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The CIBMTR score predicts survival of AML patients undergoing allogeneic transplantation with active disease after a myeloablative or reduced intensity conditioning: a retrospective analysis of the Gruppo Italiano Trapianto Di Midollo Osseo

Leukemia (2013) 27, 2086–2091; doi:10.1038/leu.2013.208

The prognosis of acute myeloid leukemia (AML) patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) not in complete remission is poor, although this treatment option remains the only possible curative approach for these patients. A retrospective analysis recently published by European Group for Blood and Marrow Transplantation (EBMT) on primary refractory AML allotransplanted with unrelated donors showed that factors associated with improved survival were the following: having received fewer than three courses of induction therapy, the presence of a lower percentage of bone marrow blast infiltration at transplant and patient cytogeneric seronegativity. This allowed the development of a scoring system that identified four groups with survival rates ranging between 44 and 0%. However, the largest retrospective analysis on AML patients with active disease at the time of conditioning (1673 patients) has been conducted by the Center for International Blood and Marrow Transplant Research (CIBMTR), which, on five pretransplantation variables (duration of first complete remission (CR) <6 months, circulating blasts, donor other than HLA-identical sibling, Karnofsky score less than 90 and poor-risk cytogenetics), also set up a pre-HSCT score defining a 3-year overall survival (OS) ranging from 42 to 6%. Here we report outcome data obtained in Italy in a similar cohort of AML patients (523 patients) allotransplanted with active disease. The primary aim of the study was to externally validate the CIBMTR score in a multicenter, retrospective study setting, evaluating the prognostic power of the score in a wider patient population that included not only those receiving a myeloablative conditioning (MAC) but also those treated with a reduced-intensity conditioning (RIC). (as detailed in Supplementary Table 1) and those grafted with a cord blood. Twenty Italian centers belonging to the Gruppo Italiano Trapianto di Midollo Osseo (GITMO) participated in this retrospective observational study. Data were retrieved from the GITMO database, and missing data or specific queries were asked to each center. Overall, 523 patients (no one enrolled into prospective trials) from 20 GITMO centers were included in this study.
| Characteristics                              | Univariate analysis | Multivariate analysis |
|---------------------------------------------|---------------------|-----------------------|
|                                             | N (%)               | Overall survival at 3 years | P-value | Hazard ratio | 95% CI | P-value |
| **Age at transplant**                      |                     |                       |         |             |        |         |
| ≤47                                         | 269 (51)            | 0.759                 | 1.00    |              |        |         |
| > 47                                        | 254 (49)            |                       | 1.01    | 0.83–1.23    | 0.924  |         |
| **Sex**                                     |                     |                       |         |             |        |         |
| Male                                        | 265 (51)            | 0.15                  | 1.00    |              |        |         |
| Female                                      | 258 (49)            | 0.18                  | 0.90    | 0.75–1.07    | 0.233  |         |
| **Diagnosis**                               |                     |                       |         |             |        |         |
| De novo                                     | 370 (71)            | 0.16                  | 1.00    |              |        |         |
| Secondary to MDS/CMML                      | 120 (23)            | 0.02                  | 1.01    | 0.79–1.29    | 0.053  |         |
| Secondary to CMN/therapy-related            | 28 (5)              | 0.08 at 1.5 yrs       | 1.87    | 1.21–2.88    | 0.005  |         |
| Missing                                     | 5 (1)               |                       | 3.80    | 1.49–9.71    | 0.005  |         |
| **Disease status at transplant**            |                     |                       |         |             |        |         |
| PRF                                         | 166 (32)            | 0.10                  | 1.00    |              |        |         |
| Untreated I relapse                        | 44 (8)              | 0.26                  | 1.94    | 0.72–5.19    | 0.187  |         |
| Untreated MDS-related AML                  | 27 (5)              | 0.57                  | 0.85    | 0.33–2.18    | 0.737  |         |
| Refractory I relapse                       | 179 (34)            | 0.16                  | 1.95    | 0.77–4.92    | 0.156  |         |
| > I relapse                                 | 77 (15)             | 0.12                  | 2.38    | 0.91–6.19    | 0.076  |         |
| Missing                                     | 30 (6)              |                       | 2.49    | 0.96–6.49    | 0.061  |         |
| **Previous transplant in CR**               |                     |                       |         |             |        |         |
