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ORIGINAL ARTICLE

Chronic GVHD is associated with lower relapse risk irrespective of stem cell source among patients receiving transplantation from unrelated donors

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Chronic GVHD (cGVHD) has been associated with reduced risk of relapse after allo-SCT for onco-hematological disease due to a graft-vs-malignancy effect. Here we retrospectively analyzed a series of 802 adult patients transplanted from unrelated donors and found that cGVHD was associated with significantly lower relapse and that the limited form was associated with a survival advantage: hazard ratio for OS = 0.63 (0.46 – 0.87); $P = 0.004$; this was due to combination of relapse reduction and similar non-relapse mortality with respect to patients without cGVHD. Importantly, the graft-vs-malignancy effect observed here did not differ when PBSC or BM were used as stem cell source, thus suggesting that the protective effect of limited cGVHD is similar after PBSC- or BM-based transplantation. These findings could have practical implications and suggest no qualitative difference between cGVHD occurring after transplantation performed with different stem cell sources.

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INTRODUCTION

Development of GVHD after hematopoietic SCT (HSCT) is associated with relevant morbidity and mortality and represents the most common cause of long-term non-relapse mortality (NRM).[1] The presence of GVHD also decreases disease relapse and it could improve post-transplant outcome,[2] depending on its severity and the success of a graft-vs-malignancy effect.[3–5] Notably, although acute GVHD (aGVHD) has been reported to be responsible for higher NRM and therefore not always associated with improved progression-free survival,[5–7] the development of chronic GVHD (cGVHD) could confer a significantly better outcome due to lower relapse risk and NRM comparable to patients without cGVHD.[5,8–10] In the context of HSCT from sibling or unrelated donor, the use of PBSC as stem cell source has been identified as one of the main risk factors for cGVHD,[11] together with other donor-, patient- and transplant-related factors.[12–14]

However, it is not known whether the graft-vs-malignancy effect during cGVHD is different among recipients receiving BM vs PBSC, that is, whether a patient with limited cGVHD after HSCT from BM has the same reduction in relapse risk that another patient in an identical situation but after PBSC transplant has. To address this question, we updated information on a cohort of patients having received HSCT from unrelated donors[15] and analyzed the impact of cGVHD on transplant outcome on all patients and according to the stem cell source used. Moreover, factors associated with the development of cGVHD were identified, in particular HLA matching between patient and donor.

PATIENTS AND METHODS

A total of 802 transplants were the subject of the present analysis. Three patients were lost to follow-up and therefore excluded from the original dataset.[15] Data were facilited by the Gruppo Italiano Trapianto di Midollo Osseo and the Italian Bone Marrow Donor Registry, after obtaining consent by each participating center; patients' information was updated as of 20 April 2011 through the Gruppo Italiano Trapianto di Midollo Osseo registry database. HSCTs were performed between January 1999 and June 2006. Patients and donors were typed at high resolution level at loci A, B, C, DRB1 and DQB1; when available, a 10/10-matched donor was preferred, otherwise one or more antigenic or allelic mismatches were allowed. When more than one potential donor with same HLA matching were present, donor choice was based on patient/donor CMV serostatus, donor's sex, weight, patient/donor blood group. Main characteristics and definitions of disease status at transplantation were reported elsewhere.[15] More than half of the transplants (57%) were performed using BM as the stem cell source.

Transplant outcomes were defined according to the European Group for Blood Marrow Transplantation, aGVHD and cGVHD were classified following established criteria.[16,17] Relapse-related death (RRD) was defined as the event of death due to relapse or progression after HSCT.

Fine and Gray model for competing risks[18] was used to assess the impact of transplant variables on development of cGVHD. Those variables were: HLA matching between patient and donor, prior aGVHD grade II – IV, donor's age, patient's age, patient/donor gender match, year of HSCT, patient/donor CMV match, disease status and stem cell source. It was not possible to consider the use of *in vivo* T cell depletion by antithymocyte globulin as a variable because of the heterogeneity in timing (pre- or post-transplant), dose and brand used among transplant centers. Factors significant at univariate analysis were added in a multivariate model after stepwise procedure. Death without cGVHD and relapse before the event were considered as competing events. Sub-distribution hazard ratio (SHR) and relative 95% confidence interval (CI) were shown for Fine and Gray model. Cumulative incidences with competing risk analysis[19] were calculated to assess incidence of cGVHD in the entire cohort (considering

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only patients alive at day +100); to assess the impact of cGVHD on probability of relapse, NRM, RRD and OS, multistate models[20,21] with intermediate states represented by limited and extensive cGVHD were used. In particular, code suggested by Cortese and Andersen[20] was used for computation. Estimation of effect of cGVHD was performed by mean of univariate and multivariate Cox proportional hazard model, and hazard ratio (HR) and relative 95% CI were reported.

