ARTICLE

Redefining and measuring transplant conditioning intensity in current era: a study in acute myeloid leukemia patients

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Abstract

To address limitations of the currently used reduced-intensity/myeloablative conditioning (RIC/MAC) classification scheme we aimed to develop a tool that can capture more standardized the conditioning intensity of allogeneic hematopoietic cell transplantation (HCT). We assigned intensity weight scores for frequently used conditioning regimen components and used their sum to generate the transplant conditioning intensity (TCI) score. We retrospectively tested the impact of TCI on 8255 adult (45–65 years) acute myeloid leukemia patients who underwent HCT in first complete remission. A Cox model for early nonrelapse mortality (NRM) yielded a 3-group TCI risk scheme (low, intermediate, high) with respective TCI scores of [1–2], [2.5–3.5] and [4–6]. On multivariate modeling, TCI grouping was highly and better predictive for early (day 100 and 180) NRM, 2-year NRM and relapse (REL) as compared with the RIC/MAC classification. Validation was done on 200 bootstrap samples. Moreover, TCI scoring enabled the identification of a distinct subgroup of RIC and MAC conditioning regimens with an intermediate TCI [2.5–3.5] score that had identical outcomes and which are frequently referred as "reduced toxicity conditioning". TCI scheme provides an improvement of the RIC/MAC classification. We propose TCI as a new tool to define and measure the conditioning regimen intensity.

Introduction

The pre-transplantation conditioning regimen plays a central role in allogeneic hematopoietic cell transplantation (HCT) since it is essential for the engraftment of the infused graft [1]. Nowadays, a lot of conditioning regimens exist which fulfill this requirement but differ substantially in their intensity profile. The latter characteristic is directly related to early morbidity, nonrelapse mortality (NRM) and long term disease control. Transplant regimens were initially categorized by their intensity as "standard" myeloablative conditioning (MAC) and reduced-intensity conditioning (RIC) or nonmyeloablative (NMA) based on the expected duration of the pancytopenia (irreversible, prolonged, minimal) and on the requirement for stem cell support (essential, required, optional) [2–4]. Since these criteria are rather vague, the European Society for Blood and Marrow Transplantation (EBMT) [5] and the Center for International Blood and Marrow Transplant Research (CIBMTR) [6] proposed in 2009 operational definitions for stratification of transplant conditioning as MAC or RIC based on the total dose of the alkylating agents and/or total body irradiation (TBI) used. Briefly, RIC usually includes a purine analog and an alkylating agent or TBI at a dose which is generally reduced by at least ≥30% of the classical MAC regimens [7, 8]. The RIC/MAC classification model has served as a reliable clinical tool offering safer transplantation in older and unfit patients and is widely referenced in the scientific literature, but has never been updated or more precisely

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defined though transplantation practices change and new conditionings are now used.

The limitations of the current RIC/MAC classification scheme in the current era are exemplified by the arbitrary use of terms such as "reduced toxicity conditioning" or "sequential conditioning" by many authors [9, 10]. Novel drugs (e.g., thiotepa and optimized forms of drugs e.g., treosulfan) with reduced nonhematological toxicity are frequently used nowadays and their different toxicity profiles are not considered in the current RIC/MAC classification scheme [11, 12]. RIC/MAC operational rules ignore the additional intensity of purine analogs used for immunoablation (e.g., fludarabine, clofarabine) or of disease-specific drugs used to achieve reduction in relapse risk (e.g., cytarabine, etoposide), and thus important prognostic information is lost [13].

Therefore, we sought to develop a tool that can define and standardize the intensity of a conditioning regimen more effectively than existing nomenclature. We assigned intensity weight scores for frequently used conditioning regimen components and used the sum of the individual weights to generate the Transplant Conditioning Intensity (TCI) score. In the present study, we retrospectively tested the TCI in a large cohort of adult acute myeloid leukemia (AML) patients and compared it with the standard RIC/MAC stratification scheme in predicting outcomes.

Materials and methods

TCI score development

Components for which the myeloablative doses are defined by the EBMT [5] and/or CIBMTR [6] (TBI, busulfan, melphalan, treosulfan and thiotepa) were assigned one of three dose intensity levels by using the threshold myeloablative dose as the intermediate dose level and assigning all doses below or above to the low or high dose level, respectively. For each of these components, we assigned a weighted score of 1 for the lower dose and an extra point for every dose level, except for thiotepa which was assigned an added weighted score of 0.5 for each level because of its reduced nonhematological toxicity [11]. Components for which a "myeloablative dose" definition does not exist, such as purine analogs, carmustine, etoposide and cytarabine, were considered in terms of the dose ranges used in practice and were assigned an additional weight of 0.5 for each dose level. An international expert panel (listed in authorship) participated in a workshop organized by the Acute Leukemia Working Party (ALWP) of the EBMT and provided scientific and clinical guidance for the TCI score development. Agents and their integer weights are shown in Table 1. The TCI score for a specific conditioning regimen is based on the sum of the weights for each component given any day before the graft infusion.

Transplant data

This was a retrospective multicenter analysis. Data were provided by the ALWP of the EBMT registry in which > 500 transplant centers report annually all consecutive HCTs after patient's authorization via informed consent and approval of the study from ALWP EBMT general assembly. We focused on patients aged between 45 and 65 years with a diagnosis of AML (de novo or secondary) who had received an allogeneic HCT at first complete remission (less than 5% bone marrow [BM] blasts at transplant). Other inclusion criteria included time from diagnosis to HCT < 18 months, transplant between 2005 and 2017, peripheral blood stem cell (PBSC) or BM graft from a matched sibling

Table 1 Intensity weighted scores for common components included in transplantation conditioning regimens.

