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The hematopoietic cell transplantation comorbidity index (HCT-CI) predicts clinical outcomes in lymphoma and myeloma patients after reduced-intensity or non-myeloablative allogeneic stem cell transplantation

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Abstract

The hematopoietic cell transplantation specific comorbidity index (HCT-CI) has been developed to identify patients at high risk of mortality after an allograft. Reduced-intensity/non-myeloablative regimens have decreased the non-relapse mortality (NRM) in elderly and/or heavily pretreated patients. We performed a retrospective study to assess whether HCT-CI may predict clinical outcomes in a cohort of 203 patients with non-Hodgkin's (NHL; *n*=108), Hodgkin's lymphomas (HL; *n*=26), and multiple myeloma (MM; *n*=69), who were transplanted from a human leucocyte antigen (HLA)-matched sibling (*n*=121) or an unrelated donor (*n*=82) after a reduced-intensity regimen (*n*=154) or a low-dose total body irradiation-based non-myeloblative regimen (*n*=49). Cumulative incidence of NRM was 5, 16 and 20% at 1 year and 6, 24 and 27% at 2 years, for patients with an HCT-CI of 0, 1–2 and $\geqslant$3, respectively. By multivariate analysis, HCT-CI significantly predicted NRM (hazard ratio (HR)=1.6, *P*=0.03), overall survival (OS; HR=1.62, *P*<0.001) and progression-free survival (PFS; HR=1.43, *P*=0.002). Moreover, the Karnofsky performance status was also significantly associated with OS and NRM (HR=1.62, *P*<0.001 and HR=2.12, *P*=0.04, respectively). Conditioning type did not affect outcome after stratifying patients by HCT-CI. In the light of our study, all future prospective trials of the Gruppo Italiano Trapianti di Midollo (GITMO) will include the HCT-CI to stratify patients.

Keywords:

HCT-CI, lymphoma, myeloma, allogeneic transplant

Introduction

Reduced-intensity (RIC) and non-myeloablative conditionings have radically changed the eligible criteria for an allogeneic stem cell transplantation. Allografting in elderly patients and/or patients with non-hematological comorbidities is now characterized by a rather acceptable non-relapse mortality (NRM).[1, 2, 3, 4, 5] Many of these patients have lymphomas and myeloma, and are elderly and heavily pretreated with several lines of chemotherapy, which frequently include an autograft. Although studies to further decrease NRM are in progress, valid tools to accurately assess transplant-related risks are needed. Moreover, the range of the intensity of the currently used conditionings varies greatly from low-dose (200 cGy) total body irradiation to several combinations of cytotoxic agents and there are not yet prospective studies that compare different regimens.[6, 7, 8] We and others have previously reported that age is no longer a risk factor for NRM after a RIC or a non-myeloablative allograft.[9, 10, 11] Moreover, recent data have also shown that a RIC allograft is feasible in patients with lymphomas relapsed after an autograft.[12, 13]

The Seattle group has recently proposed the hematopoietic cell transplantation comorbidity index (HCT-CI), derived from the Charlson comorbidity index that takes into account several pretransplant medical conditions that may specifically affect clinical outcomes after an allograft.[14, 15] Furthermore, the combination of the HCT-CI and the Karnofsky perfomance status (PS), which is a widely used measure of patient health status, has resulted in an accurate risk stratification for patients treated with a non-myeloablative allograft for various hematological malignancies.[16]

In this retrospective multicenter study, we focused on patients with lymphomas and myeloma to investigate whether the HCT-CI, and secondly, Karnofsky PS were useful clinical parameters to predict outcome after a RIC or a non-myeloablative allograft.

Patients and methods

Patients and conditioning regimens

The analysis included 203 consecutive patients with non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma (HL) and multiple myeloma (MM) who underwent an allograft at three Italian transplant centers between 2001 and 2007. Informed consent was obtained at the time of transplantation in accordance to the Declaration of Helsinky. Patients not eligible for a standard myeloablative allograft because of age, presence of comorbidites or a previous autograft received either a RIC or a non-myeloablative conditioning regimen as per institutional or multicenter protocols. A non-myeloablative conditioning regimen was defined as low-dose (200 cGy) total body irradiation with/without fludarabine, whereas RIC regimens were defined as combinations of fludarabine with cyclophosphamide, thiotepa or mephalan.

Graft-versus-host disease (GVHD) prophylaxis consisted of methotrexate/cyclosporine with or without antithymocyte globulin and mycophenolate mofetil/cyclosporine for RIC and non-myeloablative regimens, respectively. Diagnosis and clinical grade of acute and chronic GVHD were performed using international standard criteria.[17, 18] Patients were transplanted from related or allele-matched unrelated donors. Human leucocyte antigen (HLA) typing was performed with either high- or low-resolution techniques for HLA-A, -B and -C antigens, whereas for HLA-DRB1 and DQB1 antigens, matching at the allele level was required. All patients received infection prophylaxis against fungi, bacteria, *Pneumocystis carinii* and *Cytomegalovirus* as per standard multicenter guidelines.

Immune-suppression withdrawal followed by donor lymphocyte infusions was allowed for persistent, progressive or relapsed disease in the absence of GVHD.

For lymphomas, pretransplant disease status and response were assessed with standard criteria by Cheson *et al*.[19, 20] For MM, the International uniform response criteria were applied and patients in near-complete remission (CR) were included in the CR group.[21]

The comorbidity scores and the Karnofsky PS were independently assigned by the principal investigators at each center using the HCT-CI and the Karnofsky scale after reviewing medical records and laboratory values of all patients.[14, 22] All reviewed patients had complete clinical data, including pulmonary function tests that allowed to assess all comorbidities included in the HCT-CI.

