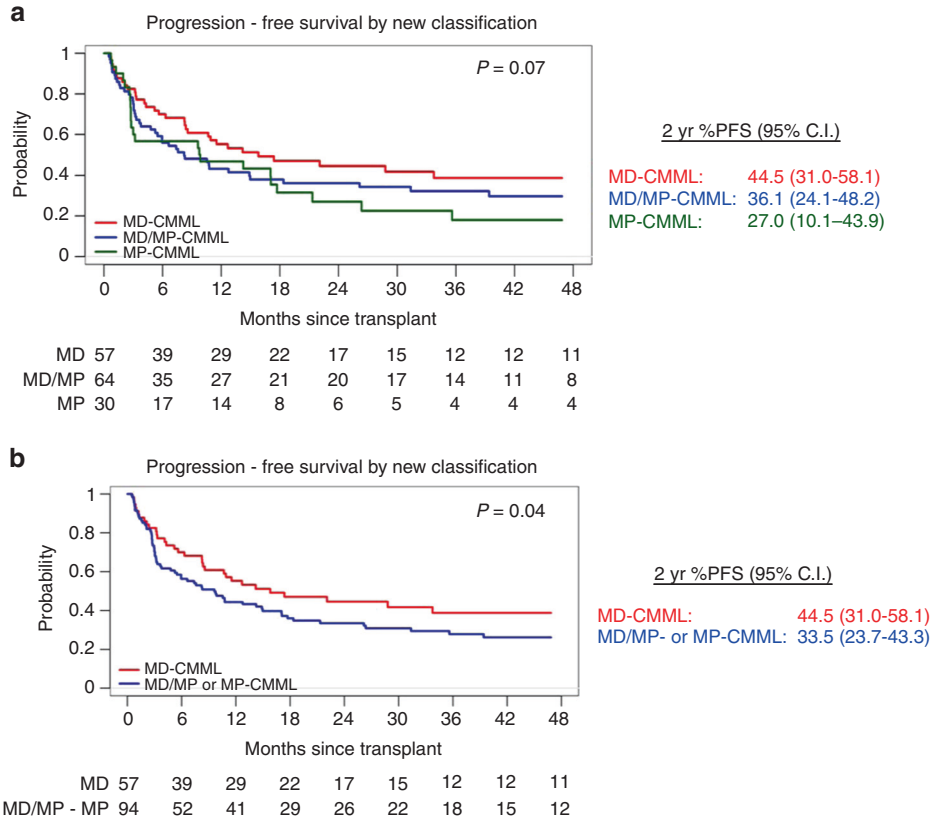

Fig. 1 Progression-free survival by the new clinically based-CMML classification system. a Progression-free survival following allogeneic transplantation according to the new CMML classification (MD- vs MD/MP vs MP-CMML) in 151 patients. **b** Progression-free survival following allogeneic transplantation according to the new CMML classification with the MD/MP- and MP-CMML groups lumped together (vs MD-CMML) in 151 patients.

Table 2. Estimates for 2-year OS and PFS.

New classification		WHO classification			
Category	**2 years % PFS (95% CI)**	**Category**	**2 years% OS (95% CI)**	**Category**	**2 years % PFS (95% CI)**
MD-CMML	44.5 (31.0–58.1)	CMML-0	54.7 (42.9–66.6)	CMML-0	38 (26.2–49.9)
MD/MP-CMML	36.1 (24.1–48.2)	CMML-1	54.1 (38.3–69.9)	CMML-1	49.7 (33.9–56.4)
MP-CMML	27.0 (10.1–43.9)	CMML-2	22.4 (5.7–39.2)	CMML-0/1	42.4 (32.9–51.9)
MD/MP and MP (merged)	33.5 (23.7–43.3)			CMML-2	24.7 (7.8–41.5)

Along the lines of previously reported findings by the International CMML Consortium [20], by univariate analysis the new clinically-based classification was able to stratify patients into subgroups according to survival outcomes, even though a borderline statistical significance was found only for PFS (log-rank test 0.07) (Fig. 1a and Table 2). In fact, possibly due to the relatively small number of patients, no difference was detected in terms of OS, cumulative incidence of relapse and cumulative incidence of NRM. Of note, by lumping together the MD/MP and MP categories, whose curves were almost superimposable, the difference in the 2-year PFS achieved statistical significance ($p = 0.036$) with the MD-CMML group showing a clearly better outcome in comparison to the other groups (44.5% vs 33.5%, respectively) (Fig. 1b and Table 2).

