Clinical Cancer Research

Impact of Chronic Graft-versus-Host Disease on Late Relapse and Survival on 7,489 Patients after Myeloablative Allogeneic Hematopoietic Cell Transplantation for Leukemia

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Abstract

Purpose: Malignancy relapse remains a major obstacle for successful allogeneic hematopoietic cell transplantation (HCT). Chronic graft-versus-host disease (cGVHD) is associated with fewer relapses. However, when studying effects of cGVHD on relapse, it is difficult to separate from acute GVHD effects as most cases of cGVHD occur within the first year after transplant at the time when acute GVHD is still active.

Experimental Design: This study based on CIBMTR registry data investigated cGVHD and its association with the incidence of late relapse and survival in 7,489 patients with acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), and myelodysplastic syndromes (MDS), who were leukemia free at 12 months after myeloablative allogeneic HCT.

Results: Forty-seven percent of the study population was diagnosed with cGVHD at 12 months after transplant. The protective effect of cGVHD on late relapse was present only in patients with CML [RR, 0.47; 95% confidence interval (CI), 0.37–0.59; $P < 0.0001$). cGVHD was significantly associated with higher risk of treatment-related mortality (TRM; RR, 2.43; 95% CI, 2.09–2.82; $P < 0.0001$) and inferior overall survival (RR, 1.56; 95% CI, 1.41–1.73; $P < 0.0001$) for all diseases. In patients with CML, all organ sites and presentation types of cGVHD were equally associated with lower risk of late relapse.

Conclusions: These results indicate that clinically relevant antileukemia effects of cGVHD on late relapses are present only in CML but not in AML, ALL, or MDS. Chronic GVHD in patients who are 1-year survivors after myeloablative allogeneic HCT is primarily associated with higher TRM and inferior survival. *Clin Cancer Res; 21(9); 2020–8. ©2014 AACR.*

See related commentary by Gill, p. 1981

Introduction

Allogeneic hematopoietic cell transplantation (HCT) following myeloablative conditioning (MAC) regimen is a standard and curative treatment option for hematologic malignancies (1). The antileukemic activity of MAC and allogeneic HCT relies not only on the effects of high-dose chemotherapy or irradiation given during the conditioning regimen, but also on the immune-mediated graft-versus-leukemia (GVL) effect (2–4). The immune reactivity between donor T cells that is responsible for the GVL effect and the recipient is also associated with the major complications

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Translational Relevance

Clinical evidence implicates graft-versus-host disease (GVHD) in enhancing malignancy control. We focused here on assessing chronic GVHD effects in 7,489 patients who were alive and free of disease at 1 year after allo-HCT. This study demonstrates the protective effect of chronic GVHD on late relapse only in patients with CML. A protective effect of chronic GVHD against late relapse was not seen in AML, ALL, or MDS. The presence of chronic GVHD was associated with significantly higher treatment-related mortality and worse overall survival across all diseases studied. As it is important to identify the setting in which chronic GVHD is most beneficial for leukemia control, these data provide support for focusing on developing better chronic GVHD therapies and prevention to improve survival of patients with leukemia after myeloablative allogeneic hematopoietic cell transplantation.

of allogeneic HCT, namely acute (aGVHD) and chronic graft-versus-host disease (cGVHD).

Chronic GVHD is a serious complication and is an important cause of morbidity and nonrelapse mortality (NRM) in patients who survive 12 months after transplantation (5). Chronic GVHD is associated with a lower risk of relapse (2, 4, 6). Despite the protective effect of cGVHD, adult patients with cGVHD experience leukemia late relapse (7). The reduction in relapse risk may be secondary to the immune-mediated graft-versus-tumor (GVT) effect associated with GVHD. This effect is most prominent during the first year after allogeneic HCT, when the peak incidence of relapse occurs (7, 8). However, onsets of acute and chronic GVHD chronologically overlap and it is difficult to decipher their relative contributions to antileukemia effects because at the time both acute and chronic GVHD are likely active (9). Given this close time overlap between aGVHD and cGVHD, this study sought to investigate antileukemic effects of cGVHD isolated from acute GVHD by assessing relapses and survival in allogeneic HCT recipients who were alive and relapse free at 1 year following MAC transplant. In addition, we evaluated whether any specific cGVHD clinical characteristics or organ manifestations are more predominantly associated with the GVL effects of cGVHD.

Materials and Methods

Data source

The Center for International Blood and Marrow Transplant Research (CIBMTR) is a research affiliation of the International Bone Marrow Transplant Registry (IBMTR), Autologous Blood and Marrow Transplant Registry (ABMTR), and the National Marrow Donor Program (NMDP), which was established in 2004 and comprises a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on consecutive allogeneic and autologous HCT to a Statistical Center at the Medical College of Wisconsin in Milwaukee and the NMDP Coordinating Center in Minneapolis. Participating centers are required to report all transplants consecutively; compliance is monitored by on-site audits. Patients are followed longitudinally. Computerized checks for discrepancies, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected Health Information used in the performance of such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the HIPAA Privacy Rule.

