	Median nucleated cell dose infused	Median time for ANC≥0.5 x 10.9/l (range), in days	Median time for platelets ≥50 x 10.9/l (range) , in days	TRM at day +100	OS at 36 months	EFS at 36 months for hematological malignancies
CB	3.7 x 10.7/kg (1.2-13.8)	28 (22-49)	42 (18-59)	25.8±7.8%	62±9.3%	39.3±12.2%
BM	5.1x10.8/kg (1.6-8.8)	22 (14-35)	27.5 (20-129)	11.4±6.2%	60.1±9.9%	51.8±12.9%
P value	NA	0.0003	NS	NS	NS	NS

ANC: Absolute Neutrophil Count; TRM: Treatment Related Mortality; OS: Overall Survival; EFS: Event Free Survival, event defined by death or relapse; NA: no available; NS: no significant

47

UNIVERSAL OUTPATIENT IMMUNOTHERAPEUTIC APPROACH FOR HEME MALIGNANCIES IN THE ABSENCE OF DONOR CHIMERISM: ANTI-TUMOR RESPONSES IN HLA-HAPLOIDENTICAL CELL INFUSIONS IN 100CGY TREATED HOSTS

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Previously, we studied cellular immunotherapy with HLA-identical sibling donors using 100cGy conditioning and infusing 1x10^8 CD3+ cells/kg from non-mobilized peripheral blood. An impressive complete response (CR) rate was achieved in 4 of 11 patients (pts) with refractory hematologic malignancies (Blood 100:442, 2002). Responding pts were transiently or permanently chimeric. However, only approximately 35% of pts otherwise eligible for allogeneic BMT have an HLA-identical sibling donor. On the other hand, nearly 100% of pts have HLA-haploidentical (HLA-H) donors, making HLA-H BMT an attractive area of investigation. We performed 15 HLA-H peripheral blood stem cell (PBSC) infusions in pts with refractory heme malignancies. The CD3+ dose was 1-2x10^8 cells/kg infused along with 2-4x10^6 CD34+ cells/kg. G-CSF (10 ug/kg for 3 days was used to mobilize PBSC. The transplant conditioning regimen was 100cGy TBI on day 0. Median age was 55 (range 50-72). Diagnoses were: AML(4), CML(1), NHL(5), MDS(1) and MM(4). Donor chimerism was measured Q2 weeks. One treatment related death (7%) occurred from grade IV AGVHD in a pt with 100% chimerism. Most pts had a transient febrile syndrome termed "haplo-immunostorm." Pts had mild pancytopenia starting 3 wks after HLA-H, most requiring brief transfusion support. Four major clinical responses occurred. All of these responses were in the absence of measurable donor chimerism (<5%). All evaluable pts with AML and one with NHL achieved a CR. In summary: 1) very low dose TBI of 100cGy followed by HLA-H transplant is a biologically active treatment that eradicated far advanced disease; 2) all tumor responses occurred outside of detectable chimerism; 3) HLA-H with PBSCT is well tolerated with minimal non-hematologic toxicity for the majority of pts; and 4) this is the first report of successful outpatient haploidentical immunotherapy achieving clinical responses for patients with end stage, refractory malignancies. Hypotheses concerning the mechanism of the biological effect include: 1) an initial graft vs. tumor cell kill after which donor cells are rejected, 2) an alteration of the host immune response augmenting tumor immunity or breaking host tumor tolerance, 3) persistent non-detectable micro-chimerism, or 4) a combination of any of the three.

