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How closely related is graft-vs-leukemia to donor/recipient disparity?

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Graft-vs-host disease (GVHD) is an unwanted complication of stem cell transplant, but the graft-vs-leukemia (GVL) effect has been shown to positively affect outcomes. GVHD and GVL have similar but not identical alloreactivity, and GVL may be affected by the source of grafts, the preparative conditioning regimen, and donor genetic elements. Human leukocyte antigen (HLA) mismatch does not appear to augment the GVL effect, and increased GVHD does not necessarily lead to decreased relapse.

Introduction

The effectiveness of allogeneic stem cell transplantation for leukemia results from more than the high-dose therapy that precedes transplant. While graft-vs-host disease (GVHD) is a negative consequence of transplant, the graft-vs-leukemia (GVL) effect significantly benefits outcome for transplant. However, GVL might just be a manifestation of GVHD.

Graft-vs-host reactivity involves a cytolytic attack on target tissues, which could also result in immunodeficiency or GVL, depending on the efficacy of the attack in various tissues. In general GVHD reactions, CD8+ T-cells lyse human leukocyte antigen (HLA) class I-expressing targets, usually in tissues of the gut, skin, and liver. In immunodeficiency, the CD8+ cells attack HLA class I-expressing thymic tissue. Also in GVHD, natural killer (NK) cells lyse targets lacking class I inhibitory killer-immunoglobulin receptor-ligand (KIR-L). Other mediators of GVHD include B cells, cytokines, and

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antibody-dependent cell-mediated cytotoxicity (ADCC), among others. For the GVL effect, CD8+ T-cells seek HLA class I-expressing targets, such as myeloid or lymphoid tissue. NK-cells, antibodies, and cytokines attack targets expressing minor histocompatibility, microbial pathogens, or tumor-associated antigens.

HLA mismatch and minor histocompatibility antigen mismatch, which is assumed to be present in fully matched unrelated and fully matched related donors, augments donor/recipient alloreactivity. This leads to more GVHD and more immunodeficiency, but it is unclear whether it also augments the GVL effect. It is uncertain whether a mismatched or unrelated donor transplant will yield augmented GVL and less relapse. To address this question in a clinical way, two large studies were conducted with data from the Center for International Blood and Marrow Transplant Research (CIBMTR) and donor/recipient specimens from the National Marrow Donor Program repository.

Unrelated vs HLA-identical sibling donor transplants

The first study used a homogeneous cohort of chronic myeloid leukemia (CML) patients in first chronic phase (CP1) [1] All patients received myeloablative conditioning and were transplanted between 1988 and 2003. Donors were either HLA-identical siblings ($n = 3537$) or unrelated but with allele-level HLA typing ($n = 1076$). Data were reported to CIBMTR. Age was similar between recipients of both donor sources (median, 36 years). For unrelated donor recipients, 51% received a transplant with an 8 of 8 HLA match, while 24% received a transplant with mismatch at 1 allele, 15% received transplant with mismatch at 2 alleles, and the remaining 10% received a transplant with mismatch at 3 or more alleles. However, most of these transplants were considered to be a complete match at the time they were performed. HLA-identical sibling transplants were conducted closer to time of diagnosis, while unrelated donor transplants occurred later. Median follow-up for HLA-identical sibling transplant recipients was 97 months (range, 2–209 months), and the median follow-up for patients who received transplants from unrelated donors was 106 months (range, 8–219 months).

Mismatching for minor or major histocompatibility antigens offered no additional protection against relapse, yet increased the risk of GVHD and transplant-related mortality (TRM). The cumulative incidence of TRM was lowest in the HLA-identical sibling cohort, followed by matched unrelated donor recipients [1]. TRM increased further with each HLA mismatch. This increase can be attributed to GVHD, as the severity of GVHD increased with unrelated donors and with HLA mismatch. However, the difference in relapse rates was not significant between a fully matched unrelated donor and an HLA-identical sibling donor or with greater degrees of HLA disparity. Relapse rates were low in all groups, with 5-year relapse incidence rates between 7% and 14%, regardless of donor type. Furthermore, there was no significant relapse benefit to a higher risk of GVHD. Leukemia-free survival was significantly better in patients receiving transplants from HLA-identical siblings, followed by matched unrelated donors and then mismatched unrelated donors.

In a second study that took place between 1995 and 2004 [2], adults with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), or CML received myeloablative treatment before transplant from HLA-identical siblings or unrelated matched donors. In contrast with the first study, only fully matched unrelated donor transplants were allowed, enabling this study to compare differences in other histocompatability antigens, but not differences in HLA. While 3158 patients received a transplant from an HLA-identical sibling, 941 received a transplant from a matched unrelated donor. The median age of recipients was approximately 38 years. Distribution among diseases was similar for the different types of donor transplants`. Most patients had CML (45% had sibling donors and 44% had unrelated donors), followed by AML (40% sibling and 36% unrelated donors), and ALL (15% sibling and 20% unrelated donors). Patients with sibling donors were more likely to receive a transplant early (70% vs 50% of unrelated donor transplants).

The 5-year relapse incidence was not significantly different between the different donor type transplants within each disease [2]. Furthermore, patients at each disease stage, first or second CR or relapse, had no significant differences in relapse due to donor type. However, a multivariate analysis showed that in AML patients there was significantly more relapse with unrelated donors and significantly less relapse in those with chronic GVHD. In ALL patients, multivariate analysis showed a smaller reduction in risk of relapse with chronic GVHD, and the difference did not quite reach statistical significance ($P = 0.058$). In CML, chronic GVHD significantly lowered the risk of relapse, according to