Statistical methods

Overall survival (OS) was defined as the time from transplant to death for any cause. Progression-free survival (PFS) was defined as the time from transplant to progression or relapse or death for any cause. Patients who responded to donor lymphocyte infusions were considered relapsed for time-to-event analysis. NRM was considered as death for any cause other than disease. OS and PFS were estimated using the Kaplan–Meier method. Comparisons of OS and PFS between groups were performed by the logrank test. NRM was defined as the probability of dying without previous disease recurrence, which was treated as a competing event. NRM and cumulative incidence of relapse (RI) were calculated by the cumulative incidence method, and comparisons between groups were analyzed by the Gray test. Multivariate analyses of NRM, OS and PFS were carried out with the Cox regression models, treating NRM and disease relapse or progression as competing events. All tests were two-sided. Correlations were evaluated by the Spearman's rank correlation test, considering a rho=0.3 as threshold for strong correlation.

Results

Pretransplant patient characteristics

Patient characteristics are reported in Table 1. Fifty-three percent (108/203) of the patients had NHL, 13% (26/203) had HL and 34% (69/203) had MM. Median age at transplant was 53 years (range=17–69). Median number of previous lines of chemotherapy was 3 (range=0–7), which included at least one autograft in 68% of the patients. No patient was treated with a planned tandem

autologous/allogeneic transplantation. Overall, 25% of the patients were transplanted in CR, 50% in partial response and 25% in progressive disease. However, most patients with MM were in partial response and progressive disease (63/69, 91%), as well as patients with HL (18/26, 69%), whereas most patients with NHL were in CR (72/108, 67%). A total of 154/203 (76%) were conditioned to transplant with a RIC conditioning, whereas 49/203 (24%) were conditioned with a non-myeloablative conditioning. The most commonly used RIC was thiotepa–fludarabine–cyclophosphamide (n=76) for sibling donors and thiotepa–cyclophosphamide–antithymocyte globulin (n=62) for unrelated donors. Low-dose total body irradiation with/without fludarabine was administered to 49 patients transplanted either from a sibling (n=33) or an unrelated donor (n=16). Patients transplanted with a non-myeloablative regimen had more frequently MM (P<0.001), had more commonly relapsed after an autograft (P<0.001) and had a lower probability of being in CR at transplant (P<0.001; Table 2). Diagnoses were equally distributed among the three centers.

Table 1 - Pretransplant patient characteristics.

Number of patients	*203*	*(%)*
Median age (years, range)	53 (17–69)	
Lymphoma	134	66
Indolent NHL	60	
Aggressive NHL	48	
Hodgkin's lymphoma	26	
Multiple myeloma	69	34
Time from diagnosis to allo-SCT (months, range)	30 (4–300)	
Previous lines of therapy (range)	3 (0–7)	
Previous auto-SCT	138	68
Pretransplant disease status		
CR	50	25
PR	103	50
PD	50	25
Donor type		
HLA identical sibling	121	60
Matched unrelated	82	40
HCT-CI		
0	65	32
1–2	62	31
⩾3	76	37
Karnofsky PS		
>80	123	60
⩽80	80	40
Conditioning regimen		
Nonmyeloablative	49	24
2 Gy TBI-fludarabine	44	
2 Gy TBI	5	
Reduced intensity	154	76
Thiotepa-fludarabine-cyclophosphamide	76	
Thiotepa-cyclophosphamide-ATG	62	
Fludarabine–melphalan-ATG or alemtuzumab	16	

Abbreviations: Allo-SCT, allogeneic stem cell transplantation; ATG, antithymocyte globulin; Auto-SCT, autologous stem cell transplantation; CR, complete remission; HCT-CI, hematopoietic cell transplantation comorbidity index; NHL, non-Hodgkin's lymphoma; PD, progressive disease; PR, partial remission; PS, performance status; TBI, total body irradiation.

Table 2 - Patient characteristics based on conditioning regimen.

	RIC (n = 154)	*Non-myeloablative (n = 49)*	P-*value*
Median age (years, range)	53 (17–69)	52 (23–63)	0.49
Disease type			< 0.001
Lymphoma (%)	118 (77)	15 (31)	
Multiple myeloma (%)	36 (23)	34 (69)	
Median number of previous treatment (range)	3 (0–7)	2 (0–5)	0.02
Previous SCT (%)	95 (62)	43 (88)	< 0.001
Donor (%)			0.24
HLA identical sibling	89 (58)	33 (67)	
Matched unrelated	65 (42)	16 (33)	
PS (%)			0.03
>80	100 (65)	23 (47)	
⩽80	54 (35)	26 (53)	
HCT-CI (%)			0.60
0	51 (33)	13 (26)	
1–2	48 (31)	15 (31)	
⩾3	55 (36)	21 (43)	
Disease status before transplant (%)			< 0.001
CR	46 (30)	2 (4)	
PR	77 (50)	28 (57)	
PD	31 (20)	19 (39)	
Interval diagnosis—transplant (months, range)	32 (4–300)	28 (9–121)	0.10

Abbreviations: CR, complete remission; HCT-CI, hematopoietic cell transplantation comorbidity index; PD, progressive disease; PR, partial remission; PS, performace status; RIC, reduced intensity conditioning; SCT, stem cell transplantation.

Patients were divided into three groups in the light of the HCT-CI at transplant: 0 (32%, 65/203), 1–2 (31%, 62/203) and ⩾3 (37%, 76/203). Median HCT-CI was 2 (range=0–8). The most common comorbidities involved pulmonary (39%) and cardiac functions (14%) and active infections at the time of transplant (14%; Table 3). Karnofsky PS was >80% in 60% (123/203) and ⩽80% in 40% (80/203) of the patients with a median value of 90% (range=40–100).

Table 3 - Absolute number and rate of each comorbidity according to HCT-CI in 203 patients.