According to the last WHO subclassification, not applicable to 12 patients without information on the marrow blast percentage at the time of transplantation, more than half of the entire population (51%) was allocated in the CMML-0 category, 29% in the CMML-1 and 20% in the CMML-2 category. Distribution of patients grouped according to the WHO subclassification system within the MD-, MD/MP-, and MP categories emerged as uneven. Indeed, cross-tabulation between the new clinically-based and the WHO subclassification systems (Table 3), unveiled the majority of patients classified as MD-CMML as belonging to the CMML-0 WHO grouping (68%), with only 15% and 17% allocated to the CMML-1 and CMML-2 sort, respectively. On the contrary, proportion of patients grouped within the CMML-0 WHO category was only 27% of those classified within the MP-CMML assemble, where the proportion of the CMML-2-categorized patients raised to almost 31%. Within the overlap MD/MP category, the proportion of high-risk patients according to the WHO was similar to the MD-group (16.7%) but those classified within the CMML-0 and CMML-1 categories were almost 47% and 37%, respectively (Table 3).

Unlike the new schema, the WHO subclassification was able to clearly separate CMML-2 as having a significant worse 2-year OS in comparison to the CMML-0/CMML-1 patients (22% vs 55–54%, respectively) (Fig. 2a and Table 2), whereas no significant differences were detected for 2-year PFS (Fig. 2b and Table 2), relapse incidence and NRM. A statistically significant difference also in the 2-year PFS, however, was achieved when patients with

Table 3. Cross-tabulation between the new clinically-based and the WHO subclassification systems ($n = 139$[a]).

WHO category	MD-CMML	MD/MP-CMML	MP-CMML	Total number
CMML-0	36 (67.9%)	28 (46.7%)	7 (26.9%)	71 (51%)
CMML-1	8 (15.1%)	22 (36.7%)	11 (42.3%)	41 (29%)
CMML-2	9 (17%)	10 (16.7%)	8 (30.8%)	27 (20%)
Total number	53	60	26	139

[a]12 patients excluded due to lacking data on marrow blast percentage at the time of transplantation.