| Autologous                                  | 58 (55)             | 0.21                  | 1.00    |              |        |         |
| Allogeneic                                  | 47 (45)             | 0.12                  | 1.00    |              |        |         |
| **Duration first CR**                       |                     |                       |         |             |        |         |
| <6 months                                   | 137 (46)            | 0.09                  | 1.00    |              |        |         |
| ≥6 months                                   | 136 (45)            | 0.24                  | 1.32    | 1.02–1.70    | 0.032  |         |
| Missing                                     | 27 (9)              | 0.31                  | 1.31    | 0.84–2.03    | 0.230  |         |
| **Chemotherapy cycles for primary refractory** |                 |                       |         |             |        |         |
| 1                                           | 34 (20)             | 0.18                  | 1.00    |              |        |         |
| ≥2                                          | 126 (76)            | 0.07                  | 1.68    | 1.12–2.52    | 0.013  |         |
| Missing                                     | 6 (4)               | 0.86                  | 1.31    | 0.34–2.17    | 0.755  |         |
| **Cytogenetics/ molecular biology**         |                     |                       |         |             |        |         |
| Favorable/intermediate I                    | 235 (45)            | 0.20                  | 1.00    |              |        |         |
| Intermediate II/adverse                     | 178 (34)            | 0.11                  | 1.29    | 1.05–1.59    | 0.014  |         |
| Missing                                     | 110 (21)            | 1.03                  | 1.03    | 0.79–1.34    | 0.819  |         |
| **Blasts at transplant**                    |                     |                       |         |             |        |         |
| BM blasts <25% or no blasts in PB          | 197 (38)            | 0.26                  | 1.00    |              |        |         |
| BM blasts ≥25% or any level in PB          | 218 (42)            | 0.12                  | 1.46    | 1.19–1.80    | 0.000  |         |
| Missing                                     | 108 (20)            | 1.30                  | 1.30    | 0.98–1.73    | 0.072  |         |
| **Karnofsky performance score at transplant** |                 |                       |         |             |        |         |
| <90                                         | 177 (34)            | 0.11                  | 1.00    |              |        |         |
| ≥90                                         | 284 (54)            | 0.21                  | 1.52    | 1.24–1.87    | 0.000  |         |
| Missing                                     | 62 (12)             | 1.47                  | 1.47    | 1.10–1.96    | 0.010  |         |
| **Graft type**                              |                     |                       |         |             |        |         |
| Bone marrow                                 | 148 (28)            | 0.12                  | 1.0515  |              |        |         |
| Peripheral stem cells                       | 342 (65.5)          | 0.18                  | 0.6215  |              |        |         |
| Cord blood                                  | 33 (6.5)            | 0.16                  | 0.59    | 1.08–2.34    | 0.020  |         |
| **Donor-recipient HLA-match**               |                     |                       |         |             |        |         |
| Identical sibling /matched unrelated        | 362 (69)            | 0.19                  | 1.00    |              |        |         |
| Cord blood                                  | 33 (6)              | 0.16                  | 1.59    | 1.28–1.98    | 0.000  |         |
| Haplo/mismatched unrelated                  | 128 (25)            | 0.09                  | 1.59    | 1.28–1.98    | 0.000  |         |
| **Donor-recipient sex**                     |                     |                       |         |             |        |         |
| M-M/F-F                                     | 270 (52)            | 0.18                  | 1.00    |              |        |         |
| M-F                                         | 147 (29)            | 0.18                  | 1.00    |              |        |         |
| F-M                                         | 99 (19)             | 0.13                  | 1.00    |              |        |         |
| Missing                                     | 7 (1)               |                       | 1.00    |              |        |         |
study. Patient, disease and transplant characteristics are listed in Table 1. The median age was 47.6 (range 18–72). At time of conditioning, AML was defined as primary refractory (patients not achieving a CR after the first induction chemotherapy), MDS-related (untreated patients with \( \geq 20\% \) bone marrow blasts), untreated first relapse (patients not receiving a salvage chemotherapy before conditioning), refractory first relapse (patients not achieving a remission after a salvage chemotherapy), second or further relapse (untreated or refractory to further salvage chemotherapy).