Comorbidity	*HCT-CI score*	N	%
Arrhytmia	1	7	3
Cardiac	1	18	9
Inflammatory bowel disease	1	1	0.5
Diabetes	1	5	2
Cerebrovascular disease	1	1	0.5
Psychiatric disturbance	1	10	5
Hepatic-mild	1	10	5
Obesity	1	14	7
Infection	1	28	14
Rheumatologic	2	2	1
Peptic ulcer	2	2	1
Moderate/severe renal	2	8	4
Moderate pulmonary	2	30	15
Prior solid malignancy	3	12	6
Heart valve disease	3	4	2
Severe pulmonary	3	49	24
Moderate/severe hepatic	3	2	1
No comorbidities	0	65	32

Abbreviation: HCT-CI, hematopoietic cell transplantation comorbidity index; *N*, number of patients.

Clinical outcomes

Median follow-up was 20 months (range=0–93). Overall, NRM cumulative incidence was 15% at 1 year and 18% at 2 years. For patients with an HCT-CI of 0, 1- and 2-year cumulative NRM were 5 and 6%, respectively, whereas for patients with an HCT-CI of 1–2 and $\geq$3, a 1-year NRM of 16 and 20%, and a 2-year NRM of 24 and 27% were observed, respectively (P=0.04; Figure 1a). NRM was not different between patients with HCT-CI of 1–2 and HCT-CI of $\geq$3 (P=0.48). By univariate analysis, the Karnofsky PS also influenced NRM: patients with a Karnofsky PS >80% had 1- and 2-year NRM of 10 and 12%, respectively, as compared to 24 and 28% of patients with a lower Karnofsky PS (P=0.02). Other factors that significantly affected NRM were age (<55 vs $\geq$55, P=0.048) and donor type (sibling vs matched unrelated, P=0.02). A previous autograft, the number of previous lines of chemotherapy, the conditioning regimen, diagnosis and pretransplant disease status were not statistically significant (Table 4).

Figure 1. Cumulative non-relapse mortality (NRM), overall survival (OS) and progression-free survival (PFS) by pretransplant HCT-CI. (a) NRM (*P*=0.04), (b) OS (*P*< 0.001) and (c) PFS (P<0.001).

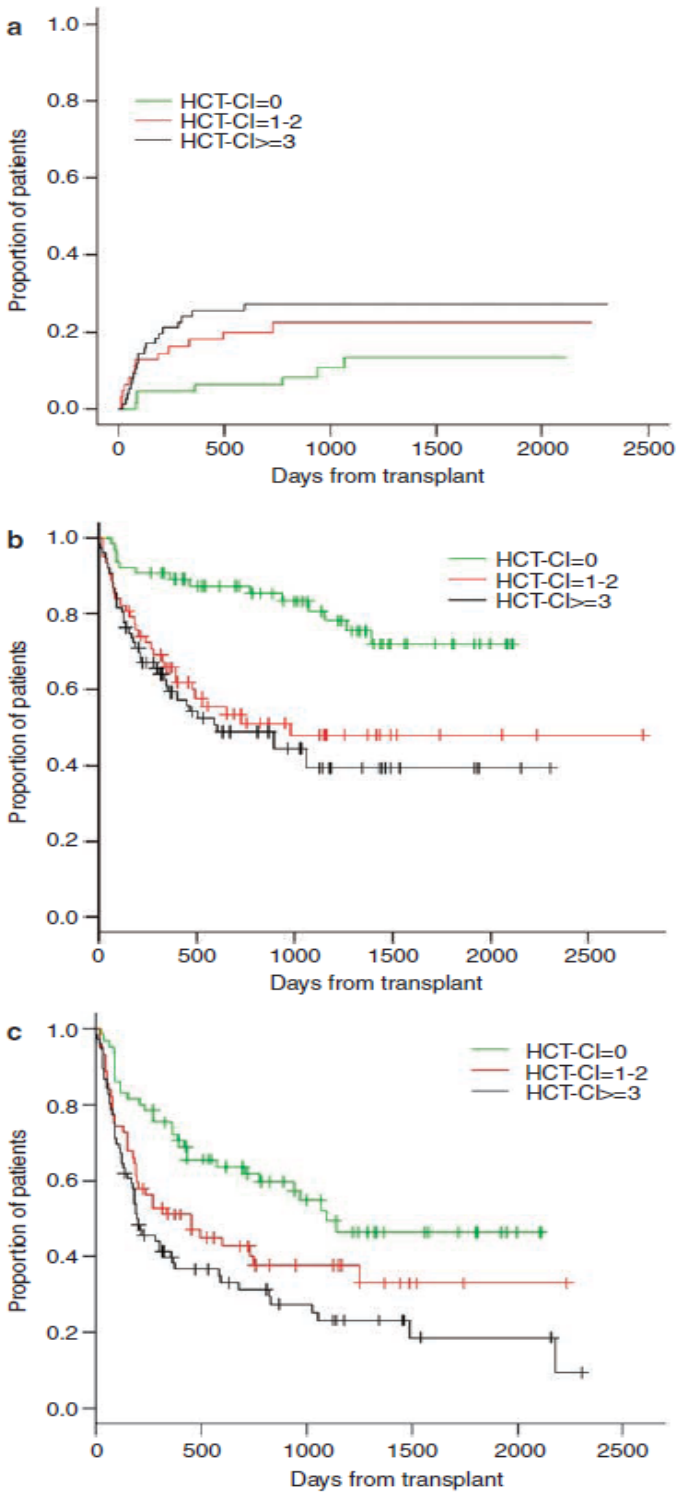


Table 4 - Univariate analysis.