Component	Dose level			Added points for each dose level
	Low	Intermediate	High	
TBI fractionated (Gray)	≤5	6–8	≥9	1
Busulphan (mg/kg)	≤6.4 iv & ≤8 po	9.6 iv & 12 po	12.8 iv & 16 po	1
Treosulfan (g/m2)	30	36	42	1
Melphalan (mg/m2)	<140	≥140	≥200	1
Thiotepa (mg/kg)	<10	≥10	≥20	0.5
Fludarabine (mg/m2)	≤160	>160		0.5
Clofarabine (mg/m2)	≤150	>150		0.5
Cyclophosphamide (mg/kg)	<90	≥90		0.5
Carmustine (mg/m2)	≤250	280–310	≥350	0.5
Cytarabine (g/m2)	<6	≥6		0.5
Etoposide (mg/kg)	<50	≥50		0.5

iv intravenously, *po* per os, *TBI* total body irradiation.

donor (MSD) or 9–10/10 HLA-matched unrelated donor (MUD) and availability of detailed conditioning information. MAC or RIC status was reported by the transplant centers according to EBMT operational definitions [5] and guidelines (MED-AB Manual, 31/1/2018) and was reconfirmed for every patient.

Statistical analysis

Early nonrelapse mortality (NRM) at day (d) 180 was used as the first endpoint for estimating the impact of TCI. Results of NRM at d 100 were also given as this endpoint is often reported in the literature. Secondary endpoints included NRM and relapse incidence (REL) at 2 years, overall survival (OS) and leukemia-free survival (LFS). A grouping scheme based on TCI score was created by merging the underrepresented scores (< 30 patients) with contiguous scores. A Cox proportional hazards model for NRM at day 180 including the TCI score as an ordered variable was used to merge the classes that did not improve the likelihood of the model, using a p value of 0.10. Univariate analyses were performed using the Gray's test for cumulative incidence functions (NRM, REL) and the log-rank test for OS and LFS. Patient, disease, and transplant-related characteristics for the TCI groups were compared using the χ^2 statistic for categorical variables and the Kruskal–Wallis test for continuous variables. All variables differing significantly ($p < 0.05$) between the TCI groups or factors known to be relevant from the literature were included in the final Cox model. Internal validation of models was performed using the bootstrap resampling method [14]. The model was refitted for each of the 200 bootstrap samples. Confidence intervals of c-statistics using either TCI or RIC/MAC categorization were estimated from the 200 bootstrap samples and used to calculate a p value for the difference, using the paired t-test. Statistical analyses were performed with SPSS 24.0 (SPSS Inc., Chicago, IL, USA) and R 3.4.0 (R Core Team 2017. R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/).

Results

Patient and transplant characteristics

The patient and transplant characteristics of the 8255 AML patients (median age 55.6 years, range 45–65) are shown in Table 2. All patients were transplanted in first complete remission. The conditioning regimens used are listed in Supplementary Table 1 and comprised RIC in 61% and MAC in 39% of the patients (Fig. 1a). Acute graft-versus-host disease (GVHD) II-IV occurred in 17.2% (95% confidence interval [CI]: 16.3–18.1), acute GVHD III-IV in

8.2% (95% CI: 7.7–8.9), chronic GVHD in 39.1% (95% CI: 38–40.3) and extensive chronic GVHD in 17.3% (95% CI: 16.4–18.2). The 2-year outcomes for the entire cohort were as follows: NRM 17% (95% CI: 16.1–17.8), REL 26.7% (95% CI: 25.7–27.7), LFS 56.4% (95% CI: 55.2–57.5) and OS 61.6% (95% CI: 60.4–62.7). Causes of NRM are given in Supplementary Table 2.

TCI scores

The TCI score ranged from 1 to 6 (median 2.5) with a median of 2 (range, 1–5.5) in the RIC group and 4 (range, 2.5–6) in the MAC group ($p < 0.001$). Those scores relating to very few patients were pooled with patient groups assigned to subsequent or previous scores: 26 patients with a TCI score of 1 were combined with patients with a score of 1.5 while 42 patients with TCI scores > 4.5 (27, 13 and 2 patients with TCI scores 5.0, 5.5 and 6.0, respectively) were combined with patients with a score equal to 4.5. After merging TCI values that did not improve the likelihood of the Cox model for NRM at d 180 ($p ≥ 0.10$), three TCI groups (low, intermediate and high) were derived with respective scores of [1,2], [2.5–3.5] and [4–6].

The distribution according to TCI score group was as follows: 38% had a low [1, 2], 41% an intermediate [2.5–3.5] and 21% a high [4–6] TCI score regimen (Fig. 1a). Table 2 shows patient, disease and transplant characteristics of TCI groups. Nearly all patients with a high TCI score [4–6] regimen received MAC (94%) and all low TCI [1,2] patients received RIC (100%), indicative of good concordance between RIC/MAC and low/high TCI score grouping. Notably, the intermediate TCI [2.5–3.5] group included patients with MAC and RIC regimens in about the same fraction (54 and 46%, respectively). As expected, there was an inverse relationship between age and TCI score with a median age of 58.1 years, 56.2 years and 50.7 years for the low, intermediate, and high TCI groups, respectively ($p < 0.001$). Patients in the low TCI group were more likely to have a low KPS and high HCT-CI ($p < 0.0001$). Graft failure was low and did not differ between TCI groups ($p = 0.68$). Figure 1b shows the TCI score for classical and commonly used conditioning regimens.

