Compared to patients in CR, HSCT conferred an intermediate prognosis status, better than refractory disease, but significantly worse than 'classic' CR. Achieving a CR prior to HSCT should remain the gold standard for patients with AML or MDS receiving HSCT for patients in CR compared to CRp. CRp conferred an intermediate prognostic status, better than refractory disease, but significantly worse than 'classic' CR. Achieving a CR prior to HSCT should remain the gold standard for patients with AML or MDS receiving HSCT.

### Table. Hazard Ratios (HR) for non-relapse mortality (NRM) and overall survival (OS) at 1 year. CR1 is used as the reference group.

<table>
<thead>
<tr>
<th></th>
<th>NRM</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR1 (n = 164)</td>
<td>1.0</td>
<td>Reference</td>
</tr>
<tr>
<td>CR2 (n = 102)</td>
<td>1.4 (p = 0.3)</td>
<td>1.3 (p = 0.3)</td>
</tr>
<tr>
<td>CRp1 (n = 48)</td>
<td>2.4 (p = 0.01)</td>
<td>2.4 (p = 0.001)</td>
</tr>
<tr>
<td>CRp2 (n = 30)</td>
<td>1.7 (p = 0.2)</td>
<td>1.9 (p = 0.05)</td>
</tr>
<tr>
<td>Pf (n = 47)</td>
<td>3.7 (p = 0.001)</td>
<td>3.6 (p = 0.001)</td>
</tr>
<tr>
<td>First relapse (n = 36)</td>
<td>4.6 (p = 0.001)</td>
<td>6.7 (p = 0.001)</td>
</tr>
</tbody>
</table>

CR = complete remission; CRp = pathologic CR; Pf = primary induction failure.

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**POST-HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) OUTCOMES IN PATIENTS WITH AML TRANSPLANTED PRIOR TO ACHIEVING PLATELET RECOVERY**

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Complete remission (CR) after chemotherapy for AML is defined by absence of blasts in bone marrow (BM) and peripheral blood (PB) sample >100/μl. This remains the primary goal following chemotherapy; however, many patients proceed to HSCT without ever achieving the platelet goal (CRp). With new therapies, the number of patients transplanted in CRp is increasing. We sought to determine if CRp was a worse prognosticator compared to classically-defined CR.

Method: A cohort of 427 patients was used. Disease status at HSCT included: first CR (CR1); second CR (CR2); first CRp (CRp1); patients with <5% BM blasts but not platelet recovery following induction chemotherapy; primary induction failure (PIF): no CR following induction therapy; CRp2: patients who after therapy for first relapse achieved <5% BM blasts but not platelet recovery; refractory (rel): patients in first relapse not responding to salvage therapy. CRp was assigned only if patients were thrombocytopenic ≥30 days from the last day of chemotherapy to the start of HSCT conditioning. Diagnoses included AML (n = 376) or high-risk MDS (n = 51). Conditioning regimens used: TBI-based (23%; n = 8), oral/IV busulfan-based ablative regimens (61%; n = 261), fludarabine/melphalan-based reduced intensity conditioning regimens (RIC) (36%; n = 133), or other (1%; n = 5). Fifty-eight percent (n = 248) and 42% (n = 179) of patients received matched sibling or unrelated donor (UD) HSCT, respectively.

Results: Median age was 50 years (range 6–74). At time of HSCT, disease status was CR1 in 38% (n = 164), CR2 in 24% (n = 102), CRp1 in 11% (n = 48), CRp2 in 7% (n = 30), PIF 11% (n = 47), and rel 8% (n = 36). Poor-risk cytogenetics were evenly distributed in patients in CR1 (93%) vs. CRp1 (44%) and in CR2 (15%) vs. CRp2 (24%). Fifty-one percent of patients died (n = 219); 31% (n = 134) progressed. Overall survival (OS) at 36-months was 49%. Among survivors, median follow-up is 42 months (range 3–134 months). Hazard ratios for non-relapse mortality (NRM) and OS at 1-year (Table) favored patients receiving HSCT in CR1 vs. CRp1 or PIF, or in CR2 vs. CRp2 or rel.