	OS	HR (CI95%)	PFS	HR (CI95%)	NRM	HR(CI95%)
Donor (sibling vs matched unrelated)	0.47	1.18 (0.75–1.83)	0.63	0.90 (0.62–1.30)	**0.02**	**1.91 (1.02–3.56)**
SCT (⩾1 vs 0)	0.71	0.91 (0.58–1.45)	0.88	0.97 (0.66–1.41)	0.67	0.87 (0.45–1.68)
Age (< 55 vs ⩾55)	**0.02**	**1.63 (1.06–2.51)**	0.19	1.29 (0.90–1.84)	**0.04**	**1.92 (1.03–3.60)**
Previous lines of therapy (⩽2 vs >2)	**0.02**	**1.55 (1.00–2.41)**	**0.01**	**1.37 (0.96–1.96)**	0.36	1.48 (0.78–2.77)
Pretransplant status (CR+nCR vs not-CR)	**0.007**	**2.25 (1.22–4.15)**	**0.01**	**1.79 (1.14–2.83)**	0.93	1.21 (0.59–2.48)
Disease (lymphoma vs myeloma)	0.95	1.01 (0.64–1.59)	0.12	1.33 (0.92–1.91)	0.08	0.58 (0.28–1.24)
Conditioning (non-myeloablative vs RIC)	0.17	0.70 (0.43–1.13)	0.14	0.73 (0.49–1.09)	0.80	0.83 (0.40–1.71)
Karnofsky performance status (⩽80 vs >80)	**<0.001**	**3.88 (2.48–6.08)**	**<0.001**	**1.92 (1.35–2.75)**	**0.01**	**2.57 (1.37–4.81)**
HCT-CI (0 vs 1–2 vs ⩾3)	**<0.001**	**1.75 (1.34–2.29)**	**<0.001**	**1.52 (1.22–1.89)**	**0.04**	**1.78 (1.20–2.64)**

Abbreviations: CR, complete remission; HCT-CI, hematopoietic cell transplantation comorbidity index; nCR, near complete remission; NRM, non-relapse mortality; OS, overall survival; PFS, progression-free survival; RIC, reduced intensity conditioning; SCT, stem cell transplantation. Significant values are shown in bold.

Variables included in multivariate analysis were age (<55 vs ⩾55), HCT-CI (0 vs 1–2 vs ⩾3), Karnofsky PS (>80 vs ⩽80%), diagnosis (lymphomas vs MM), disease status at transplant (CR vs no-CR), the number of previous lines of therapy (⩽2 vs >2), a previous autograft (⩾1 vs 0), donor type (sibling vs unrelated) and the conditioning regimen (non-myeloablative vs RIC; Table 5). By multivariate analysis, a high HCT-CI (HR=1.60, P=0.03) and a low Karnofsky PS (HR=2.12, P=0.04) and the diagnosis of lymphoma (HR=0.31 for MM, P=0.002) were correlated with a significantly higher NRM.

Table 5 - Cox multivariate analysis.

	OS	HR (CI 95%)	PFS	HR (CI 95%)	NRM	HR (CI 95%)
Donor (sibling vs matched unrelated)	0.68	1.10 (0.70–1.72)	0.41	0.86 (0.59–1.24)	0.07	1.80 (0.95–3.42)
SCT (⩾1 vs 0)	0.26	0.74 (0.44–1.25)	0.14	0.71 (0.46–1.11)	0.98	0.99 (0.47–2.07)
Age (< 55 vs ⩾55)	0.19	1.38 (0.85–2.22)	0.63	1.10 (0.75–1.63)	0.06	1.93 (0.97–3.85)
Previous lines of therapy (⩽2 vs >2)	0.42	1.23 (0.73–2.05)	0.11	1.41 (0.92–2.15)	1.00	0.99 (0.47–2.13)
Pretransplant status (CR+nCR vs not-CR)	0.40	1.34 (0.67–2.67)	0.25	1.35 (0.81–2.24)	0.85	0.92 (0.39–2.14)
Disease (lymphoma vs myeloma)	0.21	0.67 (0.37–1.24)	0.27	1.33 (0.80–2.21)	**0.02**	**0.31 (0.11–0.86)**
Conditioning (non-myeloablative vs RIC)	0.16	0.67 (0.39–1.18)	0.49	0.85 (0.54–1.35)	0.12	0.51 (0.21–1.19)
Karnofsky performance status (⩽80 vs >80)	**<0.001**	**3.10 (1.88–5.11)**	0.07	1.44 (0.97–2.16)	**0.04**	**2.12 (1.04–4.30)**
HCT-CI (0 vs 1–2 vs ⩾3)	**<0.001**	**1.62 (1.22–2.16)**	**0.002**	**1.43 (1.14–1.80)**	**0.03**	**1.60 (1.05–2.44)**

Abbreviations: CR, complete remission; HCT-CI, hematopoietic cell transplantation comorbidity index; nCR, near complete remission; NRM, non-relapse mortality; OS, overall survival; PFS, progression-free survival; RIC, reduced intensity conditioning; SCT, stem cell transplantation. Significant values are shown in bold.

Overall survival was higher in patients with lower HCT-CI: 1- and 2-year OS were 89 and 87%, respectively for an HCT-CI of 0 as compared to 65 and 51% for an HCT-CI of 1–2, and 59 and 49% for an HCT-CI of ⩾3 (P<0.001; Figure 1b). OS did not significantly differ between patients with HCT-CI of 1–2 and patients with HCT-CI of ⩾3 (P=0.46). By univariate analysis, OS was also influenced by the Karnofsky PS (P<0.001), the number of previous lines of therapy (P=0.02), pretransplant disease status (P=0.007) and age at transplant (P=0.02; Table 4). By multivariate analysis, only the HCT-CI and the Karnofsky PS significantly predicted OS (HR=1.62, P<0.001 and HR=3.10, P<0.001, respectively; Table 5).

By univariate analysis, the HCT-CI and the Karnofksy PS (P<0.001), pretransplant disease status and the number of previous lines of therapy (P=0.01) were also significant for PFS (Table 4). PFS of patients with HCT-CI of 1–2 was not significantly different compared to patients with HCT-CI of ⩾3 (P=0.13). By multivariate analysis, only the HCT-CI was statistically significant (HR=1.43, P=0.002), whereas there was only a trend for the Karnofsky PS (HR=1.44, P=0.07; Table 5).