Performance of the TCI

In univariate analysis, d 100 and d 180 NRM for patients in the low TCI [1,2] group was statistically different as compared with intermediate TCI [2.5–3.5] ($p < 0.0001$) and high TCI [4–6] group patients ($p < 0.0001$) (Table 3). Similar results were found when patients between 45 and 55 years of age (47% of the cohort) and 55–65 years of age (53% of the cohort) were analyzed separately (Fig. 2) or when the analysis was restricted to the group of patients ($n = 220$)

Table 2 Patient and transplant characteristics.

Variable	Entire cohort	TCI [1,2]	TCI [2.5–3.5]	TCI [4–6]	p value*
N (%)	8255 (100%)	3123 (37.8%)	3371 (40.8%)	1761 (21.3%)	
Follow-up (months)					
Median (IQR)	42.4 (18.7–76.2)	42.8 (19.6–76.6)	40.2 (18.7–72.7)	47.6 (16.6–82.1)	0.11
Age at HCT (years)					
Median (range) [IQR]	55.6 (45–65) [50.8–60.1]	58.1 (45–65) [53.5–61.7]	56.2 (45–65) [51.7–60.2]	50.7 (45–64.9) [47.9–54.2]	<0.01
45–55	3858 (46.7%)	1018 (32.6%)	1444 (42.8%)	1396 (79.3%)	<0.0001
≥55	4397 (53.3%)	2105 (67.4%)	1927 (57.2%)	365 (20.7%)	
Year of HCT					
Median (range) [IQR]	2013 (2005–2017)	2013 (2005–2017)	2013 (2005–2017)	2012 (2005–2017)	<0.01
Time diagnosis to HCT (months)					
Median (range) [IQR]	4.98 (0.8–18) [3.9–6.34]	5.1 (0.1–18) [4.1–6.5]	4.9 (0.4–17.7) [3.8–6.3]	4.9 (0.8–17.8) [3.8–6.3]	<0.0001
Conditioning					
MAC	3203 (38.8%)	0 (0%)	1552 (46.0%)	1651 (93.7%)	<0.0001
RIC	5052 (61.2%)	3123 (100%)	1819 (54.0%)	110 (6.2%)	
Donor					
MSD	4405 (53.4%)	1612 (51.6%)	1675 (49.7%)	1118 (63.5%)	<0.0001
UD 10/10	3068 (37.2%)	1233 (39.5%)	1325 (39.3%)	510 (29.0%)	
UD 9/10	782 (9.5%)	278 (8.9%)	371 (11.0%)	133 (7.6%)	
Patient sex					
Male	4318 (52.4%)	1596 (51.2%)	1762 (52.3%)	960 (54.7%)	0.06
Female	3927 (47.6%)	1524 (48.9%)	1607 (47.7%)	796 (45.3%)	
Missing	10	3	2	5	
Donor sex					
Male	5042 (61.5%)	1896 (61.14%)	2100 (62.65%)	1046 (59.9%)	0.14
Female	3157 (38.5%)	1205 (38.9%)	1252 (37.35%)	700 (40.1%)	
Missing	56	22	19	15	
Sex matching					
Not Female- > Male	6750 (82.1%)	2574 (82.9%)	2770 (82.34%)	1406 (80.4%)	0.09
Female- > Male	1470 (17.9%)	533 (17.2%)	594 (17.66%)	343 (19.6%)	
Missing	35	16	7	12	
Cytogenetics**					
Good	220 (2.67%)	74 (2.4%)	94 (2.8%)	52 (3.0%)	<0.0001
Interm	3479 (42.1%)	1541 (49.3%)	1372 (40.7%)	566 (32.1%)	
Poor	1225 (14.8%)	490 (15.7%)	518 (15.4%)	217 (12.3%)	
NA/failed	3331 (40.3%)	1018 (32.6%)	1387 (41.2%)	926 (52.6%)	
Type of AML					
de novo	6835 (82.8%)	2524 (80.8%)	2756 (81.8%)	1555 (88.3%)	<0.0001
Secondary AML	1420 (17.2%)	599 (19.2%)	615 (18.2%)	206 (11.7%)	
Source of stem cells					
BM	894 (10.8%)	189 (6.1%)	386 (11.5%)	319 (18.11%)	<0.0001
PBSC	7361 (89.2%)	2934 (94.0%)	2985 (88.6%)	1442 (81.9%)	
KPS at HCT					
<80	282 (3.6%)	151 (5.2%)	97 (3.0%)	34 (2.0%)	<0.0001
≥80	7505 (96.4%)	2751 (94.8%)	3108 (97.0%)	1646 (98.0%)	
Missing	468	221	166	81	

Table 2 (continued)

| Variable	Entire cohort	TCI [1,2]	TCI [2.5–3.5]	TCI [4–6]	p value*
<90	1680 (22.2%)	790 (28.2%)	632 (20.0%)	258 (15.9%)	<0.0001
≥90	5899 (77.8%)	2007 (71.8%)	2524 (80.0%)	1368 (84.1%)	
Missing	676	326	215	135	
HCT-CI score					
HCT-CI = 0	2305 (57.0%)	763 (52.5%)	1043 (55.8%)	499 (68.6%)	<0.0001
HCT-CI = 1 or 2	881 (21.7%)	326 (22.5%)	422 (22.6%)	133 (18.3%)	
HCT-CI ≥ 3	861 (21.3%)	363 (25%)	403 (21.6%)	95 (13.1%)	
Missing	4208	1671	1503	1034	
In vivo TCD					
No	3459 (42.2%)	1344 (43.2%)	1099 (32.8%)	1016 (58.4%)	<0.0001
Yes	4742 (57.8%)	1767 (56.8%)	2251 (67.2%)	724 (41.6%)	
Missing	54	12	21	21	
Patient CMV					
CMV negative	2398 (29.5%)	1008 (32.7%)	970 (29.2%)	420 (24.5%)	<0.0001
CMV positive	5727 (70.5%)	2078 (67.3%)	2353 (70.8%)	1296 (75.5%)	
Missing	130	37	48	45	
Donor CMV					
CMV negative	3577 (44.5%)	1448 (47.3%)	1471 (44.7%)	658 (38.8%)	<0.0001
CMV positive	4469 (55.5%)	1612 (52.7%)	1821 (55.3%)	1036 (61.2%)	
Missing	209	63	79	67	
Engraftment					
Graft failure	114 (1.4%)	39 (1.3%)	50 (1.5%)	25 (1.4%)	0.68
Engrafted	8035 (98.2%)	3052 (98.4%)	3265 (98.1%)	1718 (98.3%)	
Graft loss	30 (0.4%)	11 (0.4%)	15 (0.5%)	4 (0.2%)	
Missing	76	21	41	14	