A landmark analysis at 6 and 12 months was also performed to assess effect of cGVHD on each outcome, considering cGVHD as a time-fixed covariate. cGVHD was considered as 'present' if it was developed before each of the landmark points.

Analysis of RRD was performed only on acute pathologies (ALL, AML, MDS and secondary acute leukemia). Values of $P<0.05$ were considered statistically significant. All analyses were conducted using Stata (version 11.0; Stata Corp, College Station, TX, USA) and R.

RESULTS

HSCT outcome

Median follow-up of surviving patients was 63 months (8–146) with a 1-year OS of 52.5% (95% CI: 49–55.9). A total of 252 patients (31.4%) relapsed or progressed, of whom 197 died; 313 patients (39%) died without relapse.

Of the 802 patients, 546 were alive and without relapse at day +100; median day of occurrence of cGVHD was +133 (100–2002) and cumulative incidence of overall and limited cGVHD was 43.1% (95% CI: 38.8–47.2%) and 29.4% (95% CI: 25.5–33.3%), respectively.

Of the 546 patients alive at day +100, 179 patients (32.8%) relapsed or progressed, of whom 134 patients (24.5%) died while 133 (24.4%) died without a relapse. At the last follow-up, 275 patients (50.4%) were alive, whereas 4 patients were lost.

In this subset of patients, 164 (30%) and 81 (14.8%) patients developed limited extensive cGVHD, respectively.

Impact of cGVHD on HSCT outcome

Of 546 patients alive at day +100, 3-year probability of survival was 60.1% for patients without cGVHD vs 75.2% for patients with limited cGVHD vs 55.7% for extensive cGVHD (Figure 1a), thus confirming that limited cGVHD is associated with significantly higher OS (Table 1) over the other two groups (HR = 0.63 (0.46–0.87); $P=0.004$). Superior OS among patients with limited cGVHD is the result of the combination of the reduction of relapse and RRD (Figure 1b) with respect to patients without cGVHD (Relapse: HR = 0.66 (95% CI: 0.47–0.94); RRD: HR = 0.34 (95% CI: 0.19–0.60)) and decreased incidence of NRM (Figure 1c) compared with extensive cGVHD group (HR = 0.50 (95% CI: 0.32–0.76)).

Higher OS of patients with limited cGVHD vs the other two groups was found for landmark at 6 months (HR = 0.75; 95% CI: 0.51–1.11, $P=0.14$), whereas no significant differences were found at landmark of 12 months. Compared with patients without cGVHD, a reduction of relapse risk for patients with both limited (HR = 0.59; 95% CI: 0.29–1.21, $P=0.14$) and extensive cGVHD (HR = 0.35; 95% CI: 0.09–1.42, $P=0.14$) was found considering a 6-month landmark, while the role of cGVHD in relapse seems to disappear after 12 months (data not shown).

Patients with extensive cGVHD showed a higher risk of TRM, considering 6 months as landmark (HR = 1.76; 95% CI: 0.93–3.32, $P=0.08$), and this association was more pronounced when landmark at 12 months was considered (HR = 2.55; 95% CI: 1.16–5.58, $P=0.02$).

For RRD, results were similar at those found with multistate models (shown above) and no differences between 6-month and 12-month landmark analysis were highlighted.

In Table 1, results of univariate Cox regression on OS, relapse, NRM and RRD were reported. No differences in association between cGVHD and outcomes were shown after adjusting for other factors.

For RRD, a total of 356 patients with acute pathologies were considered and, among them, 103 (28.9%) and 45 (12.6%) developed limited and extensive cGVHD, respectively.

After stratification for stem cell source, we observed comparable effects of cGVHD on OS in the presence of PBSC or BM (P-value = 0.16; test for interaction between stem cell source and cGVHD), with the exception of higher probability of death among patients without cGVHD and having received PBSC (HR = 1.41 (95% CI: 1.04–1.91); $P=0.03$) (Figure 2). This difference was due to higher NRM in the absence of cGVHD compared with patients having received BM (HR = 1.59 (95% CI: 1.03–2.46), $P=0.038$). On the other hand, effects of cGVHD on RRD did not change after stratification by stem cell source (Table 1).

Importantly, no particular differences were found when analyzing the effect of cGVHD on OS, RRD and NRM also after stratification for disease status.