Lymphoma and myeloma subgroup analyses

For patients with lymphomas, 1- and 2-year NRMs were 17 and 21%, respectively and significantly higher in patients with (i) an HCT-CI score ⩾3 (6% at 1 year and 6% at 2 years for an HCT-CI of 0, 14 and 20% for an HCT-CI of 1–2, 30 and 35% for an HCT-CI of ⩾3; P=0.03; Figure 2a); (ii) a

lower Karnofsky PS (7% at 1 year and 10% at 2 years for Karnofsky PS >80, 37 and 42% for Karnofsky PS ⩽80%, $P<0.001$); (iii) age ⩾55 ($P=0.007$); (iv) a transplant from an unrelated donor ($P=0.04$). OS was 71% at 1 year and 61% at 2 years and significantly longer in patients with an HCT-CI of 0 (91% at 2 years, $P<0.001$) as compared to patients with an HCT-CI of 1–2 or ⩾3 (54 and 37% at 2 years, respectively). Other factors that influenced OS were the Karnofsky PS ($P<0.001$), pre-transplant disease status ($P=0.01$) and the conditioning ($P=0.03$, worse survival in the non-myeloablative group). One- and 2-year PFS were 53 and 46%, respectively. PFS was significantly correlated with HCT-CI (2-year PFS 69% for an HCT-CI of 0, 47% for an HCT-CI of 1–2, 23% for an HCT-CI of ⩾3, $P<0.001$), the Karnofsky PS ($P<0.001$) and pretransplant disease status ($P=0.04$). Patients with NHL had a RI of 25% at 1 year and 30% at 2 years, whereas patients with HL had a RI of 27% at 1 year and 39% at 2 years (Figure 3a and b).

Figure 2.Non-relapse mortality (NRM) for patients with lymphomas and myeloma by pretransplant HCT-CI. (a) NRM for lymphomas ($P=0.03$) and (b) NRM for myeloma ($P=0.3$).

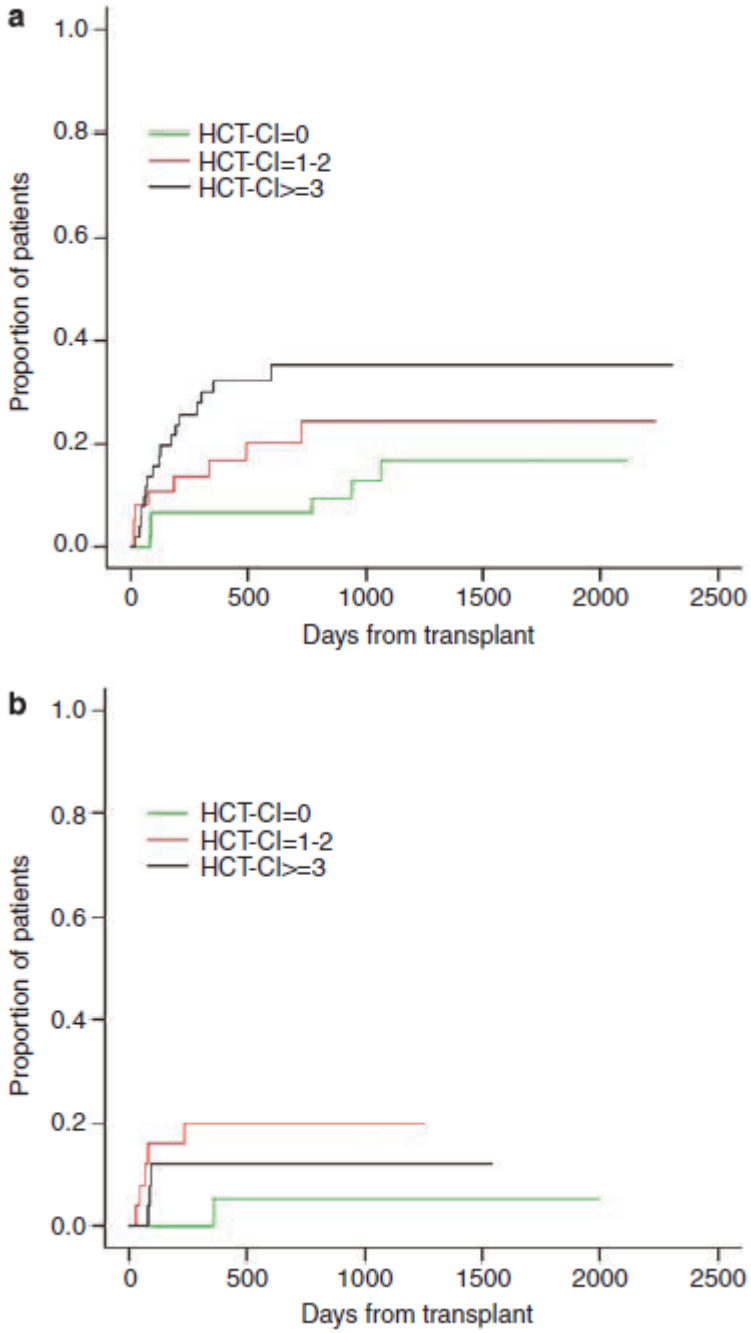
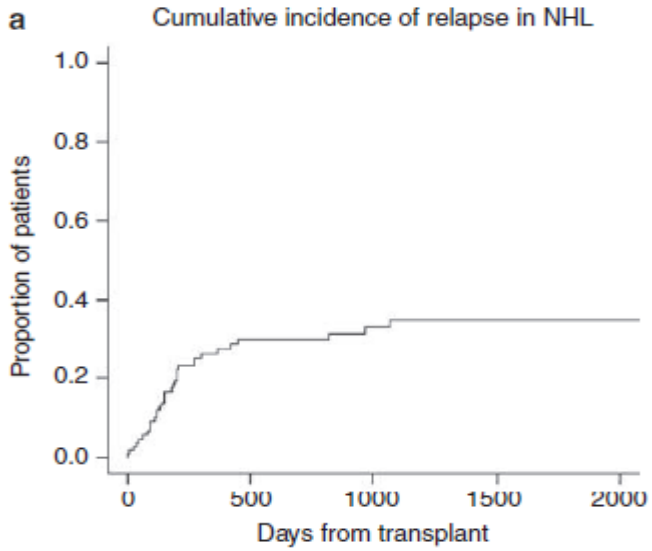
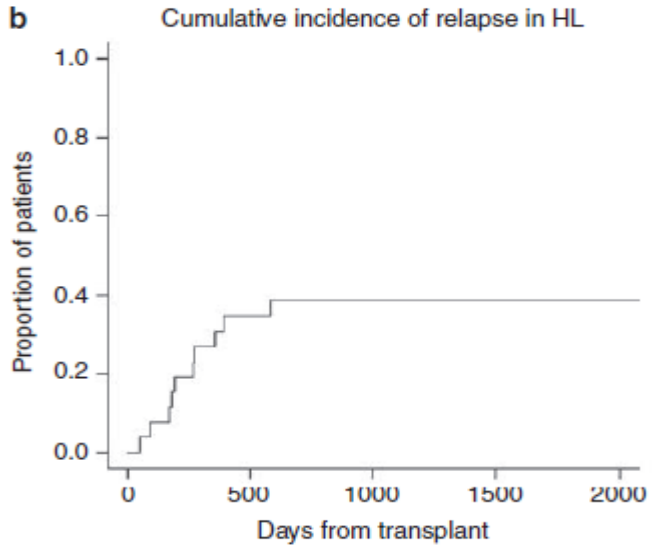
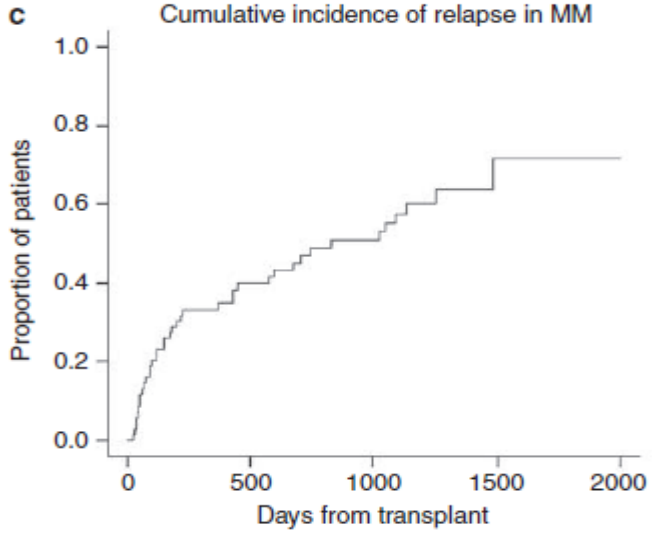


