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CCR5 expression on cells from HLA-matched unrelated marrow donors and graft-versus-host disease

Qing Ma[1], **Ted A. Gooley**[1], and **Rainer F. Storb**[1,2]

[1]Clinical Research Division, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue, Seattle, WA 98109

[2]School of Medicine and Public Health, University of Washington

Graft-versus-host disease (GVHD), a common complication that is caused by donor T cells following allogeneic hematopoietic cell transplant. Recently, the functional state of T cells has been characterized by their chemokine receptor expression pattern (1). T cells expressing chemokine receptor CCR5 contribute to the rejection of solid organ allografts (2) and development of murine GVHD (3-5). A non-functional mutant allele of CCR5, CCR5Δ32, is found with 10% frequency in Caucasians (6-7). In a study of renal-transplant survival, patients homozygous for CCR5Δ32 had significantly prolonged graft survival compared to heterozygous or wild type patients (8). Here, we retrospectively compared outcomes among patients receiving marrow grafts from unrelated donors homozygous for CCR5Δ32 to those from donors expressing CCR5.

We screened the donor DNA repository at Fred Hutchinson Cancer Center for the CCR5Δ32 mutation by a PCR method (9). Among 1273 donors, 9 were homozygous for CCR5Δ32. Recipients of those bone marrow grafts were predominantly CML patients (CML=8 and AML=1), and we therefore decided to confine our study to the CML patient group. Patients were 18-50 years old and transplanted between 1988 to 2000. They received cyclophosphamide and fractionated total body irradiation, unmanipulated marrow, and GVHD prophylaxis with cyclosporine and methotrexate (9). A total of 344 CML patients had a CCR5 wild-type donor, 39 had a CCR5Δ32 heterozygous donor, and 8 had a CCR5Δ32 homozygous donor. Logistic regression model was used to assess the association between CCR5 genotype and acute GVHD, and Cox regression was used for chronic GVHD and relapse. As shown in Table 1, there was less GVHD among patients whose donor was CCR5Δ32 homozygous compared to patients with a wild-type or heterozygous donor, although most of the differences are not statistically significant. The number of patients with a homozygous donor is small, making it difficult to derive firm conclusions even where results are suggestive of a true difference. Moreover, there are several factors that impact GVHD, relapse, and mortality. With only 8 patients with a homozygous donor, we made limited adjustments. After controlling for severity of disease (categorized as low (chronic phase) vs. intermediate (accelerated phase or blast crisis in remission) vs. high (blast crisis), the effects associated with the homozygous group are similar

Address correspondence to: Qing Ma, Section of Transplant Immunology, Department of Stem Cell Transplantation and Cellular Therapy, University of Texas M.D. Anderson Cancer Center, Unit 900, 1515 Holcombe Boulevard, Houston, TX 77030, Tel. 713-563-3327; Fax. 713-563-3364; Email: qma@mdanderson.org.

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to the unadjusted results (data not shown). Similarly, after adjusting for number of mismatched HLA alleles (considering HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1, with a range of 0 to 8 total mismatches in the 391 patients), the effects associated with the homozygous group are similar to the unadjusted results (data not shown).

In summary, the absence of functional CCR5 in marrow donors may be associated with less GVHD. With only 8 patients having a homozygous donor, these preliminary results are in need of larger numbers. Therefore, we propose screening the sample repository from the National Marrow Donor Program Foundation to identify additional patients with a CCR5Δ32 homozygous donor. Currently CCR5 antagonists are developed and approved for HIV treatment (10). Further studies may provide rationale to develop novel treatment for GVHD.

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Table 1

	+/+ (n=344)	+/- (n=39)	-/- (n=8)
Grades 2-4	309 (90%) OR=1	34 (87%) OR=0.77 (0.28-2.10, p=.61)	6 (75%) OR=0.34 (0.07-1.75, p=.20)
Grades 3-4	124 (36%) OR=1	13 (33%) OR=0.89 (0.44-1.79, p=.74)	1 (13%) OR=0.25 (0.03-2.08, p=.20)
Skin*	288 (84%) OR=1	18 (46%) OR=0.89 (0.37-2.11, p=.79)	4 (50%) OR=0.19 (0.05-0.80, p=.02)
Liver*	159 (46%) OR=1	32 (82%) OR=0.65 (0.33-1.30, p=.22)	2 (25%) OR=0.39 (0.08-1.95, p=.25)
Gut*	219 (64%) OR=1	14 (36%) OR=0.82 (0.42-1.61, p=.57)	5 (63%) OR=0.95 (0.22-4.05, p=.95)
Chronic**	207 (60%) HR=1	19 (49%) HR=0.96 (0.60-1.53, p=.85)	3 (38%) HR=0.45 (0.14-1.41, p=.17)
Relapse	66 (19%) HR=1	9 (23%) HR=1.71 (0.85-3.43, p=.13)	3 (38%) HR=1.80 (0.57-5.71, p=.32)
Mortality	167 (49%) HR=1	24 (62%) HR=1.59 (1.04-2.44, p=.03)	4 (50%) HR=1.01 (0.37-2.71, p=.99)

* organ-specific GVHD of any grade (1-4)

** clinical extensive chronic GVHD