AML acute myeloid leukemia, *CMV* cytomegalovirus, *BM* bone marrow, *HCT* allogeneic hematopoietic cell transplantation, *HCT-CI* HCT-comorbidity index, *IQR* interquartile ration, *KPS* Karnofsky Performance Status, *MAC* myeloablative conditioning, *MSD* matched sibling donor, *NA* not available, *PBSC* peripheral blood stem cells, *RIC* reduced-intensity conditioning, *TCD* T-cell depletion, *TCI* transplant conditioning intensity score, *UD* unrelated donor.

*p values between TCI groups; **Cytogenetic risk according to MRC classification (Blood 2010;116:354–65).

with good risk cytogenetics (d 180 NRM = 1.5%, 11.9% and 14.6% in TCI [1,2], [2.5–3.5] and [4–6], respectively, $p = 0.02$). TCI scores also predicted overall NRM and REL with the differences being observed in both age groups (Table 3). In multivariate analysis, there was a monotonic increase in risk of early NRM with each TCI group from low to high (Table 4). Patients in the intermediate TCI regimen group had a significantly higher NRM at d 100 (HR 2.0; 95% CI, 1.54–2.59, $p < 0.0001$) and at d 180 (HR 1.63; 95% CI, 1.35–1.98, $p < 0.0001$) when compared with the low TCI group. The HRs for d 100 and d 180 NRM in patients receiving a high TCI [4–6] score regimen was 3.06 (95% CI, 2.24–4.16, $p < 0.0001$) and 2.31 (95% CI, 1.83–2.92, $p < 0.0001$) when compared with low TCI [4–6] and 1.53 (95% CI, 1.19–1.97, $p = 0.001$) and 1.41 (95% CI, 1.15–1.73, $p = 0.0008$) when compared with the intermediate TCI [2.5–3.5] group, respectively. TCI grouping was also highly significantly associated with overall NRM

and REL (Table 4). Compared with low TCI group patients, the relapse risk for patients receiving intermediate and high score TCI regimens was significantly decreased with an HR of 0.81 (95% CI, 0.73–0.89, $p < 0.0001$) and 0.70 (95% CI, 0.61–0.8, $p < 0.0001$), respectively. The HRs for NRM for the intermediate (1.27; 95% CI, 1.12–1.44) and the high TCI (1.44; 95% CI 1.22–1.69) groups also remained highly predictive ($p = 0.0003$ and $p < 0.0001$ relative to the low TCI group, respectively). We re-run the multivariable Cox model in the patients with available HCT-CI information ($n = 4047$, 50% of the entire cohort) and TCI remained significantly associated with early NRM, NRM and REL (Supplementary Table 3).

When the RIC/MAC categorization was used in the multivariate model, RIC/MAC also predicted early NRM, overall NRM and REL (Supplementary Table 4). In both classification systems (TCI or RIC/MAC), early NRM was also independently influenced by age, performance status
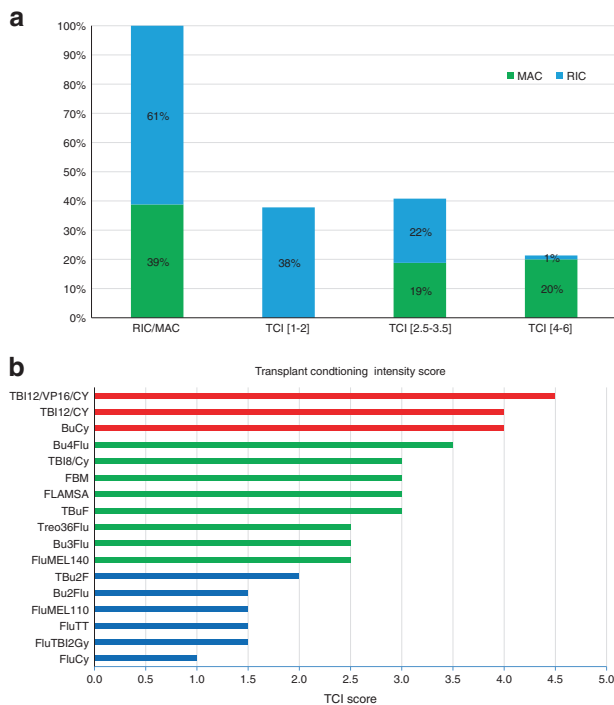
Fig. 1 **Distribution of conditioning regimes according to their intensity. a** The graphic shows the distribution of the conditioning regimens used in 8255 patients with AML transplanted at first complete remission according to their intensity. RIC/MAC is according to EBMT definition. Transplant Conditioning intensity (TCI) score was calculated for each individual transplant and was allocated to the low TCI [1,2], intermediate TCI [2.5–3.5] or high TCI [4–6] group. **b** The graphic shows the calculated TCI score for classical and commonly used conditioning regimens. The different colors denote the different TCI groups (green: low TCI [1,2], blue: intermediate TCI [2.5–3.5] and red: high TCI [4–6]). TBI(12)/VP16/CY = 12 Gray TBI, Etoposide 50 mg/kg, Cyclophosphamide 60 mg/kg; TBI(12)/CY = 12 Gray TBI, Cyclophosphamide 120 mg/kg; BuCy = Busulfan 4 days 3.2 mg/kg/day IV or 4 mg/kg/day oral), Cyclophosphamide 120 mg/kg; Bu(4/3/2)Flu = Busulfan 4,3,2 days, Fludarabine 90–150 mg/kg; FBM = Fludarabine 120 mg/kg, Carmustine (BCNU) 300 mg/m2, Melphalan 110 mg/m2; FLAMSA = Fludarabine 120 mg/kg, Busulfan 2 days (or TBI 4 Gray), Aracytine 8 g/m2, Cyclophosphamide 80 mg/kg and Amsacrine 400 mg/m2; TBu(3/2)F = Busulfan 3/2 days, Thiotepa 5 mg/kg, Fludarabine 120–150 mg/kg; Treo36Flu = Treosulfan 36 mg/m2, Fludarabine 120–150 mg/m2; FluMEL (140/110) = Fludarabine 90–150 mg/kg, Melphalan 110/140 mg/m2; FluTBI (2 Gy) = Fludarabine 90 mg/kg, TBI 2 Gray; FluTT = Fludarabine 90 mg/kg, Thiotepa 15 mg/kg; FluCy = Fludarabine 90–120 mg/kg, Cyclophosphamide 50 mg/kg.