Patient selection

Between 1995 and 2004, 19,861 patients with acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), and myelodysplastic syndromes (MDS) received allogeneic HCT. Patients who received reduced intensity conditioning regimen ($n = 2{,}620$), died or relapsed ($n = 9{,}162$) within the first year after allogeneic HCT were excluded from the analysis. Patients who received second allergenic HCT ($n = 146$) within the first posttransplant year or syngeneic HCT were excluded as were patients who had relevant data missing from the CIBMTR database ($n = 444$). The final study population consisted of a total of 7,489 patients that received MAC regimen who were alive and free of disease at 1 year after transplantation.

Study definitions and endpoints

Patients were considered to have early disease whether they were in first remission (acute leukemia) or first chronic phase (CML) or MDS with refractory anemia or refractory anemia with ringed sideroblasts (RA, RARS); intermediate disease: second or later complete remission (acute leukemia), second or later chronic phase/accelerated phase (CML); advanced disease: relapse or primary induction failure (acute leukemia) or blast crisis (CML) or MDS with refractory anemia with excess blasts or excess blasts in transformation (RAEB, RAEB-t). The NMDP classification of HLA matching status that allows adequate adjustment for donor-recipient HLA compatibility while accounting for best available resolution of typing was used to categorize HLA-matching status as well-matched, partially matched, or mismatched (10). Acute GVHD was grouped as none versus grade 1 versus grade 2–4 and was graded according to IBMTR criteria based on the pattern of severity of abnormalities in skin, gastrointestinal tract, and liver (11). cGVHD was diagnosed according to standard CIBMTR criteria, which included all patients with clinical criteria of cGVHD with or without positive histology, irrespective of time of onset of symptoms (9, 12). The NIH consensus criteria were not available at the time of data collection for this analysis (13).

The primary endpoint was leukemia relapse and was defined as time to onset of disease recurrence (by hematologic or cytogenetic criteria) with treatment-related mortality (TRM) as a competing risk. Secondary endpoints were overall survival (OS), TRM, and disease-free survival (DFS). Outcomes were assessed up to 5 years after HCT. TRM was defined as death in continuous remission, and DFS was defined as either death or relapse with the time calculated from date of transplant. OS was calculated from date of transplant. Death from any cause was treated as an event and surviving patients were censored at the date of last contact.

Statistical analysis

Variables related to patient, disease, and transplant characteristics were summarized using descriptive statistics. Cumulative incidence for relapse was calculated treating TRM as a competing risk (14). Patient-related, disease-related, and treatment-related

variables were included in the multivariate analyses using a stepwise forward selection technique and $P \leq 0.01$ was the criterion for inclusion in final models. Patient- and transplant-related variables tested in the models included recipient age, sex, donor type, graft type (bone marrow or peripheral blood), donor-recipient gender mismatch, donor parity, donor-recipient cytomegalovirus (CMV) serology, use of total body irradiation (TBI), use of ATG or alemtuzumab, GVHD prophylaxis, presence and grade of prior aGVHD, and year of transplantation. Disease-related variables were diagnosis and disease status pretransplant. Chronic GVHD-specific variables included platelet count at diagnosis ($<100 \times 10^9$/L and $\geq 100 \times 10^9$/L), serum bilirubin at diagnosis (<1, 1–2, and >2 mg/dL), type of onset of cGVHD (progressive, interrupted, *de novo*), Karnofsky Performance Scale/Lansky score (KPS/L) at diagnosis, severity of cGVHD at 1 year after transplant (mild vs. moderate vs. severe), and organ involvement of cGVHD at 1 year after transplant.

In the multivariate analysis, all the endpoints were analyzed using the Cox proportional hazards model and all variables were tested for affirmation of the proportional hazards assumption. Variables that did not satisfy the proportional hazards assumption were adjusted for by stratification. A stepwise model-building procedure was used to develop models for each outcome with a threshold of 0.05 for both entry and retention in the model. Interaction between the main variable and adjusted variables were tested, and no significant interactions were identified at $P < 0.01$.

Results

Patients

The study included 7,489 patients who were alive and disease-free 1 year after HCT. Patient and donor characteristics are summarized in Table 1. The median age at HCT was 32 years for AML, 17 years for ALL, 36 years for CML, and 37 years for MDS. At 1 year after HCT 44%, 41%, 54%, and 54% of the AML, ALL, CML, MDS patients, respectively, had developed cGVHD. Chronic GVHD characteristics are summarized in Table 1.

Relapse

The cumulative incidence of relapse after the first post-HCT year for each disease is shown in Table 2. In multivariate analysis, a protective effect of cGVHD was seen only in patients with CML [RR, 0.47; 95% confidence interval (CI), 0.37–0.59; P <0.0001; Fig. 1A and B]. Other factors protective against late relapse were aGVHD in the first 29 days after HCT, GVHD prophylaxis other than T-cell depletion, well-matched or partially matched unrelated donor (URD; as compared with HLA-identical sibling), and early disease status at transplant (Table 3, Supplementary Table S1).