Donor/patient HLA matching and cGVHD

When analyzing HLA matching between the patient and his/her donor, no significant difference in cGVHD incidence was observed. Cumulative incidence of cGVHD was 40.8, 45.1 and 44.3% among 10/10-, 9/10- and ⩽8/10-matched pairs ($P=0.35$). Moreover, when considering together 9/10- and ⩽8/10- matched pairs,

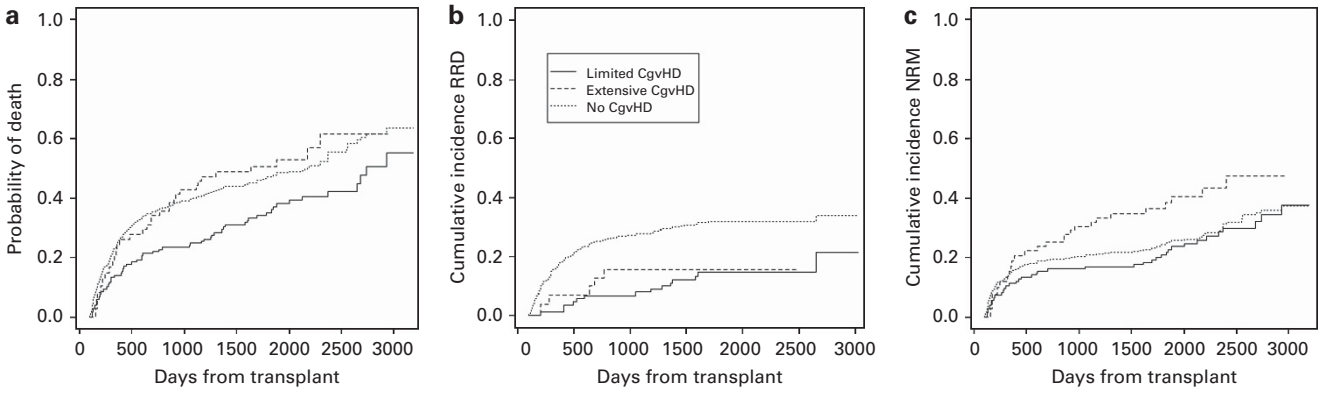

Figure 1. Probability of death (**a**) and cumulative incidences of RRD (**b**) and NRM (**c**) stratified for grade of cGVHD. Solid and long-dashed lines represent patients who developed limited and extensive cGVHD, respectively, during follow-up, whereas dashed lines represent patients who did not develop cGVHD.

Table 1. Results from univariate Cox regression on OS, NRM, relapse and RRD

Factors	*All sample* (n = *546*)		*PBSC* (n = *301*)		*BM* (n = *243*)	
	HR (95% CI)	P-*value*	*HR (95% CI)*	P-*value*	*HR (95% CI)*	P-*value*
OS						
Chronic GVHD						
No	1.00		1.00		1.00	
Limited	0.63 (0.46–0.87)	0.004	0.51 (0.34–0.75)	<0.001	0.88 (0.52–1.51)	NS
Extensive	1.06 (0.72–1.55)	NS	0.88 (0.50–1.55)	NS	1.27 (0.74–2.18)	NS
Relapse						
Chronic GVHD						
No	1.00		1.00		1.00	
Limited	0.66 (0.47–0.94)	0.022	0.58 (0.37–0.90)	0.016	0.93 (0.53–1.65)	NS
Extensive	0.59 (0.34–1.02)	NS	0.76 (0.38–1.53)	NS	0.43 (0.17–1.09)	NS
NRM						
Chronic GVHD						
No	1.00		1.00		1.00	
Limited	0.88 (0.59–1.33)	NS	0.73 (0.44–1.20)	NS	1.14 (0.54–2.41)	NS
Extensive	1.78 (1.13–2.81)	0.014	1.30 (0.67–2.52)	NS	2.40 (1.25–4.59)	0.009
	All sample (n = *356*)		*PBSC* (n = *213*)		*BM* (n = *143*)	
RRD						
Chronic GVHD						
No	1.00		1.00		1.00	
Limited	0.34 (0.19–0.60)	< 0.001	0.34 (0.18–0.66)	0.001	0.29 (0.09–0.94)	0.039
Extensive	0.37 (0.15–0.90)	0.029	0.46 (0.14–1.48)	NS	0.31 (0.07–1.28)	NS

Abbreviations: CI = confidence interval; HR = hazard ratio; NRM = non-relapse mortality; NS = not significant; RRD = relapse-related death. HRs for patients who developed limited or extensive chronic GVHD (cGVHD) with respect to patients who did not. HRs were obtained by the mean of Cox regression in multistate models. OS, relapse, NRM and RRD were considered as different outcomes. Results for all sample and for only PBSC or BM stem cell source are showed.