and donor and overall NRM was in addition predicted by female to male transplant, in vivo T-cell depletion, year of HCT and CMV serostatus (Table 4). Relapse associated with secondary AML, poor cytogenetics, unrelated donor, female to male transplant and a PBSC graft. On multivariate analysis, neither LFS or OS were associated with conditioning intensity stratified by TCI (Table 4) or RIC/MAC status (Supplementary Table 4).

Validation of the TCI and comparison with RIC/MAC

The TCI continued to be strongly associated with early NRM, overall NRM and REL on 200 bootstrap samples. The predictive ability of the TCI estimated by *c*-statistics is shown in Table 5. Compared with the model including RIC/MAC with bootstrapping, the *c*-statistics for early and overall NRM, REL, LFS and OS were significantly better ($p < 0.0001$ for NRM, REL and LFS, $p = 0.007$ for OS).

The intermediate TCI [2.5–3.5] group

We focused on the intermediate TCI [2.5–3.5] group ($n = 3371$, median age 56.2 years) in which nearly half (54%) of the patients had received MAC and the other 46% received a RIC regimen (Fig. 1a). Within this group, the median TCI score of RIC patients was 2.5 (range, 2.5–3.5) and of MAC patients was 3.5 (range, 2.5–3.5) ($p < 0.0001$). In the univariate analysis, d 100 NRM, d 180 NRM, overall NRM, REL, LFS, and OS were not different between patients who had received a TCI [2.5–3.5]-RIC or a TCI [2.5–3.5]-MAC regimen (Table 6).

Discussion

Risk assessment for allogeneic HCT is based on scores and indices developed specifically to measure comorbidity burden (e.g., HCT-CI) [15], disease risk (e.g., DRI) [16] and conditioning regimen intensity (RIC/MAC). As transplantation practices change, these prognostic tools need to be updated [17]. In this study, we evaluated a new tool for a better and more standardized stratification of transplant conditioning intensity, which we favor to replace the current RIC/MAC classification scheme.

The TCI was developed in a way that refines the currently used RIC/MAC classification system. We used the generally accepted myeloablative threshold doses to define the middle drug intensity [5, 6]. We incorporated in the TCI components that are not considered in the current RIC/MAC classification (purine analogs, cyclophosphamide, cytarabine, etoposide and carmustine), but we intentionally gave them a lower integer weighting adhering to the RIC/MAC consensus that these drugs add less to the regimen intensity stratification. All of these agents have a well-documented toxicity and antileukemic activity and thus it is very likely that they influence NRM and REL [13]. Thus, TCI is generally based on consensus RIC/MAC definitions and can be easily and reproducibly calculated for every regimen.

Although TCI scoring stratified the regimens on a continuum (Fig. 1b), it is unlikely that the clinical impact of TCI is linear. We evaluated TCI categories with possible

Table 3 Univariate analysis of transplant outcomes.