A marrow blast infiltration \( \geq 25\% \) or any level of peripheral blood (PB) blasts was found in 42%. Donors were HLA identical sibling or matched unrelated in 69%, a family or unrelated mismatched in 25% and a cord blood unit in 6%. More than 60% of patients received a MAC and 37% received a RIC program. A T-cell depletion was performed in vivo in 37% and ex vivo in 8% of patients as described elsewhere.9–11

Neutrophil and platelet engraftment was achieved in 87% of patients after a median of 17 (9–63) and 18 (2–117) days, respectively. Acute graft versus host disease (GVHD) was registered in 46% of patients (grade \( \geq 2 \) in 60% of cases), whereas chronic GVHD occurred in 31% (judged as extended in half of cases). The 1-year cumulative incidence of acute GVHD was 39%, being 28% for grade 1–2 and 11% for grade 3–4, whereas that of chronic GVHD was 20%. In all, 75 patients (14%) died early, within 45 days from allotransplant, 282 patients (54%) achieved CR after allotransplant. Of these latter patients 155 (55%) relapsed after a median time of 3.7 months (0.4–83). Among the 427 patients who died after HSCT (82%), 91 were leukemia free. The median follow-up of the whole patient cohort was 5.3 months (0.10–133),

![Table 1](https://example.com/table1.png)

**Table 1.** (Continued )

| Characteristics | Univariate analysis | Multivariate analysis |
|-----------------|---------------------|----------------------|
|                 | N (%) | Overall survival at 3 years | P-value | Hazard ratio | 95% CI | P-value |
| Donor anti-CMV antibodies | | | | | |
| Positive | 311 (60) | 0.17 | 0.8963 | |
| Negative | 160 (31) | 0.18 | |
| Missing | 51 (9) | 1.00 | |
| Patient anti-CMV antibodies | | | | | |
| Positive | 421 (80) | 0.18 | 0.1908 | |
| Negative | 61 (12) | 0.17 | |
| Missing | 41 (8) | 1.00 | |
| Conditioning regimen | | | | | |
| RIC | 191 (37) | 0.16 | 0.9511 | |
| MAC | 324 (62) | 0.17 | |
| Missing | 8 (2) | 0.96 | 0.79–1.17 | 0.690 | |
| Type of conditioning | | | | | |
| Busulfan/TBI > 600 Gy | 288 (55) | 0.13 | 0.1614 | |
| Others | 219 (42) | 0.19 | |
| Missing | 16 (3) | 1.12 | 0.50–2.53 | 0.780 | |
| GVHD prophylaxis | | | | | |
| Ex vivo T-cell depletion | 42 (8) | 0.05 | 0.0370 | |
| (Tacrolimus or CsA) + MTX ± other | 307 (59) | 0.18 | |
| (Tacrolimus or CsA) ± other | 77 (15) | 0.17 | |
| Other | 50 (10) | 0.25 | |
| Missing | 47 (9) | | |
| T-cell depletion in vivo | | | | | |
| No T-cell depletion in vivo | 249 (48) | 0.19 | 0.1220 | |
| ATG/ALG/Campath | 196 (37) | 0.17 | |
| Missing | 78 (15) | | |
| Acute GVHD | | | | | |
| No | 273 (52) | 0.15 | | | |
| Yes | 228 (44) | | | | |
| Grade 1 | 91 (40) | 0.21 | 0.0000 | |
| Grade 2 | 71 (31) | 0.28 | | |
| Grade 3 | 41 (18) | 0.07 | | |
| Grade 4 | 25 (11) | 0.04 | | |
| Missing | 22 (4) | | | |
| Chronic GVHD | | | | | |
| No | 286 (55) | 0.10 | 0.0000 | |
| Yes | 126 (24) | 0.39 | | |
| Missing | 111 (21) | | | |