Transplant-related mortality and OS

Multivariate analysis of risk factors associated with TRM and OS are outlined in Tables 4 and 5, respectively. The presence of cGVHD was associated with a higher risk of TRM for all diseases (RR, 2.43; 95% CI, 2.09–2.82; P <0.0001; Fig. 1C, Table 4). Other factors associated with a higher risk of TRM included aGVHD, advanced disease status at HCT, well-matched, partially matched, or poorly matched URD (as compared with HLA-identical sibling donor), use of TBI in conditioning, female donor to male recipient (vs. male donor for male recipient), and use of peripheral blood stem cells (PBSC; vs. bone marrow) as the graft source (Supplementary Table S1).

The presence of cGVHD was associated with a higher risk of overall mortality for all diseases (RR, 1.56; 95% CI, 1.41–1.73; $P < 0.0001$; Fig. 1D, Table 5). Patients undergoing HCT for CML and MDS had a lower risk of overall mortality as compared with AML, whereas patients undergoing HCT for ALL had the highest risk of overall mortality. Other factors associated with a higher overall mortality risk were aGVHD after the first 29 days of HCT, intermediate, and advanced disease status at HCT, transplant from a well-matched URD or a poorly matched URD (as compared with HLA-identical sibling donor), use of TBI, transplant from a female donor to a male recipient (as compared with male donor to a male recipient), and use of PBSC as the graft type (Supplementary Table S1).

Compared with patients without cGVHD, the presence of cGVHD was associated with worse DFS in patients with AML (RR, 1.40; 95% CI, 1.20–1.63; $P < 0.0001$), ALL (RR, 1.46; 95% CI, 1.22–1.75; $P < 0.0001$), and MDS (RR, 1.58; 95% CI, 1.16–2.14; $P < 0.0001$) whereas the presence of cGVHD in CML did not significantly affect DFS ($P = 0.4$).

Chronic GVHD characteristics and impact on relapse, TRM, and survival

Because the presence of cGVHD reduced the risk of relapse only in patients with CML compared with those without cGVHD, we evaluated cGVHD-related variables associated with protection against relapse in CML. All types of cGVHD (i.e., mild, moderate, or severe; progressive, interrupted, or *de novo*), and any site of cGVHD involvement (i.e., skin or liver) provided protection against late relapse when compared with no cGVHD (Supplementary Table S2, CML patients with and without cGVHD). Pairwise comparisons performed to evaluate the impact of each subtype of cGVHD against each other (for example, the impact of presence of skin vs. no skin cGVHD, or severe cGVHD vs. moderate cGVHD or mild cGVHD) showed that none provided better protection. This finding was similar when the analysis on cGVHD-specific variables was limited only to patients with cGVHD; in patients with CML, any site or type of cGVHD provided protection against relapse, whereas patients with in AML, ALL, and MDS, the presence of cGVHD at any site or type did not provide protection against relapse.

In patients with CML, cGVHD characteristics associated with higher TRM and lower OS were the presence of moderate or severe cGVHD, skin involvement, lower platelet count, and KPS at cGVHD diagnosis. Moderate or severe cGVHD, lower platelet count, and KPS were associated with lower DFS (Supplementary Table S3).

In patients with AML, ALL, and MDS, moderate or severe cGVHD, low KPS at cGVHD diagnosis, and liver or gastrointestinal or hematologic involvement were associated with higher TRM. Higher cGVHD severity, and gastrointestinal, liver and hematologic involvement were also associated with lower OS. Moderate or severe cGVHD, gastrointestinal or genitourinary (GU) or liver or hematologic involvement were associated with lower DFS (Supplementary Table S4).

Discussion

Allogeneic HCT is an effective immunotherapy for hematologic malignancies, which is mediated by GVL effect. Clinical