	N	NRM @ day100	NRM @ day180	NRM	Relapse
Entire population					
TCI [1,2]	3123	3.2% [2.6–3.8]	6.8% [6–7.8]	14.9% [13.6–16.3]	30.6% [28.9–32.3]
TCI [2.5–3.5]	3371	6.3% [5.6–7.2]	10.5% [9.5–11.6]	17.9% [16.6–19.3]	25.3% [23.7–26.8]
TCI [4–6]	1761	7.6% [6.5–8.9]	12% [10.5–13.6]	18.7% [16.8–20.7]	22.2% [20.2–24.3]
p value		<0.0001	<0.0001	0.0001	<0.0001
RIC	5052	4.6% [4–5.2]	8.4% [7.6–9.2]	16.4% [15.3–17.5]	28.2% [26.9–29.5]
MAC	3203	6.8% [5.9–7.7]	11.2% [10.1–12.3]	17.9% [16.5–19.3]	24.1% [22.6–25.7]
p value		<0.0001	<0.0001	0.23	<0.0001
45–55 years					
TCI [1,2]	1018	2.8% [1.9–3.9]	6.1% [4.7–7.7]	13.4% [11.3–15.8]	30% [27.1–33]
TCI [2.5–3.5]	1444	4.9% [3.9–6.1]	8.1% [6.8–9.6]	14% [12.2–16]	24.3% [22–26.7]
TCI [4–6]	1396	7.2% [5.9–8.6]	10.7% [9.1–12.4]	17.1% [15.1–19.3]	22% [19.7–24.4]
p value		<0.0001	0.0002	0.03	<0.0001
RIC	1714	3.9% [3–4.9]	7.2% [6–8.5]	14% [12.3–15.8]	27.6% [25.4–29.8]
MAC	2144	6.2% [5.3–7.3]	9.6% [8.4–10.9]	15.8% [14.2–17.5]	22.9% [21–24.8]
p value		0.001	0.006	0.20	0.0002
55–65 years					
TCI [1,2]	2105	3.3% [2.6–4.2]	7.2% [6.1–8.3]	15.7% [14.1–17.4]	30.9% [28.9–33]
TCI [2.5–3.5]	1927	7.4% [6.3–8.6]	12.4% [10.9–13.9]	20.8% [18.9–22.8]	26% [23.9–28.1]
TCI [4–6]	365	9.3% [6.6–12.6]	17.1% [13.4–21.2]	24.7% [20.2–29.5]	22.8% [18.4–27.4]
p value		<0.0001	<0.0001	<0.0001	<0.0001
RIC	3338	4.9% [4.2–5.7]	9% [8–10]	17.6% [16.3–19]	28.6% [26.9–30.2]
MAC	1059	7.9% [6.3–9.6]	14.3% [12.2–16.5]	22.1% [19.5–24.8]	26.6% [23.8–29.4]
p value		0.0002	<0.0001	0.004	0.17

Values are given in % and [range].

NRM nonrelapse mortality. Others see Table 2.
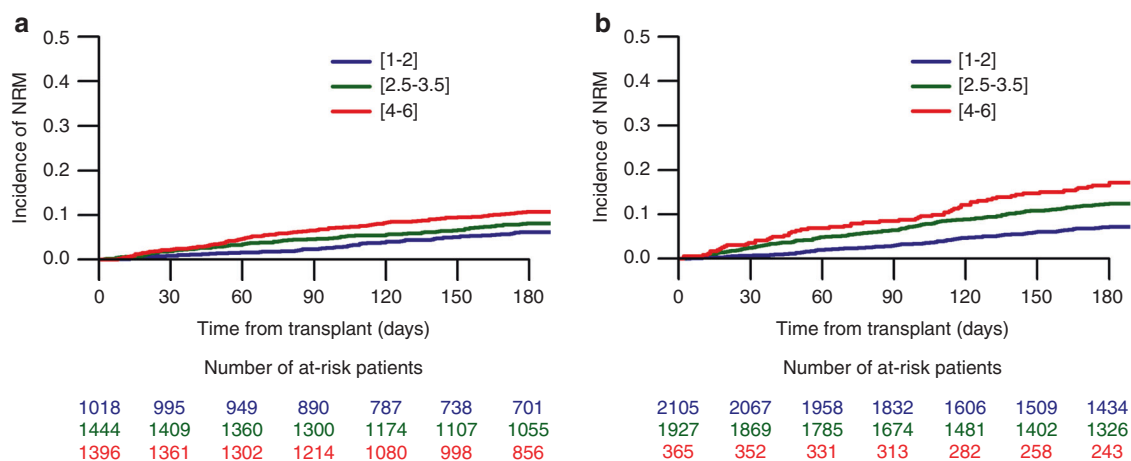
Fig. 2 Early nonrelapse mortality (NRM) according to TCI. a Early NRM in the subgroup of patients aged 45–55 years at transplant ($n = 3858$). **b** Early NRM in patients aged between 55 and 65 years ($n = 4397$).

clinical relevance regarding early NRM, which yielded a 3-group risk scheme. While a concordance between low/high TCI and RIC/MAC groups was observed, the intermediate TCI group, which captured nearly half of the patients, included both RIC and MAC regimens in the same fraction (Fig. 1a). Thus, TCI and the RIC/MAC grouping schemes differ substantially from each other and can be used as separate classification systems.

Table 4 Multivariate analysis of transplant outcomes according to TCI stratification of conditioning regimen intensity.

