induction chemotherapy (cyclophosphamide, daunorubicin, vincristine and MTX i.t.). After induction all patients had to receive a HAM consolidation course (HD-AraC 3 g/m^2 every 12 hours, days 1-4; mitoxantrone 10 mg/m^2, days 5-7 and MTX i.t.). Patients in CR received two courses of MA consolidation (MTX 1.5 g/m^2 day 1 and L-asparaginase 10^4 IU/m^2 day 2), and then underwent allo-SCT or patients without a donor were randomized either to receive autologous stem cells from peripheral blood or high maintenance therapy. The median follow-up was 4.9 years. Between 1998 and 2003, a total of 325 pts entered the study. The median age was 32 yrs range 15-72 yrs. In 248 (76%) patients CR1 was reached and 227 of them were HLA typed; 100 had an identical sibling donor and 127 had no sibling donor. Allo-SCT was performed in 69 (69%) pts and auto-SCT or high maintenance therapy in 58 (46%). The 5-year DFS of pts with a donor vs pts without a donor was 41.8% vs. 35.5% , $P = .40$, hazard ratio 0.86, 95% CI 0.61-1.22). The relapse incidence was significantly lower (37.3% vs. 58.8% $P = .004$) and treatment related mortality (TRM) was significantly higher (20.9% vs. 5.7%, $P = .0005$) in the donor group compared to the no donor group. Five-year survival in pts with and without the donor was 43.0% and 36.9% respectively. For pts ≤50 years of age 199 of them were HLA-typed; 91 had a donor and 108 had no sibling donor. The 5-yr DFS rate in the donor vs no donor group was 42.2% vs. 36.2%, $P = .36$, hazard ratio 0.84 95% CI 0.58-1.22). Relapse rate was significantly lower and TRM was significantly higher in the donor versus no donor group. Five-year survival for patients with and without a donor was 43.9% and 37.4% respectively ($P = .58$), hazard ratio 0.90 (95% CI 0.61-1.32). In conclusion, in the EORTC ALL-4 trial, the intention to treat analysis shows that DFS and survival rate for allografted pts younger than 50 years of age were not significantly different compared to those receiving auto-SCT or high maintenance. High TRM (~20%) remains the main problem of allografting.

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THE FEASIBILITY OF CONDITIONING REGIMEN OF FLUDARABINE, ATG, AND REDUCED DOSE OF CYCLOPHOSPHAMIDE IN PATIENTS WITH SEVERE APLASTIC ANEMIA WHO RECEIVED HLA-MATCHED SIBLING TRANSPLANTATION

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Background: High dose (HD) cyclophosphamide (CY, 200 mg/kg) plus ATG seems to be accepted as standard conditioning regimen in HLA-matched sibling stem cell transplantation (SCT) for severe aplastic anemia (SAA). However, HD CY causes serious cardiac toxicity in some cases which may lead to death within a few weeks. To avoid HD CY-associated cardiac toxicity we underwent HLA-matched sibling SCT using ATG, reduced CY to half dose with incorporation of fludarabine. **Methods:** Between March 2002 and August 2005, consecutive twenty-six patients with adult SAA (six patients were AA/PNH syndrome) received matched sibling SCT. The median age of patients was 41 (21-52) and median interval between Dx and SCT was 30 months (1-352). The median number of transfusions prior to SCT was 34 units (4-680). Ten patients (38%) had a history of IST before SCT. The conditioning regimen consisted of fludarabine (30 mg/m^2/day, 6 days), cyclophosphamide (50 mg/kg/day, 2 days) and ATG (2.5 mg/kg/day, 4 days, IMTIX-SangStat). Stem cell sources were BM plus CD34$^+$-selected PBSC (n = 9), BM (n = 14), or PBSC (n = 3). All patients received of cyclosporine and methotrexate as GVHD prophylaxis. **Results:** The median dose of CD34$^+$ cells infused was 3.6 × 10^6/kg (1.2-11.9). All patients achieved successful sustained engraftment, and the median time for ANC and platelet to reach 0.5 × 10^9/L and 20 × 10^9/L was 12 (6-16) and 18 (10-23) days, respectively. None of the patients developed cardiac toxicity or regimen-related toxicities. One patient developed delayed graft failure, but achieved successful engraftment after second SCT using TNI + ATG. The incidence of acute GVHD (more than grade II) was 8% (n = 2) and none developed chronic GVHD. The incidence of CMV infection requiring preemptive treatment was 38% (n = 10). Only one patient died of hepatic failure due to reactivation of chronic hepatitis C with hepatic GVHD posttransplant 3 months. PNH clone measured by flow cytometry disappeared posttransplant in 6 PNH patients. With median follow up of 12 months (2-41), the estimated probability of survival at 2 years was 96%. **Conclusions:** These data demonstrate that the conditioning regimen used in this study is feasible for patients with SAA who receive matched sibling SCT. Of note, the observations of successful engraftment as well as lesser acute GVHD and no chronic GVHD suggest that a fludarabine-based regimen has more potent immunomodulatory activity.

