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Introduction: High-dose, post-transplantation cyclophosphamide (PTCy) is effective as single-agent graft-versus-host disease (GVHD) prophylaxis after myeloablative conditioning (MAC) and human leukocyte antigen (HLA)-matched-related or -unrelated allogeneic bone marrow transplantation (alloBMT), producing grade III-IV acute GVHD and chronic GVHD rates of approximately 10-15% each. However, it is unknown whether plasma-derived proteomic biomarkers previously established using other transplantation platforms are applicable to PTCy-treated patients.

Methods: Plasma was obtained from the peripheral blood of 100 adult patients, 70 of whom received busulfan/fludarabine MAC and 30 of whom received busulfan/cyclophosphamide MAC, at month 1 and month 2-3 post-transplant. Twelve healthy controls were used as a comparative group. Plasma was analyzed using ELISA for interleukin-2 receptor alpha (IL-2rα), IL-6, tumor necrosis factor receptor-1 (TNFR-1), elafin, regenerating islet-derived 3-alpha (REG3α), suppression of tumorigenicity 2 (ST2), and chemokine (C-X-C motif) ligand 9 (CXCL9).

Results: Plasma levels of 6 of the 7 putative biomarkers were significantly elevated ($p<0.0001$) in patients at 1 month post-transplant compared with healthy controls; only elafin levels were similar between patients and controls. Plasma levels of IL-2rα ($p=0.038$), CXCL9 ($p=0.0003$), and IL-6 ($p=0.032$) at 1 month post-transplant were elevated in patients who would subsequently develop grade II-IV acute GVHD. There also was a tendency of a relationship ($p=0.06$) between elevated elafin levels at 1 month post-transplant and grade II-IV acute GVHD development. None of the 7 biomarkers at post-transplant month 1 was prognostic of chronic GVHD development. However, elevated REG3α levels at month 2-3 were prognostic of the subsequent development of chronic GVHD ($p=0.027$). Elevations in 4 of the 7 biomarkers (IL-2rα, $p=0.014$; IL-6, $p=0.024$; TNFR-1, $p=0.033$; and ST-2, $p=0.0032$) were predictive of non-relapse mortality (NRM). Levels of the 7 biomarkers at month 1 were not predictive of permanent cessation of immunosuppressive therapy for GVHD by 1 year post-transplant.

Conclusion: Levels of all 7 tested biomarkers at month 1 or month 2-3 post-transplant were prognostic for the occurrence of acute GVHD, chronic GVHD, and/or NRM in patients treated with PTCy as single-agent GVHD prophylaxis after MAC and HLA-matched-related or -unrelated alloBMT. Testing of these biomarkers at earlier post-transplant time periods or at patient-specific time points such as initiation of treatment for GVHD may have added clinical utility in the care of PTCy-treated patients.

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CD155 Regulates Regulatory T Cell Population and Attenuates Acute Graft-Versus-Host Disease

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The leukocyte adhesion molecule DNAM-1, also known as CD226, is constitutively expressed of most $CD4^+$ T cells, $CD8^+$ T cells and natural killer (NK) cells. The poliovirus receptor CD155, which is expressed on both hematopoietic and non-hematopoietic cells, is a ligand for DNAM-1 and TIGIT. Upon ligand binding, DNAM-1 mediates an activating signal in T cells and NK cells. TIGIT acts as a marker for regulatory T cell (Treg) subset and contributes to the Treg-mediated suppression. We have recently demonstrated a critical role of DNAM-1 on donor T cells in the development of acute GVHD in a mouse model (Nabekura, et al, PNAS, 2010, 2011). Recent reports also showed that DNAM-1 on donor cells promoted acute GVHD in a $CD4^+$ T cell-dependent manner via the inhibition of donor Treg expansion. Here, we found total body irradiation upregulated CD155 expression on recipient's dendritic cell. Therefore, we examined the role of CD155 expressed on host cells in the development of acute GVHD by using CD155-deficient mice.

Lethally irradiated CB6F1 wild type (WT) or *Cd155*$^{-/-}$ mice were transplanted with 5 x 10^6 bone marrow (BM) cells together with 2 x 10^6 splenic T cells derived from C57BL/6 mice. *Cd155*$^{-/-}$ recipient mice showed body weight loss significantly greater than did WT mice after transplantation ($P < 0.05$). Furthermore, *Cd155*$^{-/-}$ mice showed significantly shorter survival than WT mice ($P < 0.01$). Similar results were obtained in an acute GVHD model (C57BL/6 → BALB/c, $P < 0.05$). Further analyses revealed that *Cd155*$^{-/-}$ recipient mice showed decreased donor-derived Treg cell population, compared with WT recipient mice ($P < 0.01$). Depletion of Treg cells from transplanted splenic T cells resulted in comparable body weight loss and mortality between WT and *Cd155*$^{-/-}$ recipient mice after transplantation. These results suggest that host CD155 regulates the number of Treg cells and attenuated the development of acute GVHD.

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Impact of Acute and Chronic Graft-Versus-Host Disease on Outcomes after Single Cord Blood Transplantation: A Retrospective Analysis By the JSHCT Gvhd Working Group

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Background: Unrelated cord blood transplantation (UCBT) has increasingly been performed. Because cord blood units

contain a relatively low number of T cells with a higher percentage of naive T cells than peripheral blood stem cells, the presence or strength of the graft-versus-leukemia (GVL) effect has been controversial. Using Japanese registry data, we analyzed the impact of acute and chronic graft-versus-host disease (GVHD) on outcomes after single UCBT.