Table 1. Patient, donor, and GVHD characteristics

	AML	ALL	CML	MDS
Patient and donor characteristics				
Characteristics	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Number of patients ($n = 7,489$)	2,541	1,798	2,498	652
Median recipient age at HCT, y (range)	32 (<1–74)	17 (<1–59)	36 (1–66)	37 (<1–65)
Age of recipient, y				
<2	58 (2)	58 (3)	1 (<1)	30 (5)
2–17	541 (21)	886 (49)	233 (9)	122 (19)
18–29	561 (22)	431 (24)	551 (22)	96 (15)
30–39	512 (20)	230 (13)	768 (31)	121 (19)
40–49	565 (22)	136 (8)	673 (27)	144 (22)
50–59	281 (11)	57 (3)	259 (10)	129 (20)
60+	23 (<1)	0	13 (<1)	10 (2)
Gender				
Male	1,346 (53)	1,121 (62)	1,469 (59)	359 (55)
Female	1,195(47)	677(38)	1,029(41)	293(45)
Disease status at HCT				
Early	1,518 (60)	804 (45)	2,110 (84)	229 (35)
Intermediate	612 (24)	862 (48)	349 (14)	6 (1)
Advanced	411 (16)	132 (7)	39 (2)	417 (64)
Graft source				
Bone marrow	1,611 (63)	1,383 (77)	1,928 (77)	434 (67)
Peripheral blood	930 (37)	415 (23)	570 (23)	218 (33)
HLA match				
HLA-identical sibling	1,503 (59)	810 (45)	1,284 (51)	264 (40)
Well-matched unrelated	445 (18)	352 (20)	434 (17)	185 (28)
Partially matched unrelated	368 (14)	385 (21)	486 (19)	132 (20)
Mismatched unrelated	225 (9)	251 (14)	294 (12)	71 (11)
Donor-recipient gender match				
Male → male	796 (31)	675 (38)	947 (38)	246 (38)
Male → female	640 (25)	375 (21)	551 (22)	155 (24)
Female → male	550 (22)	446 (25)	522 (21)	113 (17)
Female → female	555 (22)	302 (17)	478 (19)	138 (21)
Donor-recipient CMV status				
Negative → negative	727 (29)	673 (37)	791 (32)	219 (34)
Negative → positive	526 (21)	316 (18)	410 (16)	139 (21)
Positive → negative	313 (12)	267 (15)	328 (13)	81 (12)
Positive → positive	872 (34)	483 (27)	869 (35)	189 (29)
Unknown	103 (4)	59 (3)	100 (4)	24 (4)
Median donor age, years (range)	33 (<1–72)	30 (<1–73)	36 (<1–73)	36 (<1–71)
HLA-identical sibling donor age, years, median (range)	32 (<1–72)	18 (<1–73)	36 (<1–73)	36 (<1–71)
HLA-identical sibling donor age, y				
<10	135 (9)	187 (23)	32 (2)	28 (11)
10–17	181 (12)	206 (25)	86 (7)	20 (8)
18–29	360 (24)	203 (25)	269 (21)	53 (20)
30–39	330 (22)	108 (13)	388 (30)	52 (20)
40–49	297 (20)	66 (8)	326 (25)	65 (25)
50–59	140 (9)	29 (4)	124 (10)	33 (13)
60+	41 (3)	4 (<1)	31 (2)	8 (3)
Missing	19 (1)	7 (<1)	28 (2)	5 (2)
URD age, years, median (range)	35 (19–60)	35 (19–59)	35 (18–65)	35 (19–60)
URD age, y				
18–29	315 (30)	284 (29)	365 (30)	104 (27)
30–39	404 (39)	367 (37)	434 (36)	151 (39)
40–49	233 (22)	234 (24)	287 (24)	97 (25)
50–59	52 (5)	57 (6)	78 (6)	20 (5)
60+	2 (<1)	0	2 (<1)	1 (<1)
Missing	32 (3)	46 (5)	48 (4)	15 (4)
Donor parity before transplant				
Male donor	1,436 (57)	1,050 (58)	1498 (60)	401 (62)
Female, no pregnancy	420 (17)	380 (21)	324 (13)	78 (12)
1 or more pregnancies	473 (19)	266 (15)	483 (19)	128 (20)
Missing	212 (8)	102 (6)	193 (8)	45 (7)
GVHD prophylaxis				
Ex vivo T-cell depletion	246 (10)	218 (12)	204 (8)	81 (12)
Cyclosporine ± methotrexate ± other	1,900 (75)	1,362 (76)	2,008 (80)	472 (72)
Tacrolimus ± methotrexate ± other	395 (16)	218 (12)	286 (11)	99 (15)

(Continued on the following page)

Table 1. Patient, donor, and GVHD characteristics (Cont'd)