Abbreviations: ALG, anti-lymphocyte-globuline; AML, acute myeloid leukemia; ATG, anti-tymocyte-globuline; BM, bone marrow; CMML, chronic myelomonocytic leukemia; CMN, chronic myeloproliferative neoplasm; CMV, cytomegalovirus; CR, complete remission; CsA, cyclosporine; GVHD, graft versus host disease; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; MTX, methotrexate; PB, peripheral blood; PRF, primary refractory; RIC, reduced-intensity conditioning; TBI, total body irradiation.

Letters to the Editor
whereas that of survivors was 26 months (1–133) with 96 patients alive and 77 leukemia free. At 3-years, the cumulative incidence of non-relapse mortality (NRM) was 16%. The leukemia-free survival (LFS, calculated from the time of CR after transplantation to death for any cause or relapse)\(^1\) was 21%, whereas the OS was 16% (Figure 1).

Eight pre-HSCT variables that negatively influenced survival were identified by univariate and multivariate analysis: an AML secondary to a previous CMN or a therapy-related AML \((P = 0.005)\), a relapsed AML with a first CR duration \(< 6\) months \((P = 0.032)\), a primary refractory AML after \(\geq 2\) chemotherapy cycles pre-HSCT \((P = 0.013)\), an intermediate II/adverse cytogenetics \((P = 0.014)\), BM blasts \(\geq 25\%\) or any level of PB at HSCT \((P = 0.000)\), a Karnofsky performance score \(< 90\) \((P = 0.000)\), a mismatched related/unrelated donor \((P = 0.020)\) and the presence of patient anti-CMV antibodies \((P = 0.015)\) (Table 1). To elucidate the impact of the conditioning regimen on main outcomes, the clinical characteristics of patients who received a RIC \((n = 191)\) were compared with those of patients receiving a MAC \((n = 332)\) or a reduced-intensity (RIC, solid line, \(n = 191)\) conditioning regimen. (c) Incidence of relapse in patients receiving a MAC (dotted line) or RIC (solid line) conditioning regimen. (d) Non-relapse mortality (NRM) in patients receiving a MAC (dotted line) or RIC (solid line) conditioning regimen. (e) A CIBMTR scoring system validation with overall survival according to the risk score. The hazard ratio and the overall survival for score 2 and 3 proved significantly worse than 1 and 2.

Figure 1. (a) Kaplan–Meier estimates of overall survival, (OS, solid line, \(n = 523)\) and leukemia-free survival (LFS, dotted line, \(n = 282)\). (b) Kaplan-Meier estimates of overall survival for patients receiving a myeloablative (MAC, dotted line, \(n = 332)\) or a reduced-intensity (RIC, solid line, \(n = 191)\) conditioning regimen. (c) Incidence of relapse in patients receiving a MAC (dotted line) or RIC (solid line) conditioning regimen. (d) Non-relapse mortality (NRM) in patients receiving a MAC (dotted line) or RIC (solid line) conditioning regimen. (e) A CIBMTR scoring system validation with overall survival according to the risk score. The hazard ratio and the overall survival for score 2 and 3 proved significantly worse than 1 and 2.
The OS of our patient cohort was finally analyzed according to the risk categories defined by the CIBMTR score (Table 1). In the more favorable prognostic group of 28 patients (10.5%) (score 0), the OS at 3 years was 40% (HR 1.00). Similarly to what observed in the original CIBMTR cohort, in the intermediate-I risk group (score 1) (n = 76, 28%) the OS at 3 years was 26% (HR 1.39, P = 0.142), whereas in the intermediate-II risk group (score 2) (n = 77, 28.5%) and the poor risk group (score 3) (n = 90 patients, 33%) the OS was 18% (HR 1.58, P = 0.040) and 5% (HR 2.83, P = 0.000), respectively (Figure 1).