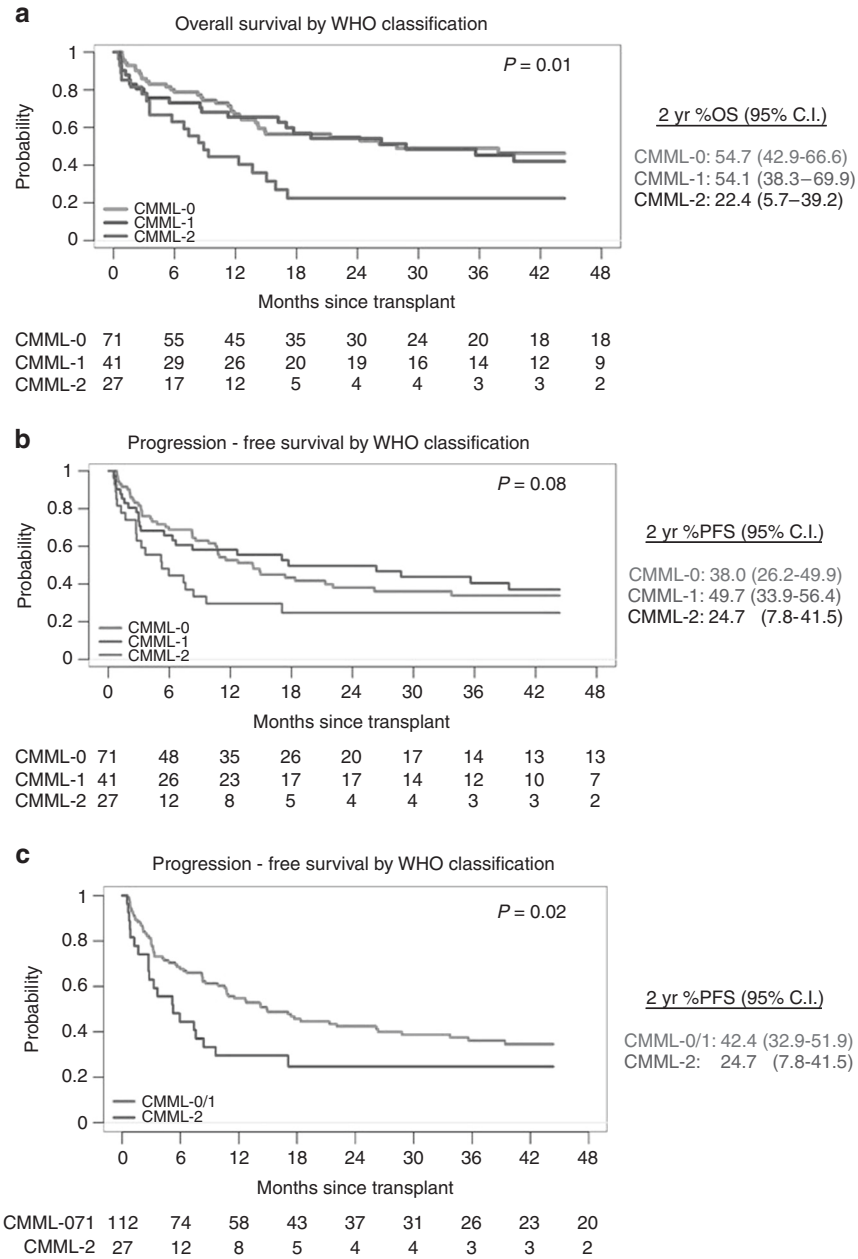

Fig. 2 Overall and progression-free survival by the 2016 WHO CMML classification system. a Overall survival following allogeneic transplantation according to the WHO classification (CMML-0 vs CMML-1 vs CMML-2) in 139 patients. **b** Progression-free survival following allogeneic transplantation according to the WHO classification (CMML-0 vs CMML-1 vs CMML-2) in 139 patients. **c** Progression-free survival following allogeneic transplantation according to the WHO classification with the CMML-0 and CMML-1 groups lumped together (vs CMML-2) in 139 patients.

Table 4. Multivariate analysis including previous CT for OS according to the WHO classification and for PFS according to the new classification.

	HR	Lower 95% CI	Upper 95% CI	*p* value
Overall survival				
CMML-2 vs CMML-0 / 1	2.20	1.24	3.89	0.007
Previous CT[a] Yes vs No	1.22	0.73	2.05	0.443
Progression-free survival				
MD/MP- or MP-CMML vs MD-CMML	1.68	1.01	2.78	0.044
Previous CT[a] Yes vs No	1.24	0.78	1.95	0.360

[a]Chemotherapy treatment given to achieve CR.

CMML-0 and CMML-1 were lumped together and compared with CMML-2 (42.4% vs 24.7%, respectively) (Fig. 2c and Table 2). Noteworthy, similar figures were observed when OS and PFS according to the WHO classification were estimated in all patients with available data on blast percentage at the time of transplantation, comprising 438 cases out of the 1614 included in the study: 2-year OS was 31% in CMML-2 vs 51.2% and 48.6% in CMML-0 and 1, respectively, $p = 0.01$; 2-year PFS was 30.9% in CMML-2 vs 41.9% and 42% in CMML-0 and 1, respectively, $p =$ NS (data not shown).

With regard to the possible pretransplant treatment effect on patient survival outcomes for the different classification groups, univariate comparisons unveiled an overall inferior OS and PFS for patients who were treated aiming to achieve CR, despite a statistical significance was never reached. As it is shown in Table 4, multivariate analysis confirmed the independent association of the CMML-2 WHO category with an inferior OS in comparison to the CMML-0/CMML-1 groups lumped together (HR 2.20), and of the new classification MD-CMML category with a superior PFS in comparison to the MD/MP- /MP-CMML groups lumped together (HR 1.68).

