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EXTRAMEDULLARY RELAPSE OF ACUTE MYELOGENOUS LEUKEMIA (AML) AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (ALLO-HCT): BETTER PROGNOSIS THAN SYSTEMIC RELAPSE

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**Introduction:** Allo-HCT is considered a curative treatment for AML; however, leukemia relapse remains the major cause of mortality after HCT. Extramedullary relapse after HCT for AML is a rare event and its characteristics and prognosis are less well defined than systemic relapse. We studied 436 AML allo-HCT patients and analyzed the characteristics and outcomes of 128 patients who had post-HCT leukemia relapse; 25 with extramedullary relapse.

**Methods:** We retrospectively studied all AML patients transplanted at the University of Minnesota (UM) between 1996 and 2008 who developed either a bone marrow or extramedullary relapse. Patient demographics, transplant-related variables and outcomes were prospectively collected and available from the UM transplant database. Data regarding site of relapse, therapy and outcome post-relapse were collected from the patients' available medical records. Survival through 6 months post-relapse was estimated using Kaplan-Meier curves.

**Results:** Of 128 patients who relapsed post-HCT, 25 occurred in extramedullary sites, either isolated (n = 13, group B) or with concomitant marrow relapse (n = 12, group BM). Relapse sites were bone (n = 1), central nervous system (n = 6), gastrointestinal (n = 4), lymphatic (n = 4), skin (n = 5), genitourinary (n = 1), pulmonary (n = 1) and unidentifiable (n = 3). The median time to relapse was longer in the extramedullary sites than marrow only (328 vs 168 days). Patients with extramedullary relapse were more likely to have had preceding grade II-IV acute GVHD (77% vs 49%; p = 0.03) or chronic GVHD (46% vs 15%; p = 0.02) compared to marrow relapse only. Among all relapsed patients, chronic GVHD and relapse within 6 months of HCT were associated with worse overall survival. However, 6 month survival post relapse was significantly better for isolated extramedullary relapse (69%) compared to combined marrow and extramedullary (8%) or marrow relapse alone (27%) (p < 0.01). In patients who had isolated extramedullary relapse, administration of systemic therapy (± local to relapse site) yielded better 6 months OS (40-56%) than local (OS 33%) alone.

**Conclusion:** This study suggests that there may be different pathogenesis for marrow versus extramedullary relapse of AML following allo-HCT. GVHD and accompanying GVL may better protect marrow versus extramedullary relapse of AML following allo-HCT. This study suggests that there may be different pathogenesis for marrow versus extramedullary relapse of AML following allo-HCT. GVHD and accompanying GVL may better protect marrow versus extramedullary relapse of AML following allo-HCT.

**Models were adjusted for age, disease severity, donor/patient gender, T-cell depletion, conditioning, and HLA mismatch.**

**Results:** 422 donors were KIR2DS1-positive, 429 donors were KIR3DS1-positive (n = 355 KIR2DS1pos, KIR3DS1pos), and 630 donors were KIR2DS2-positive. The presence of donor KIR2DS1 was associated with lower relapse [HR 0.76 (0.61-0.96), p = 0.02], even after adjusting for presence of KIR2DS2 [adjusted HR: 0.77 (0.61-0.97), p = 0.02] and presence of donor KIR2DS1, with which it shares strong positive LD [adjusted HR 0.71 (0.51-0.99), p = 0.04]. Donor KIR2DS1 was associated with reduced non-relapse mortality [HR 0.68 (0.50-0.92), p = 0.01] and decreased overall mortality [HR 0.79 (0.63-0.98), p = 0.03] even after adjusting for donor KIR2DS1. Interestingly, after adjusting for KIR2DS1, KIR2DS2 positivity had little association with relapse or mortality. Furthermore, the protective effect of donor centromeric KIR B-lymphocyte homozygosity on relapse was not statistically significant [CenBB vs. CenAA, HR 1.0 (0.80-1.25, p = .98)]. There was no statistically significant association of donor KIR2DS2 on survival, relapse, or non-relapse mortality.

**Conclusion:** Individual activating KIR may mediate independent effects in unrelated allogeneic HCT for AML, with KIR2DS1 protecting from relapse and KIR2DS2 protecting from non-relapse mortality.

