to >500/μl and platelets >20,000/μl w/o transfusion were 13 and 14 days, respectively. TRM included 1 pt each with intracranial hemorrhage at d 8, multi-organ failure/sepsis at d 28, IPS/ARDS at d 119, and grade IV GVHD with disseminated adenovirus. 2 of the 4 deaths were in MRD transplants; no serious cases of VOD were observed. Grade 2–4 GVHD was seen in 5/16 evaluable MUD pts and 3 of 29 (all sex mismatched) evaluable MRD pts. CMV reactivation was seen in nearly all CMV sero+ pts; bk activation was seen in 25 pts and hemorrhagic cystitis in 10. One case of PTLD, 3 graft failures, and adenovirus infection with nephritis, cystitis, and transient cardiomyopathy in one patient, and fatal hepatitis in a second patient were also seen. Relapse/# evaluable for different diseases are: AML 12/26 (46%), imatinib-resistant CML 3/3 MDS 0/5, MM 3/3, NHL 0/3, ALL 0/3, CLL 0/2. Relapse rates in evaluable MRD pts, 15/29 (52%), were statistically higher compared to MUD pts, 3/16 (19%) (p = .055); marrow (2/8) vs BSC, (16/37), were comparable. Alemtuzamab has been effective at controlling GVHD but infectious complications are common and high relapse rates preclude routine use of this approach in MRD patients with advanced myeloid diseases. Current use of this agent is depending on donor (MRD vs MUD) and disease (myeloid vs other) status.

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MISSING KILLER IMMUNOGLOBULIN-LIKE RECEPTOR (KIR) LIGAND CONFERS PROTECTION FROM RELAPSE IN RECIPIENTS OF UNRELATED HEMATOPOIETIC CELL TRANSPLANTATION (HCT) FOR AML

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The relationship between donor inhibitory KIR and recipient HLA has been proposed as the basis for KIR-driven alloreactivity by donor natural killer (NK) cells, leading to higher overall survival (OS) and a reduction in relapse, graft-versus-host disease (GVHD) and graft rejection in high-risk acute myelogenous leukemia (AML) patients undergoing HLA-mismatched transplants. Previous analyses of KIR effects on HLA-mismatched HCT have applied a "KIR ligand incompatibility model," which predicts NK alloreactivity when donors with class I ligands for inhibitory KIR are paired with recipients lacking the particular class I ligand group. We have developed an algorithm that recognizes that population frequencies for inhibitory KIR2DL2/3, -2DL1, and -3DL1 are close to 100%, whereas the corresponding class I ligands (HLA C1-group, C2-group, or Bw4) have population frequencies that deviate greatly from 100%, leading to the frequent situation of "missing KIR ligand," even in HLA-matched transplants. The "missing KIR ligand model" was applied in an analysis of 1765 unrelated donor HLA-A, -B, -C, -DRB1, and -DQB1 matched and mismatched HCT pairs from the IHWG. All patients received myeloablative conditioning followed by infusion of a T-replete allograft. Using the "missing KIR ligand model," KIR ligand absence/presence was correlated with overall survival (OS) and relapse (Table). There was no benefit in OS or relapse for ALL or CML patients lacking KIR ligand. In contrast, AML patients lacking KIR ligand demonstrated a significantly lower relapse rate (p=0.001), that could be exclusively attributed to the lack of the HLA C2-group ligand for donor KIR2DL1 (p<0.0001). The lower relapse likely contributes to the higher OS (p=0.04) seen in these patients. Comparison of the "missing KIR ligand" and "KIR ligand incompatibility" algorithms was then performed for AML/MDS (n=176), ALL (n=137), and CML (n=320) patients and unrelated donors mismatched at HLA-B and/or HLA-C. Neither model showed a benefit in OS or relapse for any disease group with exception of the missing ligand model in AML for relapse (p=0.008) This study indicates that lack of HLA C2-group ligand in the patient with AML is associated with a lower risk of relapse and improved overall survival, implying that release from KIR2DL1 inhibition enhances donor NK alloreactivity against AML. Adoptive immunotherapy with donor NK infusion may be particularly beneficial in these patients.

Missing KIR Ligand Algorithm and Disease-Specific Outcome

	Overall Mortality		Relapse	
	Hazard Ratio	p-Value	Hazard Ratio	p-Value
AML/MDS				
All ligands present (n = 105)	1	—	1	—
Any KIR ligand absent (n = 373)	0.86	0.27	0.55	0.001
HLA C2-Group ligand absent (n = 149)	0.73	0.04	0.34	<0.0001
CML				
All ligands present (n = 230)	1	—	1	—
Any KIR ligand absent (n = 683)	1.1	0.39	1.08	0.68
ALL				
All ligands present (n = 77)	1	—	1	—
Any KIR ligand absent (n = 297)	1.12	0.49	1.17	0.56

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TRANSFUSIONAL IRON BURDEN AFTER BONE MARROW TRANSPLANTATION

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Background: The significance of transfusional iron overload post-BMT for sickle cell disease (SCD) and hematological malignancies has not been well defined. Hence, we performed tests to assess iron burden before and after BMT that included: serum iron, ferritin, TIBC, and liver iron concentration (LIC) by liver biopsy and/or SQUID biosusceptometer (Ferritometer®, Model 5700, Tristan Technologies, San Diego) under the standardized Hamburg-Torino-Oakland protocol. We compared results in children with SCD and AML to those with thalassemia major (TM). **Results:** Fifteen children [SCD (N=4), TM (N=6), and AML (N=5)] received conventional myeloablative allografting at Children's Hospital Oakland (2000–2003). The mean (±SD) age (y) at BMT was 10 ± 2.3, 6.8 ± 5.1, and 5.4 ± 2.9 among SCD, TM, and AML patients, respectively. The mean duration of transfusion exposures was 2.5, 5, and 2 years, respectively. Results of pre-BMT iron burden are summarized in the Table. Pre-BMT liver histology was assessed in 6 patients (SCD 1 and TM 5). Inflammation was present in 4 TM patients and portal fibrosis in 1 SCD and 3 TM patients. Hepatic venoocclusive disease (VOD) developed in 5/15 patients. TM patients were more likely to develop VOD (80 vs 20%) and pre-BMT, nonspecific inflammatory liver changes were observed in 60% of TM patients (versus 10% of others). Post-BMT, six patients were treated by regular phlebotomy. There was poor correlation between serum ferritin and LIC. The serum ferritin and WBC normalized by 40 months among phlebotomized patients. However, normalization of LIC required a longer period of time. The amount of iron removed by phlebotomy correlated with the change in LIC as measured by SQUID. **Conclusion:** Pre-BMT, we observed a significant iron burden in children with SCD, TM, and AML, which, if untreated, persisted post-BMT. Liver inflammation and VOD was increased in TM patients, which might reflect liver injury that is influenced by the duration of exposure rather than simply by the magnitude of iron overload. Phlebotomy is effective in unloading iron post-BMT in SCD and TM patients. This pilot study showed that serum ferritin is an unreliable indicator of iron overload post-BMT. The significance of transfusional iron overload in patients with hematological malignancies remains uncertain, but this study suggests that there is potential for hepatic injury post-BMT. Ongoing studies are being conducted to better define the natural history of iron overload in post-BMT patients.