Therefore, the long-term overall- and event-free survival observed in this group of patients are remarkably in keeping with those reported by CIBMTR and EBMT. In the GITMO database, the observed in this group of patients are remarkably in keeping with respectively (Figure 1).

P and the poor risk group (score 3) (n whereas in the intermediate-II risk group (score 2) (n = 77, 28.5%) and the poor risk group (score 3) (n = 90 patients, 33%) the OS was 18% (HR 1.58, P = 0.040) and 5% (HR 2.83, P = 0.000), respectively (Figure 1).

Therefore, the long-term overall- and event-free survival observed in this group of patients are remarkably in keeping with those reported by CIBMTR and EBMT. In the GITMO database, the five easy-to-apply pre-HSCT variables defining the CIBMTR score were available contemporarily for only 52% of the patients analyzed, so that the score could be attributable only to a total of 271 patients. Nonetheless, we can reasonably confirm that the CIBMTR score is an effective and reproducible approach for predicting survival of this group of AML patients at poor prognosis.

However, some important differences between patients analyzed by CIBMTR, EBMT and GITMO must be underlined. First, in the CIBMTR study, only patients who received a total body irradiation or busulfan-based MAC regimen were analyzed, whereas patients receiving a Fludarabine-based or any other RIC regimen were excluded. In the GITMO cohort, a RIC was given to 37% of patients. In addition, we included also patients receiving a cord blood transplant (6%), as well as patients with an untreated, MDS-related AML (5%). In the EBMT experience, patients were limited only to those with a primary refractory AML and those who received an unrelated donor transplant. Despite these differences, our results confirm the EBMT analysis as to the negative impact of a positive serology of the patient while the negative impact of a heavy leukemic bone marrow infiltration and the role of the total number of chemotherapy cycles before the conditioning regimen. The prognostic role played by CMV was also underlined in both analysis, although the GITMO results point out the negative impact of a positive serology of the patient while the EBMT suggests that of the negative patient serology. In this study, patients with an AML secondary to a previous CMN or therapy-related had a remarkably poor outcome, and this turned out to be a novel significant adverse prognostic factor. However, the poor outcome of AML developing in patients with a previous history of chronic myeloproliferative disorders is not surprising. Importantly, by univariate and multivariate analysis, the conditioning intensity did not have an impact on 3-year OS and LFS on the entire GITMO cohort. Although the retrospective nature of the study suggests caution, this result may represent a new finding and it is tempting to speculate that for chemo-resistant disease the MAC may not be effective anyhow, so that only patients with an active graft versus leukemia reaction may actually benefit from the transplant.

In conclusion, we have validated the CIBMTR prognostic score in this relatively large patient population with active AML at allotransplant. It may therefore be possible to identify the patients with advanced AML, who may benefit more from an allogeneic transplant, and this may be relevant for patient counseling. The fact that RIC regimens could also be effective is encouraging for the older patient population, who may be eligible for this procedure.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

ACKNOWLEDGEMENTS
This work was supported in part by grants from Associazione Italiana per la Ricerca contro il Cancro (AIRC) and Associazione Italiana Lotta alla Leucemia (AIL).
Clonal mast cell disease not meeting WHO criteria for diagnosis of mastocytosis: clinicopathologic features and comparison with indolent mastocytosis