48

SUSTAINED ENGRAFTMENT OF HLA-MATCHED RELATED, T-CELL DEPLETED (TCD), PERIPHERAL BLOOD STEM CELL (PBSC)/BONE MARROW (BM) TRANSPLANTS IN ADULTS WITH HEMATOLOGIC MALIGNANCIES WITHOUT THE USE OF ANTITHYMOCYTE GLOBULIN (ATG)

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Acute and chronic GvHD, major causes of post-transplant morbidity and mortality, can be prevented by TCD. A limitation to the effectiveness of such transplants is the risk of graft rejection(GR)/failure(GF) caused by radioresistant, donor-reactive host T cells, which regenerate after transplant. Initial trials of TCD BM grafts from HLA matched siblings, showed a GF incidence of <14% in adults, vs.<5% for similarly matched unmodified BM grafts. Previous work identified a conditioning regimen of hyperfractionated total body irradiation (HTBI), thiotepa and cyclophosphamide with ATG which reduced GF to <2%. However, studies of ATG recipients demonstrated delayed immune reconstitution, and a prolonged time 'at risk' for opportunistic infections.We hypothesized that high CD34+ cell doses coupled with HTBI, thiotepa (5mg/kg)x2d and fludarabine (25mg/me2)x5d might obviate the need for ATG. Such a regimen has been evaluated in 22 adult transplants. PBSC and BM grafts were depleted of T cells by Isolex 300i CD34 selection + E-rosetting, and SBA agglutination + E-rosetting, respectively . There were 13 males and 9 females, median age 46 yrs(range 19-60). Diseases: AML CR1(7), AML CR2(1), ALL CR1(1), biphenotypic acute leukemia CR1(2), CML(4), MDS-RAEBIT(2), NHL(5). Median follow-up: 201d(13-446). Two patients received BM and 20 PBSC grafts. By d+30, 21 patients had an ANC)500 (1 patient too early (TE)), and 14 had platelets (plts) > 50k (1 TE). By d+100, 21 had an ANC >500 (1 TE), and 15 had >50k plts (1 TE, 2 died early). Median time to ANC >500 for all patients was 12d(range 10-21), and to plts >50k for 15 patients was 18d(range 14-96). No patient developed acute (20 evaluable) or chronic (15 evaluable) GvHD. Chimerism studies on BM at d+100 showed 12/15 patients were 100%, 2/15 were 95-98% donor (1/15 not evaluated). There have been no GR/GFs. Two patients with secondary AML relapsed, one at 2 months responded to DLI, and is 100% donor in remission at 6 months, and 1 at 10 months who died of complications. These results suggest that this regimen is sufficient to secure engraftment of HLA-matched TCD transplants without the addition of ATG. The influence of this regimen on immune reconstitution is under study.

49

MALE PREDOMINANCE AMONG JAPANESE ADULT PATIENTS WITH LATE-ONSET HEMORRHAGIC CYSTITIS (HC) AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

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Background: Late-onset HC after HSCT is mainly caused by viral infections, and therefore, its incidence and risk factors may differ among populations. Patient and methods: We retrospectively analyzed the records of 141 Japanese adult patients who underwent first allogeneic HSCT from June 1995 to August 2002 at the University of Tokyo Hospital. Prevention of cyclophosphamide-induced HC was performed with mesna and forced diuresis. HC was diagnosed based on macroscopic hematuria or sustained microhematuria with clinical symptoms de novo at least 10 days after HSCT. Hematuria associated with generalized bleeding tendency or bacteriuria was excluded. Urine samples were subjected to PCR and/or culture to detect viral infections. Results: Nineteen patients developed HC a median of 51 days (range 11-380) after HSCT with a 2-year cumulative incidence of 14.2%. Adenovirus (AdV) was detected in the urine samples of 10 HC patients, of whom 8 had AdV type 11. Five of their 6 available serum samples were also positive for AdV type 11. The 3-year survival after the onset of HC was only 27%. Male sex and the development of acute GVHD were identified as significant risk factors for HC by univariate analyses and both were shown to be independently significant using proportional hazard modeling with relative risks of 7.52 (95% CI; 1.00-56.4, P=0.050) and 4.37 (95% CI; 1.65-11.6, P=0.0031), respectively. Conclusion: AdV type 11 infection appeared to play a major role in late onset HC in Japanese population. In addition, we identified male sex as a significant risk factor for HC. These findings suggested that late onset HC after HSCT may be caused by the reactivation of latent infection, because the male predominance has been already known in children with AdV-induced acute HC and also, its incidence was reported to be higher among Japanese children.