	AML	ALL	CML	MDS
ATG and/or alemtuzumab used				
None	2,131 (84)	1,399 (78)	2,088 (84)	519 (80)
Yes	312 (12)	332 (18)	318 (13)	113 (17)
Missing	98 (4)	67 (4)	92 (4)	20 (3)
Total body irradiation use in the conditioning regimen				
No	1,314 (52)	228 (13)	1,268 (51)	379 (58)
Yes	1,227 (48)	1,570 (87)	1,230 (49)	273 (42)
Year of transplant				
1995–1999	1,332 (52)	1,011 (56)	1,724 (69)	351 (54)
2000–2004	1,209 (48)	787 (44)	774 (31)	301 (46)
Prior aGVHD grade				
0–1	1,537 (60)	864 (48)	1,334 (53)	317 (49)
2–4	1,004 (40)	934 (52)	1,164 (47)	335 (51)
Median follow-up of survivors, months (range)	80 (12–179)	80 (12–175)	93 (12–172)	80 (12–168)
Chronic GVHD characteristics				
cGVHD present at one-year after HCT	1,117/2,541 (44%)	742/1,798 (41%)	1,344/2,498 (54%)	350/652 (54%)
Time from HCT to cGVHD months (range)	5 (1–11)	5 (1–11)	5 (1–11)	5 (1–11)
Severity of cGVHD				
Mild	485 (43)	265 (36)	425 (32)	136 (39)
Moderate	243 (22)	159 (21)	307 (23)	67 (19)
Severe	70 (6)	48 (6)	77 (6)	14 (4)
Missing	319 (29)	270 (36)	535 (40)	133 (38)
Onset of cGVHD				
Progressive	366 (33)	306 (41)	509 (38)	130 (37)
Interrupted	277 (25)	204 (27)	339 (25)	96 (27)
De novo	392 (35)	179 (24)	422 (31)	91 (26)
Missing	82 (7)	53 (7)	74 (6)	33 (9)
Organ involvement				
Skin	597 (53)	445 (60)	733 (55)	189 (54)
Eyes	331 (30)	170 (23)	401 (30)	105 (30)
Mouth	560 (50)	331 (45)	685 (51)	173 (49)
Lung	93 (8)	53 (7)	109 (8)	34 (10)
Gastrointestinal	217 (19)	177 (24)	273 (20)	89 (25)
GU	33 (3)	12 (2)	29 (2)	13 (4)
Liver	425 (38)	213 (29)	517 (38)	122 (35)
Musculoskeletal	59 (5)	54 (7)	110 (8)	21 (6)
Hematologic	109 (10)	95 (13)	138 (10)	45 (13)
Number of organs involved in cGVHD				
1	259 (23)	195 (26)	304 (23)	82 (23)
2	258 (23)	177 (24)	342 (25)	74 (21)
3	212 (19)	127 (17)	251 (19)	59 (17)
4	138 (12)	76 (10)	149 (11)	49 (14)
5	35 (3)	21 (3)	46 (3)	15 (4)
6	5 (<1)	2 (<1)	9 (1)	2 (1)
Missing	210 (19)	144 (19)	243 (18)	69 (20)
KPS at diagnosis of cGVHD, *n* (%)				
<80	215 (19)	154 (21)	367 (27)	90 (26)
80–100	704 (63)	453 (61)	789 (59)	173 (49)
Missing	198 (18)	135 (18)	188 (14)	87 (25)
Platelet count at diagnosis cGVHD $\times 10^9$/L, *n* (%)				
<100	294 (26)	214 (29)	450 (33)	95 (27)
≥100	639 (57)	409 (55)	682 (51)	183 (52)
Missing	184 (16)	119 (16)	212 (16)	72 (21)
Serum bilirubin at diagnosis of cGVHD mg/dL, *n* (%)				
<1	665 (60)	445 (60)	638 (47)	191 (55)
1–2	152 (14)	86 (12)	311 (23)	66 (19)
>2	159 (14)	117 (16)	220 (16)	37 (11)
Missing	141 (13)	94 (13)	175 (13)	56 (16)

evidence implicates acute and chronic GVHD in enhancing malignancy control and is best demonstrated in patients with acute leukemia and CML after MAC (2, 4, 6, 7, 15). GVHD is also a major complication of allogeneic HCT substantially contributing to overall TRM but its prevention or treatment with systemic immunosuppression may have harmful effects on GVL. Currently, there are no established clinical strategies to guide the intensity of systemic immunosuppressive therapy for GVHD based on presumed leukemia relapse risk. It would be useful to know more precisely in which setting GVHD is most beneficial for leukemia control versus those which predominantly increase TRM. Because occurrence and effects of acute and chronic GVHD overlap during the first year after transplant, it is difficult to study antitumor effects

Table 2. Incidence of late relapse and death

Cumulative incidence of late relapse (up to 5 years post HCT) according to diagnosis among patients who were disease free at 1 year after HCT

	AML	ALL	CML	MDS	Total
No relapse	2,170 (85.4%)	1,472 (81.87%)	2,176 (87.11%)	582 (89.26%)	6,400 (85%)
Relapse	371 (14.6%)	326 (18.13%)	322 (12.89%)	70 (10.74%)	1,089 (15%)
Total	2,541	1,798	2,498	652	7,489

Cumulative incidence of late relapse according to diagnosis among patients who were disease free and had no cGVHD at 1 year after HCT

	Probability (95% CI) at different time points after HCT			
Time after HCT	AML $n = 1,424$	ALL $n = 1,056$	CML $n = 1,154$	MDS $n = 302$
2 years	9 (7–10)	12 (10–14)	8 (6–10)	5 (3–8)
3 years	11 (10–13)	15 (13–18)	12 (11–15)	8 (5–12)
5 years	15 (13–17)	18 (16–21)	17 (14–19)	10 (7–14)

Cumulative incidence of late relapse according to diagnosis among patients who were disease free and had cGVHD at 1 year after HCT

	Probability (95% CI) at different time points after HCT			
Time after HCT	AML $n = 1,117$	ALL $n = 742$	CML $n = 1,344$	MDS $n = 350$
2 years	7 (6–9)	13 (11–15)	4 (3–5)	5 (3–8)
3 years	11 (9–13)	15 (13–18)	6 (5–8)	7 (5–11)
5 years	13 (11–15)	18 (16–21)	8 (6–9)	10 (7–13)

Cumulative incidence of death (up to 5 years after HCT) according to diagnosis among patients who were disease free at 1 year after HCT

	AML	ALL	CML	MDS	Total
Alive	1,922 (75.6%)	1,354 (75.31%)	2,018 (80.78%)	474 (72.7%)	5,768 (77%)
Dead	619 (24.3%)	444 (24.6%)	480 (19.2%)	178 (27.3%)	1,721 (23%)
Total	2,541	1,798	2,498	652	7,489