Leukemia (2013) 27, 2091–2094; doi:10.1038/leu.2013.227

Mastocytosis results from a clonal proliferation of morphological and immunophenotypically abnormal mast cells. Extracutaneous involvement is commonly seen in adults, and the diagnosis of systemic mastocytosis (SM) is established as per World Health Organization (WHO) criteria. Patients are frequently referred with episodic symptoms of ‘mast cell activation’ (MCA), wherein an underlying allergic or autoimmune disorder cannot be identified. In the absence of cutaneous involvement by mastocytosis, the next step typically is to determine whether SM is present. Increasingly, during such testing, patients who do not satisfy full diagnostic criteria for SM are identified; the major criterion (compact infiltrates of ≥15 mast cells) is not met; instead, only one or two minor criteria are met. Previous reports have implicated such patients in the context of idiopathic anaphylaxis or anaphylaxis following Hymenoptera sting; however, the full spectrum of clinical presentation is currently not understood. Given the paucity of data regarding these patients, variously described as having monoclonal MCA syndrome (MMCAS) or pre-diagnostic indolent SM (ISM), we sought to describe their clinicopathologic characteristics, and to compare them with ISM cases, or those with MCA symptoms without clonal mast cells.

This study was approved by the Mayo Clinic Institutional Review Board and adhered to the tenets of the Declaration of Helsinki. We retrospectively studied consecutive patients who were referred to our institution for evaluation for SM. Every patient had symptoms attributed by the referring physician as being related to mast cell degranulation. The diagnostic assessment included a bone marrow biopsy with tryptase immunostaining and mast cell immunophenotyping for CD25/CD2 expression by flow cytometry and/or immunohistochemistry. Bone marrow histology was reviewed by two experienced hematopathologists (DC and CAH) and/or immunohistochemistry.

In the sub-diagnostic SM group, none met the major SM diagnostic criterion (that is, those meeting 1–2 minor criteria for SM only), ISM (that is, those meeting WHO diagnostic criteria for SM) and those with MCA symptoms without clonal mast cells. In the group with sub-diagnostic SM, those with cutaneous mast cell infiltration (for example, urticaria pigmentosa) were excluded. Similarly, patients with non-ISM were also excluded from the study. All statistical analyses considered clinical and laboratory parameters obtained at time of referral. Differences in the distribution of continuous variables between categories were analyzed by either Mann–Whitney or Kruskal–Wallis tests. Patient groups with nominal variables were compared by χ² test.

A total of 83 patients were studied; 40 patients had ISM, 21 had sub-diagnostic SM and 22 had MCA symptoms without clonal mast cells. Clinical and laboratory characteristics at the time of referral are shown (Table 1).

In the ISM group, 63% exhibited cutaneous mast cell infiltration, 90% were KITD816V positive and 77% exhibited a baseline serum tryptase level >20 ng/ml (Table 1). Thirty-three patients (83%) exhibited multifocal compact mast cell infiltrates in bone marrow biopsy sections plus at least one minor criterion, whereas the remainder satisfied ≥3 minor criteria.

In the sub-diagnostic SM group, none met the major SM diagnostic criterion (that is, compact mast cell infiltrates). Instead, the bone marrow mast cell infiltrate as identified by tryptase and in some cases CD117 immunostaining, was uniformly sparse with an interstitial distribution of individual mast cells (Figure 1). The estimated mast cell burden was <5%, and more typically <1% of total marrow cellularity. Twelve patients (57%) demonstrated a population of overtly spindle-shaped mast cells and two patients (11%) had a baseline serum tryptase level of >20 ng/ml (Table 1). In terms of the WHO minor diagnostic criteria, 17 patients (81%) with sub-diagnostic SM met only one criterion (KITD816V alone = 7 or mast cell CD25/CD2 expression alone = 10). An additional four patients met two minor criteria (that is, KITD816V plus mast cell CD25/CD2 expression). Notably, three patients each did not undergo testing or had inconclusive results after screening for KITD816V or mast cell CD25/CD2 expression—here, even if the additional test were positive, criteria for SM would not have been met (that is, would have met <3 minor diagnostic criteria). A serum tryptase level above the normal range (>11.5 ng/ml) and >20 ng/ml was noted on at least one occasion during follow-up in 61% and 37% of sub-diagnostic