Variable		NRM @ day100	NRM @ day180	NRM	Relapse	LFS	OS
TCI	[1,2]	1 (reference)	1	1	1	1	1
	[2.5–3.5]	2 (1.54–2.59), <0.0001	1.63 (1.35–1.98), <0.0001	1.27 (1.12–1.44), 0.0003	0.81 (0.73–0.89), <0.0001	0.96 (0.89–1.04), 0.28	1.02 (0.94–1.1), 0.68
	[4–6]	3.06 (2.24–4.16), <0.0001	2.31 (1.83–2.92), <0.0001	1.44 (1.22–1.69), <0.0001	0.7 (0.61–0.8), <0.0001	0.93 (0.84–1.03), 0.17	1 (0.89–1.11), 0.97
Patient age	(per 10 years)	1.34 (1.09–1.64), 0.005	1.45 (1.24–1.69), <0.0001	1.43 (1.28–1.6), <0.0001	1.07 (0.98–1.17), 0.12	1.2 (1.12–1.28), <0.0001	1.25 (1.16–1.34), <0.0001
Year of HCT		0.98 (0.95–1.01), 0.29	0.99 (0.96–1.01), 0.29	0.98 (0.96–0.99), 0.02	1 (0.99–1.02), 0.70	0.99 (0.98–1), 0.22	0.99 (0.98–1), 0.10
Sec. AML		1.07 (0.83–1.38), 0.59	0.89 (0.72–1.09), 0.25	1.04 (0.9–1.19), 0.63	1.27 (1.14–1.42), <0.0001	1.18 (1.08–1.28), 0.0002	1.15 (1.05–1.25), 0.003
Cytogenetics	Good	1 (reference)	1	1	1	1	1
	Interm	0.80 (0.43–1.48), 0.48	0.81 (0.51–1.3), 0.39	0.89 (0.64–1.26), 0.52	1.54 (1.07–2.2), 0.02	1.19 (0.93–1.52), 0.16	1.26 (0.96–1.65), 0.09
	Poor	0.925 (0.48–1.77), 0.81	0.89 (0.54–1.46), 0.64	0.99 (0.7–1.43), 0.99	3.22 (2.24–4.64), <0.0001	2.02 (1.57–2.6), <0.0001	2.1 (1.6–2.77), <0.0001
	NA/failed	1.2 (0.65–2.21), 0.56	1.13 (0.71–1.79), 0.61	1.14 (0.81–1.59), 0.46	1.74 (1.21–2.49), 0.003	1.42 (1.11–1.81), 0.005	1.53 (1.17–2), 0.002
KPS at HCT	≥90	0.63 (0.50–0.79), <0.0001	0.67 (0.57–0.80), <0.0001	0.72 (0.63–0.81), <0.0001	0.99 (0.9–1.11), 0.94	0.87 (0.80–0.94), 0.0007	0.84 (0.77–0.91), <0.0001
Donor	MSD	1 (reference)	1	1	1	1	1
	UD 10/10	1.64 (1.28–2.09), <0.0001	1.64 (1.36–1.98), <0.0001	1.52 (1.33–1.73), <0.0001	0.79 (0.71–0.87), <0.0001	1.01 (0.93–1.09), 0.82	1.07 (0.99–1.17), 0.10
	UD 9/10	2.01 (1.45–2.8), <0.0001	2.25 (1.75–2.88), <0.0001	1.94 (1.61–2.34), <0.0001	0.83 (0.70–0.97), 0.02	1.16 (1.03–1.31), 0.02	1.27 (1.12–1.44), 0.0002
Female to male		0.86 (0.65–1.14), 0.30	1.03 (0.83–1.26), 0.81	1.28 (1.12–1.47), 0.0004	0.8 (0.70–0.9), 0.0003	0.97 (0.88–1.06), 0.5	1.04 (0.95–1.14), 0.41
PB vs BM		0.98 (0.72–1.35), 0.91	1.06 (0.82–1.36), 0.67	1.16 (0.97–1.39), 0.11	0.84 (0.73–0.97), 0.02	0.96 (0.86–1.07), 0.44	1.02 (0.91–1.15), 0.69
in vivo TCD		0.97 (0.77–1.24), 0.82	0.85 (0.71–1.01), 0.07	0.771 (0.68–0.88), <0.0001	1.03 (0.93–1.14), 0.53	0.93 (0.86–1), 0.06	0.91 (0.84–0.99), 0.03
Patient CMV		1.04 (0.82–1.31), 0.76	1.14 (0.95–1.36), 0.17	1.16 (1.02–1.32), 0.02	1.02 (0.92–1.13), 0.68	1.07 (0.99–1.16), 0.09	1.08 (0.99–1.17), 0.08
Donor CMV		1.03 (0.83–1.28), 0.81	1 (0.85–1.19), 0.96	1.14 (1.02–1.29), 0.03	0.98 (0.89–1.08), 0.66	1.04 (0.97–1.12), 0.30	1.06 (0.98–1.14), 0.16

Values are given in HR (95% CI), p value.

LFS Leukemia-free survival, OS Overall survival. Others see Table 2.

Table 5 Validation of TCI versus RIC/MAC on 200 bootstrap samples.

	NRM @ day 100	NRM @ day 180	NRM	Relapse	LFS	OS
Cox (HR, 95% CI)						
TCI [1,2]	1 (reference)	1	1	1	1	1
TCI [2.5–3.5]	1.77 (1.38–2.27)	1.63 (1.36–1.97)	1.27 (1.14–1.45)	0.79 (0.71–0.87)	0.94 (0.87–1.03)	1.02 (0.94–1.09)
TCI [4–6]	2.97 (2.2–4.06)	2.36 (1.88–2.94)	1.51 (1.28–1.77)	0.7 (0.63–0.82)	0.95 (0.85–1.07)	1 (0.9–1.12)
p, TCI [2.5–3.5] vs [1,2]	0.005	0.01	0.03	0.01	0.64	0.94
p, TCI [4–6] vs [1,2]	0.005	0.005	0.005	0.005	0.79	0.95
C-statistic (95% CI)						
TCI grouping	0.6747	0.6416	0.6201	0.5861	0.5604	0.5779
	(0.6729–0.6764)	(0.6401–0.6430)	(0.6190–0.6212)	(0.5852–0.5869)	(0.5597–0.5611)	(0.5771–0.5787)
RIC/MAC	0.6436	0.6219	0.6113	0.5784	0.5595	0.5713
	(0.6419–0.6454)	(0.6205–0.6234)	(0.6102–0.6124)	(0.5776–0.5793)	(0.5588–0.5602)	(0.5705–0.5721)
p value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.007

Table 6 The intermediate TCI [2.5–3.5] group.