Figure 3. Cumulative incidence of relapse (RI) in non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma (HL) and multiple myeloma (MM) patients. (a) RI in NHL, (b) RI in HL and (c) RI in MM.







For patients with MM, NRM was 12 and 13% at 1 and 2 years, respectively. NRM was not significantly different between patients with an HCT-CI of 0 (0% at 1 year and 5% at 2 years) vs those with a higher HCT-CI (20% at 1 and 2 years for HCT-CI of 1–2 and 12% at 1 and 2 years for HCT-CI of $\geq$3, respectively; P=0.3; Figure 2b). The 1-and 2-year OS were 71 and 64%, respectively. Patients with an HCT-CI of 0 and a Karnofsky PS >80% showed a slightly better OS (P=0.09 and P=0.07, respectively) that was significantly influenced by a previous autograft (P<0.02). PFS was predicted by the number of previous lines of therapy (P=0.002) and a previuos autograft (P=0.02), but not by a high HCT-CI (P=0.24) or low Karnofsky PS (P=0.91). Patients with MM had a RI of 33% at 1 year and 45% at 2 years (Figure 3c).

Correlation of HCT-CI with other clinical factors

Hematopoietic cell transplantation comorbidity index was not correlated with age (P=0.38), time from diagnosis to transplant (P=0.68) and pretransplant disease status (P=0.73). A significant correlation was found between the HCT-CI and the Karnofsky PS (P<0.001, rho=-0.34) and between the HCT-CI and the number of previous lines of therapy (P=0.002, ρ=0.21).

Overall incidence of grade II–IV acute GVHD was 33%. For patients with an HCT-CI of 0, 1–2, and $\geq$3, the incidence was 29, 34 and 36%, respectively. By univariate analysis, we did not observe any statistically significant correlation between acute GVHD and the presence of comorbidities (P=0.72). The incidence of chronic GVHD was 30% at 1 year. Patients with an HCT-CI of 0, 1–2 and $\geq$3 had an incidence of 31, 28 and 26%, respectively (P=0.77).

HCT-CI and conditioning regimens

In the RIC group, 1- and 2-year NRM cumulative incidence was 6 and 8% for an HCT-CI of 0, 15 and 20% for an HCT-CI of 1–2 and 20 and 25% for an HCT-CI of $\geq$3 respectively (P=0.27). The 1- and 2-year NRM were 8 and 10% for Karnofsky PS >80 and 20 and 31% for Karnofsky PS $\leq$ 80%, respectively (P=0.01). PFS was influenced by the HCT-CI (P=0.006) and Karnofsky PS (P<0.001). OS was significantly worse for an HCT-CI score $\geq$3 (P=0.001) and a Karnofsky PS$\leq$80 (P<0.001; Figure 4a).