Conclusion: Significantly better OS and NRM were seen following HSCT for patients in CR compared to CRp. CRp conferred an intermediate prognostic status, better than refractory disease, but significantly worse than ‘classic’ CR. Achieving a CR prior to HSCT should remain the gold standard for patients with AML or MDS receiving allogeneic HSCT.

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**POLYCLONAL PRAME-SPECIFIC CYTOTOXIC T LYMPHOCYTES GENERATED USING PROTEIN-SPANNING POOLS OF OVERLAPPING PENTADEPETHALOSIDES TARGET CHRONIC MYELOID LEUKEMIA**

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Following allogeneic hematopoietic stem cell transplantation, GVL is likely mediated not only by alloreactive T cells, but also by donor lymphocytes recognizing tumor associated antigens over-expressed by leukemic cells. Selective expansion of tumor-specific CTLs could augment GVL without increasing the risk of GVHD. The cancer tests antigen PRAME is a potential target for adoptive immunotherapy of hematologic and solid tumors. We have shown that PRAME-CTL can be expanded ex vivo, using a combination of artificial antigen presenting cells (aAPC) (K562 cell line genetically modified to express the HLA-A*02 and costimulatory molecules) and cytokines. Four HLA-A*02 PRAME-depeptied epitopes have previously been identified using a proteosome mediated digestion analysis, that relying only on the major cleavage site of the immune proteosome, may limit their relevance. We have now adopted a method that uses a L55 overlapping pentadecapeptide library spanning whole PRAME protein. We evaluated whether novel immunogenic HLA-A*02-restricted epitopes can be identified and used to consistently generate polyclonal PRAME-CTL lines from healthy donors and patients with hematologic malignancies. CD8+ T cells from 14 healthy donors and 5 patients with chronic myelogenous leukemia (CML) were primed with autologous CD40L-activated B blasts loaded with the PRAME library in the presence of IL-12, IL-7 and IL-15, and then expanded by weekly stimulation with peptide loaded aAPC.
and IL2. Using this approach we consistently generated PRAME-CTLs in 12/14 HLA-A*02 healthy donors (526 ± 101 SFC/10^6 cells as assessed by IFNg Elispot assay). Similarly, PRAME-CTLs were generated from all 5 CML patients (630 ± 120 SFC/10^6 cells). These PRAME-CTLs were also able to target autologous tumor blasts (57 ± 6 IFNg SFC/10^6), demonstrating that the epitopes were presented physiologically. A C1 ELISPOT assay confirmed that the PRAME-reactive T cells were cytotoxic, lysing autologous-PHA blasts loaded with PRAME-library (63 ± 14% at a 20:1 E:T ratio), but not with irrelevant library. Using sub-pools, we found that the responses of our expanded PRAME-CTLs were polyclonal, since they consistently released IFNg in response to 1 to 6 pentapeptides pools. Moreover, this approach has allowed to identify 6 potential new immunogenic 15mer peptides that are processed and presented by tumor cells, and should facilitate expansion of polyclonal PRAME-CTLs for adoptive transfer in patients with PRAME+ malignancy.

156 GVHD PROPHYLAXIS USING LOW-DOSE CYCLOSPORINE IS SAFE AND REDUCES THE RISK OF RELAPSE AND DEATH IN LEUKEMIC RECIPIENTS OF HLA-IDENTICAL SIBLING TRANSPANTS