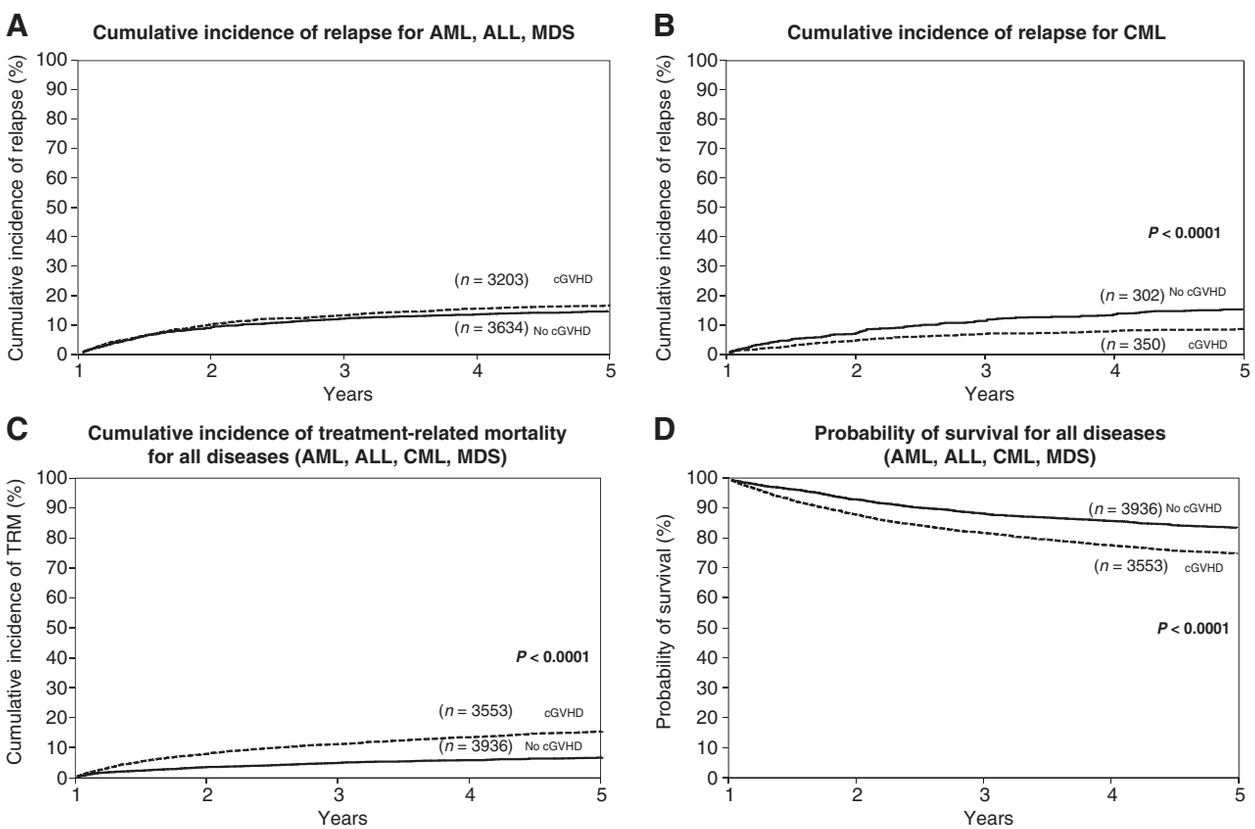

Figure 1.
A and B, cumulative incidence of late relapse according to prior history of chronic GVHD among patients who are disease free at 1 year after HCT. C and D, cumulative incidence of TRM and OS according to prior history of chronic GVHD among patients who are disease free at 1 year after HCT.

Table 3. Multivariate analysis of late relapses up to 5 years after HCT

	Number	RR (95% CI)	*P*
AML patients			
No cGVHD	1,424	1.00	
cGVHD	1,117	0.93 (0.75–1.14)	0.4809
ALL patients			
No cGVHD	1,056	1.00	
cGVHD	742	1.09 (0.87–1.37)	0.4423
CML patients			
No cGVHD	1,154	1.00	
cGVHD	1,344	0.47 (0.37–0.59)	<0.0001
MDS patients			
No cGVHD	302	1.00	
cGVHD	350	1.12 (0.70–1.79)	0.6391
Acute GVHD			<0.0001
none	4,051	1.00	
aGVHD in first 29 days after HCT	2,446	0.74 (0.63–0.85)	<0.0001
aGVHD after day 29 after HCT	986	1.15 (0.96–1.37)	0.1223
Disease status at transplant			<.0001
Early	4,661	1.00	
Intermediate	1,823	1.57 (1.35–1.83)	<0.0001
Advanced	999	2.57 (2.13–3.10)	<0.0001
HLA status			0.0200
Sibling donor	1,861	1.00	
Well-matched unrelated	1,412	0.83 (0.69–0.99)	0.0370
Partially matched unrelated	1,369	0.78 (0.65–0.93)	0.0049
Poorly matched unrelated	841	0.85 (0.69–1.04)	0.1143
GVHD prophylaxis			0.0043
T-cell depletion	748	1.00	
Cyclosporine ± methotrexate ± other	5,738	0.75 (0.62–0.91)	0.0032
Tacrolimus ± methotrexate ± other	997	0.68 (0.53–0.88)	0.0026

NOTE: Factors tested, but not listed in table: Recipient age, sex, graft type, donor-recipient gender mismatch, donor parity, donor-recipient CMV serology, use of TBI, use of ATG, aGVHD grade, year of transplant, platelet count at cGVHD diagnosis, serum bilirubin at cGVHD diagnosis, type of cGVHD onset, KPS/L at cGVHD diagnosis, severity of cGVHD at 1 year after transplant, organ involvement of cGVHD at 1 year after transplant.

attributed specifically to cGVHD in the proximity of acute GVHD and therapy-related systemic immunosuppression. We focused here on assessing cGVHD effects isolated from acute GVHD by studying only patients who were alive and free of disease at 1 year after HCT, when acute GVHD effects were sufficiently distant.