Figure 4. Overall survival (OS) of patients treated with an allograft after a RIC or a non-myeloablative regimen stratified by the HCT-CI. (a) OS after a RIC allograft (*P*=0.001) and (b) OS after a non-myeloablative allograft (*P*=0.02).

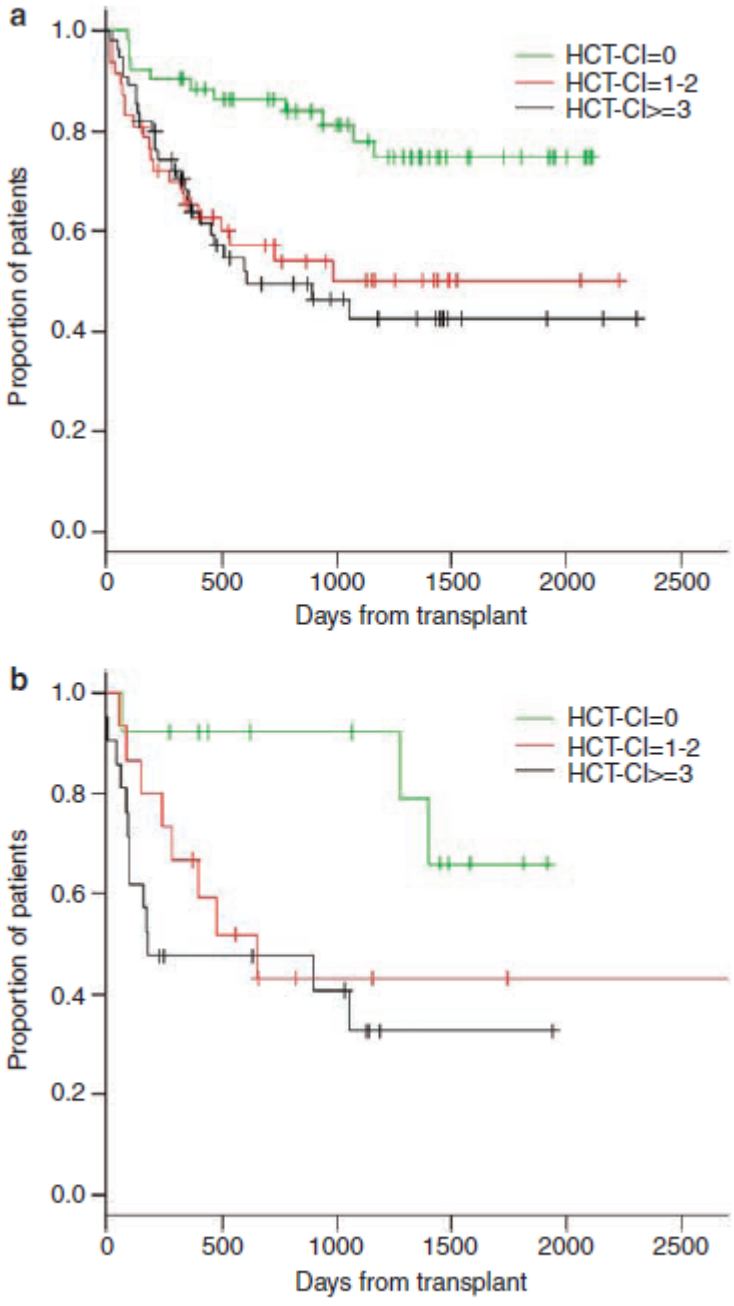


Figure 4 Overall survival (OS) of patients treated with an allograft after a RIC or a non-myeloablative regimen stratified by the HCT-CI. (**a**) OS after a RIC allograft ($P=0.001$) and (**b**) OS after a non-myeloablative allograft ($P=0.02$).

In the non-myeloablative group, the cumulative incidence of NRM at 1 and 2 years was 0% for patients with an HCT-CI score of 0, 20% for HCT-CI of 1–2, and 33% for HCT-CI score of $\geqslant$3, respectively (P=0.06). NRM for patients with a Karnofsky PS >80 was 17% at both 1 and 2 years, whereas for patients with a Karnofsky PS $\leqslant$80%, it was 23% at both 1 and 2 years (P=0.58). PFS was not correlated either with the HCT-CI or the Karnofsky PS (P=0.09 and P=0.58, respectively). OS was significantly reduced according to HCT-CI category (P=0.02), whereas it was not

influenced by Karnofsky PS (P=0.12; Figure 4b). However, regardless of the conditioning regimen used, in patients with the same HCT-CI of 0, HCT-CI of 1–2 or HCT-CI of ⩾3, there was no significant difference in NRM (P=0.19 for HCT-CI=0, P=0.87 for HCT-CI=1–2, P=0.33 for HCT-CI of ⩾3), in OS (P=0.94 for HCT-CI=0, P=0.76 for HCT-CI=1–2, P=0.18 for HCT-CI of ⩾3) and in PFS (P=0.55 for HCT-CI=0, P=0.62 for HCT-CI=1–2, P=0.19 for HCT-CI of ⩾3).

Discussion

Patients with lymphomas and myeloma are often not eligible for a standard myeloablative allograft because of age ⩾55 years, comorbidities and/or the intensity of previous therapies. Though allografting after RIC or non-myeloablative regimens is now feasible in elderly and/or medically unfit patients, the risk of NRM remains a relevant issue. Our retrospective study aimed at providing a valid tool to assess transplant-related risks and help physicians in the decision-making process when patients with lymphomas or MM are evaluated for an allograft. For this purpose, we evaluated a cohort of 203 consecutive patients treated with an allograft at three Italian transplant centers with a large experience on the treatment of lymphomas and MM.

