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Impact of Donor Age on Outcome after Allogeneic Hematopoietic Cell Transplantation

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A B S T R A C T

As older patients are eligible for allogeneic hematopoietic cell transplantation (HCT), older siblings are increasingly proposed as donors. We studied the impact of donor age on the tempo of hematopoietic engraftment and donor chimerism, acute and chronic graft-versus-host disease (GVHD), and nonrelapse mortality (NRM) among 1174 consecutive patients undergoing myeloablative and 367 patients undergoing nonmyeloablative HCT from HLA-matched related or unrelated donors with granulocyte colony–stimulating factor–mobilized peripheral blood mononuclear cell allografts. Sustained engraftment rates were 97% and 98% in patients undergoing myeloablative and nonmyeloablative conditioning, respectively, for grafts from donors $<$ 60 years old (younger; n = 1416) and 98% and 100%, respectively, for those from donors $\geq$60 years old (older; n = 125). No significant differences were seen in the tempo of neutrophil and platelet recoveries and donor chimerism except for an average 1.3-day delay in neutrophil recovery among myeloablative patients with older donors ($P = .04$). $CD34^+$ cell dose had an independent effect on the tempo of engraftment. Aged stem cells did not convey an increased risk of donor-derived clonal disorders after HCT. Myeloablative and nonmyeloablative recipients with older sibling donors had significantly less grade II to IV acute GVHD than recipients with grafts from younger unrelated donors. Rates of grade III and IV acute GVHD, chronic GVHD, and NRM for recipients with older donors were not significantly different from recipients with younger donors. In conclusion, grafts from donors $\geq$60 years old do not adversely affect outcomes of allogeneic HCT compared with grafts from younger donors.

INTRODUCTION

With reductions in the intensity of conditioning regimens and improvements in supportive care, older patients have increasingly become eligible for allogeneic hematopoietic cell transplantation (HCT) [1,2]. As the age of allogeneic HCT recipients has increased, the age of sibling donors has increased, as well. The impact of patient age and medical comorbidities on transplantation outcome has been explored extensively [3-6]. However, the impact of increasing donor age on the functional fitness of hematopoietic cells has been controversial [7-16]. Most of the work on stem cell aging has been conducted in mice. As de Haan et al. observed, "the discrepant conclusions of these studies, however, could be partly caused by differences in mouse strains used, because strain-dependent increases or decreases in primitive hematopoietic cell frequency and function have been reported" [17]. Also, the longevity of hematopoietic stem cells makes them ideal targets for mutagenic changes, which raises the theoretical concern that recipients of aged stem cells are at an increased risk of developing malignant clonal disorders [15]. The uncertainties raised both by these theoretical considerations and the preclinical work prompted the current clinical report. In allogeneic HCT for treatment of human blood disorders, a relatively small inoculum of donor hematopoietic cells is called upon to recapitulate a diverse and fully functional hematopoietic system in the recipient. In earlier reports, we described polyclonal normal hematopoiesis and normal or near-normal immune function in younger patients (3 to 40 years old at the time of HCT) who had younger donors (4 to 50 years old) and were studied 20 to 30 years after transplantation [18,19]. The first questions posed by the current

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study were whether increasing age of donor hematopoietic cells impaired their ability to repopulate the recipient hematopoietic niche, resulting in a delay of neutrophil and platelet recoveries, and whether aged stem cells increased the risk of post-transplantation clonal disorders. Another question was whether grafts from older donors adversely affected long-term transplantation-related outcomes apart from relapse of the underlying disease. To obtain the answers, we used data from a single center and studied the impact of donor age on the tempo of hematopoietic engraftment, the development of clonal disorders and acute and chronic graft-versus-host disease (GVHD), and on the 5-year nonrelapse mortality (NRM) after allogeneic HCT among 1541 patients, the majority of whom had hematologic malignancies.

PATIENTS AND METHODS

The decision to analyze patients given myeloablative conditioning and nonmyeloablative conditioning separately was based on several considerations: (1) the greater degree of marrow ablation with the former compared with the latter regimen imposes greater immediate replicative demands on the donor hematopoietic cells; (2) the incidence of acute GVHD at our center is historically higher among myeloablative compared with nonmyeloablative recipients [20]; and (3) as a rule, patients given nonmyeloablative conditioning at our center are either ≥55 to 65 years old or, if younger, have medical comorbidities that preclude myeloablative conditioning.