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DONOR KIR2DS1 AND KIR3DS1 ARE ASSOCIATED WITH IMPROVED OUTCOMES FOLLOWING UNRELATED ALLOGENEIC STEM CELL TRANSPANTATION FOR ACUTE MYELOID LEUKEMIA


**Background:** Current concepts of NK alloreactivity are based on donor/receptor KIR ligand mismatching and on donor KIR genotype variants, while little is known about the role of specific activating KIR genes. Specifically, the importance of the telomeric KIR2DS1 and KIR3DS1 genes, and the centromeric KIR2DS2 gene has not been studied in detail. We tested the hypothesis that individual donor activating KIR genes would influence the outcome of AML patients undergoing unrelated allogeneic HCT.

**Methods:** Donor KIR genotyping was performed for 1228 AML patients receiving transplants between 1989 and 2008 from 9/10 or 10/10 HLA-matched unrelated donors with outcome data provided by the CIBMTR. HLA genotyping was verified through the NMDP retrospective typing program. Cox regression was used to examine the association between donor KIR genotype and HCT outcome.

**Donor KIR2DS1 and KIR3DS1 are associated with improved outcomes following unrelated allogeneic stem cell transplantation for acute myeloid leukemia (AML) after allogeneic hematopoietic stem cell transplantation (ALLO-HCT): Better prognosis than systemic relapse.**

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T-CELL COSTIMULATORY MOLECULE GENOTYPES ARE ASSOCIATED WITH THE RISK OF EARLY CYTOMEGALOVIRUS INFECTION AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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**Objectives:** Donor T lymphocytes play a critical role in graft-versus-host disease (GVHD) and infection prevention in allo-HSCT. CD28 is the primary T-cell costimulatory molecule constitutively expressed on T cells, which transduces a signal that enhances the activation and proliferation of T cells. Another member of the CD28 family is inducible co-stimulator (ICOS). Although not constitutively expressed, ICOS is rapidly upregulated on T cells upon activation. Cytotoxic T-lymphocyte antigen 4 (CTLA-4), a homologous molecule of CD28, is a T-cell costimulatory molecule maintaining tolerance by producing a negative signal to T cells. The aim of this study was to analyze donor and recipient T-cell costimulatory molecule gene polymorphisms associated with CMV infection within 100 days after HSCT.

**Methods:** We analyzed 5 single nucleotide polymorphisms (SNPs): CD28 -594(A/G), ICOS -693(G/A) and CTLA-4 -1722(A/G), -802(A/G), -594(A/G), -478(A/G), and -327(A/G). The incidence of CMV infection remains high and provide the first report of relationship between T-cell costimulatory molecule gene polymorphic features to the risk of early CMV infection.

**Results:** (1) All patients and donors are CMV seropositive before HSCT (only one donor from Taiwan is CMV seronegative). 117 patients (57.6%) had experienced early CMV infection with a median onset of 26 days (range2-64) after HSCT. 23% of 117 patients developed infection during granulocytopenia and 77% after neutrophil recovery. 92.3% of 117 patients developed CMV-DNA positive antigenemia without disease, only 9 patients developed CMV disease (7 patients with pneumonia and 2 patients with enteritis). (2) Patients receiving stem cells from a donor with CTLA-4 CT60 AA genotype had a higher incidence of early CMV infection than those with AG/ GG genotypes in both the unrelated and sibling cohorts. (3) Multivariate analysis identified four risk factors for early CMV infection: patients with CMV reactivation pre-HSCT (RR: 0.668, 95%CI: 0.454-0.983, P = 0.041), unrelated donor (RR: 0.528, 95%CI: 0.349-0.8, P = 0.003), patients experiencing aGVHD (RR: 1.606, 95%CI: 1.074-2.403, P = 0.021) and donors with CTLA-4 CT60 AA genotype (RR: 2.369, 95%CI: 1.461-3.841, P < 0.001).

**Conclusion:** Although CMV disease has been reduced in the era of antiviral prophylaxis and preemptive therapy, our findings suggest the incidence of CMV reactivation remains high. The first report of relationship between T-cell costimulatory molecule gene polymorphic features to the risk of early CMV infection.