The Seattle group[23] recently showed that 1- and 2-year NRM and OS are significantly better for patients with an HCT-CI of 0 compared to patients with an HCT-CI of 1–2 or ⩾3. Moreover, the study clearly suggested that NRM of patients with an HCT-CI of 0 is as low as that observed following an autograft and that even the presence of a single comorbidity can significantly affect post-transplant outcome. Other groups tested the reproducibility of HCT-CI, and some discordant results have been reported.[24, 25] Xhaard *et al.*[24] assessed the impact of HCT-CI on the outcome of patients receiving either a RIC or a myeloablative conditioning for several hematological diseases. In this study, HCT-CI was not predictive of NRM and OS but, as the authors highlighted, 70% of pulmonary function tests were lacking and this may have prevented complete analyses and comparisons with other patient characteristics. In our series, all patients were evaluated for all the comorbidities included in the HCT-CI score, and 39% of them had abnormal pulmonary function tests, suggesting the relevant role of this parameter. The Canadian group reported that Karnofsky PS, but not HCT-CI was predictive for outcome in 187 patients undergoing an allogeneic stem cell transplantation.[25] Patient characteristics, including disease types, age at transplant and conditioning regimens were largely different from our study, making any comparison impossible. Furthermore, the long period during which transplants were performed (from 1991 to 2006) may have affected clinical outcomes given the significant improvement in supportive care. The authors also suggested that owing to international discrepancies in healthcare, the universality of the HCT-CI may be controversial. Nevertheless, our multicenter analysis, performed at European Centers, confirmed the results of the Seattle group. We observed a significant difference in OS, NRM and also in PFS between patients with HCT-CI of 0 compared to patients with HCT-CI of 1–2 and ⩾3. The predictive value of the HCT-CI for OS was confirmed for both RIC and non-myeloablative regimens. Importantly, multivariate analyses showed that the HCT-CI, the Karnofsky PS and the diagnosis were the only significant variables to predict NRM. These findings are rather encouraging as they confirm the reliability and the reproducibility of these simple tools to evaluate transplant-related risks and underline that age is not an independent predictor of NRM, as reported previously.[9, 10, 11]

The fact that outcomes between HCT-CI of 1–2 and ⩾3 were not significantly different can suggest two considerations: first, the sensitivity of HCT-CI could be improved to detect differences among patients with increasing number of comorbidities; second, further studies should be focused to decrease NRM in patients with one or two comorbidities receiving a RIC or non-myeloablative allogeneic stem cell transplantation. A recently published study by the Minnesota group aimed at showing the feasibility of cord blood transplant in patients above 55 years has reported worse NRM, OS and PFS for patients with HCT-CI ⩾3, whereas patients with HCT-CI of 0 and 1–2 had similar outcomes.[26] In this study, patient characteristics were highly different from our series with regard to

age, diagnosis type, stem cell sources, the number of prior autologous transplants and conditioning regimens. In particular, the use of cord blood and age over 55 years may have increased NRM in HCT-CI of 0 (6-month TRM 14%) reducing the gap with HCT-CI of 1–2. Moreover, TRM was defined as death within 180 days, which greatly differs from our definitions.

Patients with at least one comorbidity experienced a worse PFS compared to those without. Interestingly, we noticed that the number of previous lines of chemotherapies correlated with a higher HCT-CI. Sorror *et al.*[16] observed that patients with a higher HCT-CI had also a higher relapse risk. However, no correlation between the HCT-CI and the number of previous chemotherapies was reported in their study. Furthermore, in contrast with other studies,[16, 27] we did not observe any correlation between age and HCT-CI. Our finding may be due to the fact that our patients had failed several lines of therapies, including, in most cases, an autograft. Therefore, the intensity of the treatment may have determined the comorbidities, such as an impaired pulmonary function, that significantly affect NRM regardless of patient age. In summary, our results support the notion that the higher the number of pre-transplant treatments, the higher the presence of comorbidities at transplant and fewer the chances of long-term disease control with acceptable toxicity. We find these data of interest as they clearly show that an appropriate timing for allografting in the treatment plan of lymphomas and MM is fundamental to improve clinical outcomes in the future.

In the subgroup analysis by disease diagnosis, NRM and OS were better for patients with an HCT-CI of 0, although this difference was not statistically significant in MM. The fact that only 9% of the patients affected by myeloma were in CR/nCR at transplant compared to 67% for patients affected by NHL can explain the lack of significance of disease stage in predicting PFS for MM. The advanced disease and the high relapse incidence along with the limited number of patients can also explain the lack of significance of HCT-CI in this setting.

As previously reported by the Seattle group, the Karnofsky PS was inversely correlated with the HCT-CI[16] and was strongly correlated with NRM and OS, and, to a lesser extent, with PFS. As observed for HCT-CI, the minor influence on PFS may be due to the high rate of progression in MM patients, whereas Karnofsky PS was significantly correlated with PFS in lymphomas.

We initially hypothesized that the incidence of GVHD may have been correlated with comorbidities as organ damage may predispose to untoward immune responses.[28, 29] However, no significant correlation between grade II and IV acute or chronic GVHD and the HCT-CI has been observed, although there was a slight increase of acute GVHD in patients with an HCT-CI score of $\geqslant$1.

Finally, though the diagnoses were not equally distributed between the RIC group and the non-myeloablative group, which comprised more patients with MM who had undergone a previous autograft, we did not observe any impact of the HCT-CI on outcomes, such as NRM and OS, with respect to the conditioning used. These results support the feasibility of a wide range of conditionings in lymphoprolipherative disorders regardless of patient age and number of comorbidities.

In conclusion, our study shows that the HCT-CI is a simple and reliable tool to predict NRM, OS and partly PFS in patients with lymphomas and MM undergoing a RIC or a non-myeloablative allograft in a multicenter setting. Taking into account the limits of a retrospective analysis, our results suggest that the HCT-CI should invariably be part of the pretransplant work-up to evaluate transplant-related risks in all prospective control trials and help define those patients who may benefit most from an allograft.

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