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Four doses of methotrexate (MTX) and low-dose cyclosporine (CsA), starting at 1 mg/kg/day i.v. with early discontinuation, were given to 171 consecutive HLA-identical sibling recipients with leukemia. Apart from MTX, retrospective controls (n = 40) received CsA starting at 5–7.5 mg/kg/day i.v., and discontinued 1 year post-transplant. The target CsA trough levels were 100 ng/ml and 200–300 ng/ml in the low-dose and the control group, respectively. In the low-dose group, the risk of acute GVHD grades I-II was augmented (66% vs. 49%, p < 0.01), whereas grades III-IV did not differ between the groups (9% vs. 8%). The risk of chronic GVHD was markedly increased in those receiving low-dose CsA (50% vs. 29%, p < 0.01), and the cumulative proportion of relapse at 5 years post-transplant was in the control group (51% vs. 26%, p < 0.01). Moreover, the 5-year survival rate was 63% in the low-dose group compared to 40% in the controls (P = 0.04). In a multivariate analysis, low-dose CsA was the only factor associated with acute GVHD grades I-IV (RH 2.40, P = 0.02). Significant predictors of chronic GVHD were low-dose CsA (RH 2.56, p < 0.01), chronic myeloid leukemia (RH 1.92, p < 0.01), and administration of donor lymphocyte infusions (RH 1.66, P = 0.03). The risk of relapse was counteracted by chronic GVHD (RH 0.46, p < 0.01), whereas chronic GVHD (RH 0.53, p < 0.01) and acute GVHD grades III-IV (RH 4.35, p < 0.01) were the strongest factors associated with patient death. Importantly, the transplant-related mortality at 5 years post-transplant was similar in the low-dose CsA and control groups (18% vs. 20%, respectively, P = 0.58). In conclusion, a low-dose CsA regimen in leukemia recipients of HLA-identical sibling transplants increases the rate of chronic GVHD, which seems to attenuate the risk of relapse, thereby improving patient survival.

157 ISOLATED EXTRA-MEDULLARY RELAPSE OF ACUTE LEUKEMA AFTER ALLOGENIC STEM-CELL TRANSPLANTATION (SCT) IN ACUTE LEUKEMA: THE ROLE OF DOSE INTENSITY

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Allogeneic SCT with both myeloablative and reduced-intensity conditioning (RIC) is effective therapy in acute leukemia. To better define the role of dose intensity in SCT, we retrospectively analyzed SCT outcomes in 356 consecutive adult patients (pts) with MDS/AML (n = 277) and ALL (n = 79) given SCT over an 8-year period in a single institution. The median age was 51 (range, 17–75). The donors were HLA-matched siblings (n = 191), matched unrelated (n = 139) and alternative (n = 26). Pts meeting standard eligibility criteria were routinely given myeloablative conditioning (MAC, Cy/TBI or BuCy, n = 141). Pts non-eligible for MAC were given either RIC (fludarabine and reduced doses of busulfan or melphalan, n = 116) or modified myeloablative conditioning (modMAC, fludarabine with myeloablative doses of busulfan or treosulfan, n = 99). Disease status at SCT was CR1/CR2 (n = 176), previously untreated or untreated relapse (n = 63) and chemo-refractory (n = 117). With a median follow-up of 30 months (range 1–103), 159 pts are alive and 197 died; 75 of treatment-related causes and 122 of relapse. The estimated 5-yr overall survival (OS) in this relatively high-risk pt group was 34% (95%CI, 27–41). The status of disease at SCT was the most important factor predicting OS; 48, 51 and 16% for pts in CR, untreated or chemo-refractory leukemia, respectively (p < 0.001). Multivariable analysis (MVA) identified SCT not in CR, SCT from unrelated and alternative donors as adverse prognostic signs with hazard ratios (HR) of 2.7, 1.5, and 2.2, respectively. The conditioning regimen used was not a significant factor in the whole pt group with 5-yr OS of 38, 35 and 51% after MAC, modMAC and RIC, respectively (p = NS). However, RIC was associated with reduced OS in 2 subgroups. Among pts with MDS/AML given SCT not in CR, 5-yr OS was 34, 24 and 13% after MAC, modMAC and RIC, respectively (p = 0.03) with HR of 1.6 for RIC in MVA. In the group of ALL pts, MVA identified RIC and SCT not in CR as adverse prognostic signs with HR of 2.9 (p = 0.02) and 2.0 (p = 0.04), respectively. In conclusion, MAC should still be considered the standard of care for SCT in acute leukemia in eligible pts. RIC is associated with inferior outcome in pts with ALL and pts