This study demonstrates the protective effect of cGVHD on late relapse only in patients with CML. A protective effect of cGVHD against late relapse was not seen in AML, ALL, or MDS. Data in this study also confirm that the presence of cGVHD is associated with significantly higher TRM and worse OS across all diseases studied (9).

Several retrospective studies have demonstrated that cGVHD decreases relapses in AML, ALL, and especially in CML (2, 4, 6, 16). These studies evaluated antileukemia effects from time of transplant to relapse and did not account for possible confounding effects by acute GVHD. The lack of impact of cGVHD on late relapse in acute leukemia and MDS in this study may be due to differences in biology and susceptibility to immune responses in each disease.

Relapse of leukemia following allo-HCT could be due to failure of GVL or immune clonal escape of the leukemia cells, including downregulation of MHC class I and II antigens, associated with a decreased ability to stimulate allo-geneic–proliferative T-cell responses, and decreased susceptibility to lysis by cytotoxic T lymphocytes or natural killer cells. Because GVL requires time to become fully established after immune reconstitution, the degree to which GVL can control leukemia after allo-HCT may depend on the growth kinetics of the leukemia. Thus, patients with CML compared with patients with acute leukemia may be more susceptible to a durable GVL effect because of their slower pace of proliferation.

The majority of leukemia relapses occur within the first year after HCT. Similar risk of relapse has been observed using URD transplant or HLA-identical sibling donors in AML, ALL, and CML (15). In this study, late relapses occurred in all leukemia types and a beneficial cGVHD effect was detected only in those with CML. Differential susceptibility to GVL effects has been observed after administration of donor leukocyte infusion, which is more effective in relapsed CML than other hematologic malignancies (17–20).

Despite the expectation of protective effects of cGVHD in all diseases, the 5-year incidence of relapse was only lower in CML. For this reason, we analyzed whether any of the cGVHD-specific clinical characteristics or organ manifestations, showed a more dominant association with relapse in patients with CML, as such findings could lead toward a better understanding of GVL mechanisms dependent on cGVHD. We found that all sites and types of cGVHD involvement equally affected relapse, suggesting that patients with CML with minimal cGVHD clinical manifestation may benefit from its antitumor effect.

This study has several limitations. Chronic GVHD was not classified in the study per NIH consensus criteria and the data analysis used retrospective design. Specific treatment

Table 4. Multivariate analyses of risk factors for late transplant-related mortality

	Number	RR (95% CI)	*P*
Prior chronic GVHD			
No prior diagnosis of cGVHD	3,936	1.00	
Prior cGVHD	3,547	2.43 (2.09–2.82)	<0.0001
Acute GVHD history			<0.0001
None	4,051	1.00	
aGVHD in first 29 days after HCT	2,446	1.40 (1.21–1.63)	<0.0001
aGVHD after day 29 after HCT	986	1.58 (1.32–1.91)	<0.0001
Disease Status at HCT			<0.0001
Early	4,661	1.00	
Intermediate	1,823	0.93 (0.78–1.10)	0.3908
Late	999	1.43 (1.20–1.69)	<0.0001
HLA match			<0.0001
Sibling donor	1,861	1.00	
Well-matched unrelated	1,412	1.39 (1.15–1.67)	0.0006
Partially matched unrelated	1,369	1.36 (1.13–1.63)	0.0013
Poorly matched unrelated	841	1.56 (1.25–1.93)	<0.0001
TBI in the conditioning regimen			
No	3,186	1.00	
Yes	4,292	1.47 (1.27–1.70)	<0.0001
Donor-recipient gender match			<0.0001
Male → male	2,662	1.00	
Male → female	1,720	0.63 (0.77–1.11)	0.4146
Female → male	1,629	1.55 (1.32–1.83)	<0.0001
Female → female	1,472	1.11 (0.93–1.33)	0.2623
Graft source			
Bone marrow	5,354	1.00	
Mobilized blood stem cells	2,129	1.48 (1.26–1.73)	<0.0001

NOTE: Factors tested, but not listed in table: Recipient age, sex, donor parity, donor-recipient CMV serology, use of ATG, GVHD prophylaxis, aGVHD grade, year of transplant, disease, platelet count at cGVHD diagnosis, serum bilirubin at cGVHD diagnosis, type of cGVHD onset, KPS/L at cGVHD diagnosis, severity of cGVHD at 1 year after transplant, organ involvement of cGVHD at 1 year after transplant.