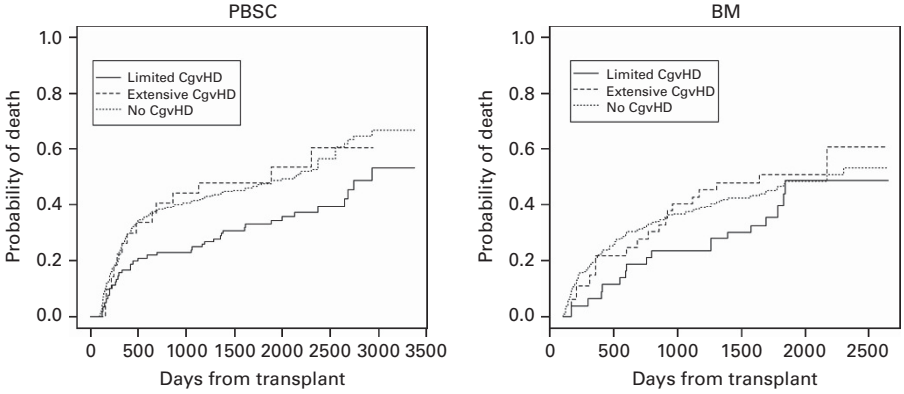

Figure 2. Probability of death stratified for PSBC (left) and BM (right). No particular differences between PBSC and BM on probability of death after developing cGVHD were found.

cumulative incidence was not statistically different compared with 10/10-matched pair (SHR = 1.21; $P = 0.15$).

When maximum grade of cGVHD was considered separately in the analysis for limited form, the same results were obtained, whereas a significantly higher cumulative incidence of extensive was found for 9/10- vs 10/10-matched pair (SHR = 1.67; $P = 0.046$).

Significant predictive factors for cGVHD were: use of PBSC (SHR = 1.53; $P = 0.001$), disease status (SHR (intermediate vs early) = 0.61; $P = 0.066$; SHR (advanced vs early) = 0.62; $P = 0.05$) and year of transplant (SHR = 0.88 (1-year increase); $P < 0.001$). Furthermore, higher cGVHD was found for those patients with prior grade II–IV aGVHD (SHR = 1.37; $P = 0.018$). No differences in effect of single factors were noticed when the multivariate model was performed.

DISCUSSION

Limited cGVHD is associated with better survival compared with patients without cGVHD or with extensive cGVHD in this multicenter, registry-based series of HSCT from unrelated donor among adult patients affected by hematological malignancies. Importantly, this protective role of limited cGVHD is similar when PBSC or BM was used as stem cell source, indicating that the graft-vs-malignancy effect is not different according to the type of stem cell used.

These data are in line with several previous reports, indicating an antitumor effect when GVHD is present:[2–5] in our series, limited as well as extensive cGVHD were associated with reduced relapse and consequently RRD, but a survival advantage among extensive cGVHD patients was not observed because the

improvement in disease control was offset by increased NRM due to severity of cGVHD in those patients. Landmark analysis at 6 and 12 months confirmed these findings; however, the total lack of association with OS and relapse at 12 months may be explained by the reduced number of patients at risk at this time point and by the fact that although cGVHD-associated TRM is a late event, most relapse events occur within 1 year after HSCT.[22]

It has been demonstrated that the use of PBSC as stem cell source is associated with higher risk of developing cGVHD;[11,23,24] use of PBSC has also shown to provide better outcome in advanced patients because of a lower risk of relapse[25] and/or graft failure compared with BM.[13,26] Although this is not the aim of the present study, our findings confirm the association between PBSC and cGVHD, because patients receiving PBSC had a 53% additional risk of developing cGVHD than those receiving BM.

As concerns severity of cGVHD, we found in our series a lower incidence of extensive cGVHD compared with limited cGVHD, with a ratio 1:2; this could be explained by the wide use of *in vivo* T-cell depletion among Italian transplant centers in the presence of unrelated donors.[15] This is in line with a recent French registry-based analysis, finding 4% cumulative incidence of extensive cGVHD among leukemia patients receiving antithymocyte globulin during conditioning regimen for HSCT from unrelated donor, compared with 32% among no antithymocyte globulin transplants.[27]

Of note, our data also suggest that after the development of cGVHD, the antitumor effect appears to be similar between PBSC and BM, also adjusting for disease status at transplantation that remains the most relevant risk factor for relapse and RRD. This has practical implications because the relapse risk of a patient developing limited cGVHD after BM-based HSCT could be estimated to be similar to that of a patient in the identical situation but after PBSC-based HSCT. This supports the hypothesis that there is no qualitative difference considering cGVHD post-BM- and post-PBSC-based transplantation.

Our data also suggest that globally HLA mismatch between patient and donor did not significantly increase the risk of cGVHD; we previously demonstrated on the same series[15] that one or more HLA mismatches were associated with higher risk of aGVHD. This is in line with recent evidence that HLA matching has distinct impact on aGVHD or cGVHD[12,13,28] and that risk factors for aGVHD or cGVHD are not always superposable, indicating that mechanisms involved in aGVHD and cGVHD could be different.[12]

In conclusion, this study confirms the finding that higher disease control is present when a limited cGVHD develops after HSCT, with the relevant additional information that this protective effect is similar after PBSC- or BM-based transplantation. This could have practical implications and suggests no qualitative difference between cGVHD occured after HSCT with different stem cell sources.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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