Methods: We analyzed patients with acute leukemia or myelodysplastic syndrome who underwent the first UCBT (n = 3,224) between 2000 and 2012 in Japan. The effect of acute GVHD (aGVHD) on overall mortality, relapse, and non-relapse mortality (NRM) was analyzed after adjusting for other significant variables among the engrafted patients, whereas the effect of chronic GVHD (cGVHD) was analyzed among the engrafted patients who survived without relapse for at least 100 days. The occurrence of GVHD was treated as a time-dependent covariate.

Results: The occurrence of grade 3 or 4 (G3-4) aGVHD was significantly associated with a higher risk of NRM (hazard ratio [HR] 3.08, $P < 0.001$) than the occurrence of G0-1 aGVHD, in both the standard- and high-risk groups. The occurrence of G2 or G3-4 aGVHD, as compared with G0-1 aGVHD, was significantly associated with a low relapse rate (G2 aGVHD: HR 0.80, $P = 0.003$; G3-4 aGVHD: HR 0.71, $P = 0.005$). These resulted in the significant association between G2 aGVHD and low mortality (HR 0.79, $P < 0.001$), and G3-4 aGVHD and high mortality (HR 1.70, $P < 0.001$), as compared with G0-1 aGVHD. The association between G3-4 aGVHD and high mortality was stronger in the standard-risk group (HR 2.46, $P < 0.001$) than in the high-risk group (HR 1.40, $P < 0.001$). The occurrence of extensive cGVHD was associated with a low relapse rate as compared with no cGVHD (HR 0.77, $P = 0.046$). The effect of limited cGVHD was significant only in the high-risk group (standard-risk: HR 1.07, $P = 0.673$; high-risk: HR 0.65, $P = 0.007$). The occurrence of extensive chronic GVHD was significantly associated with high NRM only in the standard-risk group (standard-risk, HR 1.46, $P = 0.037$; high-risk: HR 0.93, $P = 0.701$). These resulted in the significant association between limited cGVHD and low mortality in both groups, whereas extensive cGVHD was associated with low mortality only in the high-risk group.

Conclusions: Similar to transplantations from a matched sibling or an unrelated donor, G3-4 aGVHD should be prevented because of its associated high overall and non-relapse mortality rates, although acute GVHD was associated with low relapse rates. Extensive cGVHD should be prevented particularly in the standard-risk group because of its associated high NRM. In the high-risk group, cGVHD was associated with low relapse rates. The significant association between aGVHD or cGVHD and a low relapse rate supports the presence of GVL effect in the UCBT even in the high-risk group.

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Prospective Longitudinal Study of Late Acute Graft Versus Host Disease after Hematopoietic Cell Transplantation: A Report from Chronic GVHD Consortium

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Background: Late acute (LA) graft vs. host disease (GVHD) is persistent, recurrent or new onset acute GVHD symptoms more than 100 days after hematopoietic cell transplantation (HCT). The aim of this analysis is to describe the onset, course, and the morbidity and mortality associated with LA GVHD.

Methods: A prospective cohort of patients was enrolled as part of an observational study of immune mediated disorders after HCT within the Chronic GVHD Consortium at 13 centers. Patients with previous diagnosis of LA or chronic GVHD prior to enrollment were excluded.

Results: Out of 913 patients in the study, 85 developed LA GVHD with a cumulative incidence of 11% at 2-year after HCT (2-persistent, 40-recurrent and 43 de-novo). Median age was 53.2 years, 70% received URD transplants, and graft source was peripheral blood in 87%. 44% received myeloablative conditioning, and 7% received ATG/Alemtuzumab. Median time of onset for LA GVHD was 160 days (IQR 128-204) days after HCT. Median follow-up for survivors after LA GVHD diagnosis was 10.2 (range 0.7-25.9) months. 60% of patients had biopsy proven LA GVHD. Single organ involvement at diagnosis was seen in 59 patients (skin 39%, liver 14% and gut 47%), while 26 patients (31%) had ≥2 organ involvement. 21% of patients with liver GVHD had only transaminitis without elevated bilirubin and hence were not included for acute

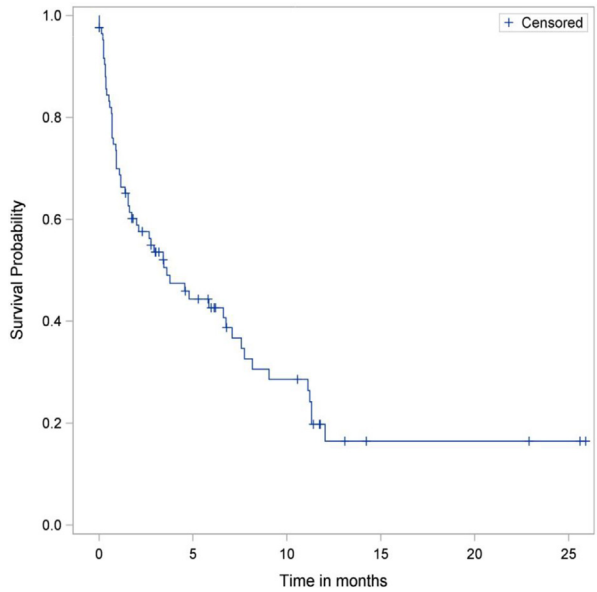

Figure. Failure free survival in patients with late acute GVHD