Table 5. Multivariate analyses of risk factors for overall mortality among patients who were alive and disease free at 1 year after HCT

	Number	RR (95% CI)	*P*
Presence of cGVHD			
No cGVHD	3,936	1.00	
cGVHD	3,547	1.56 (1.41–1.73)	<0.0001
Acute GVHD history			<0.0001
None	4,051	1.00	
aGVHD in first 29 days	2,446	1.11 (0.93–1.24)	0.0716
aGVHD after day 29	986	1.46 (1.28–1.67)	<0.0001
Disease			<0.0001
AML	2,541	1.00	
ALL	1,798	1.26 (1.10–1.45)	0.0008
CML	2,498	0.73 (0.64–0.83)	<0.0001
MDS	652	0.84 (0.70–1.00)	0.0521
Disease status at HCT			<0.0001
Early	4,661	1.00	
Intermediate	1,823	1.25 (1.10–1.41)	<0.0001
Advanced	999	1.83 (1.59–2.11)	0.0005
HLA match			0.0191
Sibling donor	1,861	1.00	
Well-matched unrelated	1,412	1.18 (1.03–1.36)	0.0199
Partially matched unrelated	1,369	1.12 (0.92–1.29)	0.1148
Poorly matched unrelated	841	1.26 (1.07–1.49)	0.0049
TBI in the conditioning regimen			
No	3,186	1.00	
Yes	4,292	1.20 (1.07–1.34)	0.0015
Sex match			<0.0001
Donor male/recipient male	2,662	1.00	
Donor male/recipient female	1,720	0.94 (0.83–1.08)	0.3982
Donor female/recipient male	1,629	1.43 (1.27–1.62)	<0.0001
Donor female/recipient female	1,472	1.03 (0.90–1.18)	0.7114
Graft source			
Bone marrow	5,354	1.00	
Mobilized blood stem cells	2,129	1.24 (1.10–1.40)	0.0004

NOTE: Factors tested, but not listed in table: Recipient age, sex, donor parity, donor-recipient CMV serology, use of ATG, GVHD prophylaxis, aGVHD grade, year of transplant, platelet count at cGVHD diagnosis, serum bilirubin at cGVHD diagnosis, type of cGVHD onset, KPS/L at cGVHD diagnosis, severity of cGVHD at 1 year after transplant, organ involvement of cGVHD at 1 year after transplant

information for cGVHD is not ascertained and variability in treatment modalities for acute and chronic GVHD during the first year after HCT may have affected the incidence of late relapse. However, any such effects should be balanced out by the very large number of patients in this study cohort. This study was selected to evaluate a specific question: impact of cGVHD on late relapse (after 1 year after HCT). To classify patients accurately and determine cutoff points for analysis, we evaluated time to onset of cGVHD. Most patients (>95%) developed cGVHD within 1 year of HCT. Hence, we chose this time point for evaluation. Patients who developed cGVHD after 1 year and were eligible to be included in the dataset were classified as patients with non-cGVHD. This may also have affected the analysis. In addition, patients who developed cGVHD during the first year after allogeneic HCT and were successfully treated for their cGVHD may have been reported to the registry as not having active cGVHD. This would be quite unlikely, considering the usually slowly receding nature of cGVHD, and the standard procedure of 12 months registry data collection, which requires reporting events during the whole previous observation period. Data on the use of tyrosine kinase inhibitors (TKI) before allogeneic HCT were not available in patients with CML; however, during this study period of 1995 to 2004, only a minority of patients could have had prior TKI exposure.

This report findings only applies to cGVHD effects after MAC. The more recently expanded use of reduced intensity conditioning (RIC) or truly non-MAC regimens has shifted some of the burden of tumor cell kill after allogeneic HCT from the conditioning regimen to the immune-mediated GVL effects (18). Weisdorf and colleagues (21) recently investigated the effects of acute and chronic GVHD on late relapse after RIC and MAC conditionings regimens in patients with AML and MDS. Similar to this study, in patients with AML and MDS following MAC they found the risk of late relapse not significantly affected by cGVHD. However, following RIC regimens, in patients who had both acute and cGVHD late relapse rates were significantly lower. Baron and colleagues (22) also evaluated the GVL effects of cGVHD in patients with AML that underwent RIC allo-HCT. In a landmark analysis of patients who were leukemia free at 18 months after HCT, patients with cGVHD before the landmark day had a lower relapse rate than those without cGVHD. These data combined, demonstrate a differential effect of cGVHD on late relapse based on the type of conditioning used in allo-HCT.

In conclusion, this study suggest that cGVHD impact on late relapse of leukemia after MAC HCT is not clinically relevant in AML, ALL, and MDS and the beneficial effects on late relapse are confined to patients with CML. The potentially positive impact of the GVL effects on survival after MAC HCT are blunted by a higher cGVHD-related mortality resulting with higher TRM and lower OS for all studied diseases. These data may have practical clinical implications, as developing more aggressive strategies to prevent and treat cGVHD may be justified for hematologic malignancy patients after HCT with MAC regimens. Future studies aiming to advance the understanding of the cGVHD role in controlling hematologic malignancy should be done prospectively in contemporary patient cohorts and incorporating high level of detail on cGVHD clinical data collection.

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