DISCUSSION

The new clinically-based classification proposal of CMML [20] originated by the observation that, so far, for this malignancy none of the available prognostic models centered on hematological and clinical variables has been clearly demonstrated to be superior to the others [11]. Indeed, in CMML, the utmost heterogeneity of patient clinical and laboratory characteristics makes it very difficult to identify independent prognostic factors that may be universally validated as clinically useful in all patients. On the other hand, even though the integration of specific gene mutations in the most recently proposed models has led to a possible improvement of our prognostication capacity [12–17], molecular profiles are very different depending on the disease phenotype, with some mutations being present only in a small proportion of patients (<10%) and/or clearly associated with the proliferative variant of CMML [14]. Unlike in the patient population in which the new subclassification proposal was proven to distinctly stratify the groups of patients according to their OS probability [20], in this study we could only show a significant difference for post-transplantation PFS between MD-CMML and other subgroups. Many reasons may likely explain such findings, including the considerably smaller patient population size, the much shorter median follow-up time, the assumption that presence of circulating blasts could be taken as a functional surrogate for the presence of the whole immature myeloid circulating cell population (data not reported in the EBMT Registry)—the latter being originally included among criteria for the new CMML subclassification—and last but not least, a possible allo-transplantation effect on the pretransplant risk category allocation. Indeed, worth to be emphasized, this EBMT-CMWP study aimed to verify the power of the new clinically-based subclassification, determined at the time of transplantation, in stratifying patients for transplant outcomes. Further elements to be considered are that, besides a tendency for a longer median time of the interval between diagnosis and transplantation for MD-CMML group in comparison to the MD/MP- and MP-CMML ones, though not statistically significant, at the time of transplantation some patients with MP- or MD/MP-CMML might have been downstaged in the MD/MP- or MD-category as a consequence of the pretransplant administered treatments, possible determinants in lowering total WBC count and potential disappearance of circulating blasts and/or spleen size normalization. Alike, with regard to the WHO subclassification, some patients allocated in the higher categories at diagnosis might have been downstaged at transplantation as a consequence of pretransplant treatments. Nonetheless, after having taken into account all the above-mentioned factors, the following have to be highlighted as novel and possibly useful findings of the present study:

(1) For patients having achieved a CR disease status as a consequence of pretransplant treatments, the probability of being classified as MD-CMML at the time of transplantation appears to be much higher in comparison to other categories. This observation, however, is expected as per the definition of hematological CR (i.e., marrow blasts <5% and CBC within normal ranges), where instead patients classified in the MD/MP- and MP-CMML groups and reported in CR before transplantation could only have a marrow CR. The significantly better post-transplantation PFS in the MD-CMML group, therefore, appear to be in line with the finding previously reported by our EBMT-CMWP, where the presence of CR at transplantation was the only significant prognostic factor for survival in a retrospective analysis of a much larger series of CMML allotransplanted patients ($n = 513$) [22].
(2) In agreement with the results reported by the International CMML Consortium [20], the new clinically-based CMML subclassification system appears to be more efficient in the identification of patients belonging to a low-risk category (i.e., MD-CMML) in comparison to the WHO subclassification, whereas the latter appears to be more suitable for the stratification of high-risk patients (i.e., CMML-2). Precisely, the WHO subclassification in our series was unable to show any difference both in OS and PFS between CMML-0 and CMML-1 patients, possibly suggesting that under the 10% and 5% thresholds, respectively in the marrow and in peripheral blood, blast percentage is not significantly associated with survival after transplantation.

CONCLUSIONS

In this retrospective analysis performed on a limited number of patients who underwent allo-HCT for CMML, we show that a simple clinically–based subclassification system including WBC

count, presence of circulating blasts and presence of splenomegaly assessed at the time of transplantation is able to identify a subgroup of myelodysplastic phenotype patients with a significantly higher pre-transplantation CR rate and a significantly better PFS in comparison to patients with overlap or proliferative characteristics. On the contrary, the WHO subclassification system, based on marrow and blood blast percentage, appears superior in identifying patients with high-risk disease and inferior post-transplantation survival outcomes.

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AUTHOR CONTRIBUTIONS

FO wrote the manuscript, designed the study, and interpreted the data. GS and SI designed the study, performed the statistical analyses, interpreted the data, and edited the manuscript. LK provided EBMT Registry Data. MR, PH, and IYA designed the study, interpreted the data, and edited the manuscript. AR, KS, NK, JS, GS, JC, XP, LR, JHB, JF, JP, US, HCS, YB, SM, ED, AG, SZ, BL, and RR reviewed the manuscript and provided clinical data. All authors approved the final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL APPROVAL

The current study has been approved by the scientific board of the CMWP of the EBMT.

ADDITIONAL INFORMATION

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