Patients

Myeloablative conditioning

We retrieved data for all patients receiving myeloablative conditioning and granulocyte colony–stimulating factor–mobilized peripheral blood mononuclear cell (G-PBMC)–derived allografts from an HLA-matched related or unrelated donor for any diagnosis at Fred Hutchinson Cancer Research Center between January 1, 1999 and December 31, 2009 (n = 1174). Characteristics of patients undergoing myeloablative allogeneic HCT during the study period are given in Table 1. Patients had HLA-identical sibling donors (n = 604, 51%) or HLA-matched unrelated donors (n = 570, 49%). Ninety-six percent of related older donors had 2 days of G-PBMC collections, where 4% had more than 2 collections. Forty-two percent of patients were conditioned with total body irradiation (TBI)–based regimens, whereas the remaining 58% received chemotherapy-only conditioning. Most donors (95%) were younger than 60 years of age, whereas 60 (5%) of donors were 60 or older at the time of hematopoietic cell collection. The majority of recipients of grafts from older donors were 50 years or older, whereas most of the recipients of grafts from younger donors were less than 50 years old.

Nonmyeloablative conditioning

We also retrieved data on all patients receiving allogeneic HCT with a G-PBMC–derived graft on prospective trials registered with ClinicalTrials.gov for any diagnosis after nonmyeloablative conditioning, which we defined as 2 Gy TBI with or without fludarabine 90 mg/m^2 as reported previously

Table 1
Characteristics of Recipients of Allogeneic Hematopoietic Cell Transplantation after Myeloablative Conditioning

Characteristic	Related Donor <60 yr (n = 545)	Unrelated Donor <60 yr (n = 569)	Donor ≥60 yr (n = 60)
Patient age, yr			
<50	361 (66)*	355 (62)*	5 (8)
≥50	184 (34)	214 (38)	55 (92)
Patient sex			
Female	235 (43)	258 (45)	21 (35)
Male	310 (57)	311 (55)	39 (65)
Ideal body weight			
Data available, n	488	515	55
Median (range), kg	66 (7-119)	66 (7-173)	68 (50-85)
Donor			
Related	545 (100)	0	59 (98)
Unrelated	0	569 (100)	1 (2)
Recipient/donor CMV status			
−/−	179 (33)	194 (34)	20 (34)
−/+	75 (14)	57 (10)	6 (10)
+/−	105 (19)	199 (35)	14 (24)
+/+	183 (34)	119 (21)	19 (32)
Missing			
Received TBI			
No	324 (59)†	310 (54)†	44 (73)
Yes	221 (41)	259 (46)	16 (27)
CD34$^+$ cell dose/kg × 10^6			
Data available, n	512	513	55
Median (range)	7.5 (2.1-31.5)*	7.9 (.7-57.9)*	5.7 (2.1-17.4)
TNC cell dose/kg × 10^8			
Data available, n	512	513	55
Median (range)	11.6 (3.4-43.0)*	10.5 (2.0-46.7)*	14.7 (5.9-45.0)
Transplantation yr			
1999-2000	105 (19)	34 (6)	7 (12)
2001-2002	114 (21)	132 (23)	9 (15)
2003-2005	188 (35)	235 (41)	22 (37)
2006-2009	138 (25)	168 (30)	22 (37)
Diagnosis			
AML	210 (39)	242 (43)	24 (40)
MDS	137 (25)†	166 (29)†	28 (47)
CML	70 (13)†	38 (7)	4 (7)
ALL	63 (12)†	93 (16)†	1 (2)
CLL/HL/NHL	46 (8)	19 (3)	2 (3)
Other	19 (3)	11 (2)	1 (2)
Median follow-up, mo	50	49	43

CMV indicates cytomegalovirus; TNC, total nucleated cells; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; CML, chronic myeloid leukemia; ALL, acute lymphocytic leukemia; CLL, chronic lymphocytic leukemia; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma.
Data presented are n (%) unless otherwise indicated.
† $P < .05$ versus older donor group.
* $P < .001$ versus older donor group.