RIC/MAC	N	NRM @ day 100	NRM @ day 180	NRM	Relapse	LFS	OS
RIC	1819	6.9% [5.8–8.1]	10.9% [9.5–12.4]	18.7% [16.9–20.6]	24.5% [22.4–26.6]	56.8% [54.4–59.3]	62.2% [59.8–64.6]
MAC	1552	5.7% [4.6–6.9]	10.1% [8.7–11.7]	17% [15.0–19.0]	26.2% [23.9–28.5]	56.8% [54.2–59.5]	61.2% [58.6–63.8]
p value		0.15	0.43	0.02	0.05	0.92	0.62

Values are given in % and [range].

The TCI proved to be the most important determinant of early and overall NRM with multivariable analysis, also when adjusted for HCT-CI in nearly 4000 cases with available data. The risk groups based on the TCI scores were more evenly distributed and provided better discrimination (based on the *c*-statistic) of NRM than the risk groups defined by the RIC/MAC classification. This improvement is probably attributed to the use of weighted scores based on the threshold of myeloablative doses, which subdivided the MAC group by placing 19% of the "borderline" MAC regimens in the intermediate TCI group. Moreover, the assignment of weighted scores for all components probably captured a group of patients who received an "intensified" RIC. Indeed, about 15% of the RIC regimens incorporated at least three components instead of the commonly used two in "standard" RIC regimens (Supplementary Table 1).

TCI was highly predictive for relapse risk and performed better than RIC/MAC. The correlation between regimen intensity and relapse in AML has been documented in many retrospective reports [18, 19] and prospective studies [20–22]. Not surprisingly, both TCI and RIC/MAC grouping had a weak association with LFS and OS on multivariate analysis. This reflects the contradictory effect of conditioning intensity in NRM and relapse and the strong likelihood of selection bias in the choice of conditioning. Two prospective randomized trials comparing MAC versus RIC in AML [20] and secondary AML or MDS [21] found no significant difference in LFS and OS. Another

randomized trial suggested a better OS in AML patients treated with MAC versus RIC, however, data closure in this study was at 18-months post-transplant and thus additional follow-up is warranted until a definitive conclusion can be done [22].

A large component of the improvement in intensity reclassification achieved by the TCI is that it identifies a distinct subgroup of RIC and MAC regimens that had identical outcomes in all aspects (Table 6). This intermediate TCI [2.5–3.5] group probably captured the so called "reduced toxicity conditioning" regimens that were specifically designed by various transplant groups in a way to optimize dose intensity while safely minimizing NRM and which were not readily amenable to the earlier RIC/MAC approach [7]. This is illustrated in Fig. 1b which gives examples of some very commonly used "reduced toxicity conditioning" regimens, such as fludarabine-based regimens which incorporate two alkylating agents in sub-myeloablative doses (e.g., Fludarabine–BCNU–Melphalan [9], Thiotepa–Busuplhan–Fludarabine [23]), the sequential conditioning regimens (e.g., FLAMSA) [10] or the Busulfan–Fludarabine regimen which has lower toxicity when directly compared with classical MAC Busulfan–Cyclophosphamide combination [24].

There are limitations in this study. First, weightings were based on scientific and clinical background and not on statistical consideration. However, we used RIC/MAC consensus rules to define dose levels and integer weights for

most components, and thus it is likely that the TCI has at least the same validity as the original RIC/MAC scheme. Second, we have attempted to minimize the possible limitations inherent in retrospective registry-based studies by studying a large patient cohort, by double-checking the RIC/MAC information and by using early NRM as primary endpoint for estimating the impact of TCI, an outcome which is very reliable documented in registry databases and is not influenced by events that evolve over time (e.g., chronic GVHD). Third, beyond the internal bootstrap validation used in this study an external validation in a truly distinct database or, even better, prospectively is warranted [25, 26]. Fourth, to confirm generalizability it is necessary to determine in future studies whether the model continues to perform as well across different diseases (except AML) and disease risk groups. However, since NRM is not influenced by disease risk [16], it is very likely that the predictive ability of TCI for early NRM applies to the entire spectrum of HCT patients. Fifth, the applicability and the value of TCI in other age groups, e.g., pediatrics, should be further evaluated. Sixth, one must keep in mind that drugs have differing mechanisms of actions and toxicity profiles and therefore both NRM and relapse may be besides intensity gradient also influenced in a regimen-specific manner [18, 27]. The integer weights are given arbitrarily and do not measure such "qualitative" factors (e.g., drug–drug interactions, drugs given in targeted doses, pharmacokinetics). In addition, the current TCI does not account for antisera used for GVHD prevention or for drugs given after graft infusion, such as post-transplant cyclophosphamide [28]. Future prospective trials including such aspects and the use of machine learning algorithms will be important to strengthen and recalibrate this index [29]. The prototype TCI presented here provides the baseline against which the predictive ability of these refined indices can be compared.

We propose the TCI scheme as a valid improvement on the RIC/MAC stratification system to define and measure transplant conditioning intensity. Compared with RIC/MAC, TCI provided better assessment of NRM and relapse risk; provided finer categorization and better discriminating ability; accounts for new regimens that were not readily amenable to the RIC/MAC approach; could be easily and precisely calculated for any patient; and could capture subtle regimen intensity variations (e.g., when reducing the dose of a component due to patient-related factors). TCI was effective in predicting NRM and relapse independently of other validated prognostic factors and thus TCI may be used in association with HCT-CI, DRI and donor type to assess transplant outcome. In every day clinical practice TCI may help to optimize conditioning intensity, thereby providing personalized treatment. We hope that future research will further confirm and validate the TCI in different patient groups, will refine the integer weights of each

agent and modify the TCI to improve its sensitivity and specificity. This TCI concept may readily accommodate new conditioning regimen components, rendering it future-proof. We anticipate that the TCI scheme has the potential to become a universal, well-defined and standard terminology for use in registry databases, in the literature and in clinical trials, thus facilitating comparative studies.

Compliance with ethical standards

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