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RESPIRATORY VIRUS INFECTION AMONG HEMATOPOIETIC CELL TRANSPLANTATION (HCT) RECIPIENTS: QUANTITATIVE VIRAL LOAD IN SYMPTOMATIC AND ASYMPTOMATIC INFECTIONS

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Background: Influenza (flu), respiratory syncytial virus (RSV), and parainfluenza virus (PIV) may cause serious respiratory disease following HCT, with infection rates of 2-10%. The extent of infection and disease due to human metapneumovirus (MPV) is largely unknown. We assessed viral infectious episodes after HCT using conventional and quantitative molecular detection. **Methods:** Weekly symptom surveys, nasal washes and throat swabs were collected from HCT recipients for 100 days post-HCT between Jan. 2001-June 2004. Samples were tested by culture and DFA for RSV, PIV and Flu, and by RT-PCR for RSV, PIV, MPV, and flu (detection limit 1100 copies/ml). Longitudinal analysis was performed for patients with ≥5 serial samples or a positive test or death. **Results:** Of 119 patients, 29 had 31 (26%) separate infectious episodes due to RSV (5), PIV (16), MPV (6), flu (3), RSV and flu (1). Median time to viral detection was 48 (range 3-96) days after HCT; median duration of viral shedding was 14 (range 5-42) days in 19 evaluable episodes. Six patients with PIV remained asymptomatic at the time of positivity, conventional testing was negative in 5. No asymptomatic shedding of RSV, MPV or flu was found. PCR testing nearly doubled first identification of RSV and PIV infectious episodes: 11 were detected by PCR plus conventional methods (in 2 patients, PCR detection preceded conventional methods) and 9 were detected by PCR alone. Median virus copy number in samples from asymptomatic weeks (2.3 × 10^4 copies/ml) differed from samples from symptomatic weeks (8.6 × 10^5 copies/ml; P value .004). Similarly, viral load in samples from patients with 0 or 1 symptoms (2.4 × 10^4 copies/ml) was significantly lower compared with patients that reported >1 symptom (1.8 × 10^6; P value .001). PIV was the only virus that showed a lower viral load in patients with 0 or 1 symptoms compared with >1 (P value .04). **Conclusion:** Both symptomatic and asymptomatic viral shedding among allogeneic HCT recipients were detectable using virus-specific molecular testing. Utilization of PCR viral detection methods increased yield of detectable episodes. PIV infections were more likely to be transiently asymptomatic than RSV, MPV, or flu. Asymptomatic shedding of PIV provides a possible explanation of why infection control programs emphasizing symptoms are highly effective against RSV but often not versus other viruses such as PIV. These data may guide implementation of more effective diagnosis and infection control strategies.

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ALLOGENEIC STEM CELL TRANSPLANTATION FOR ADULT ACUTE LEUKAEMIA IN CR1 AND CR2 WITH A NOVEL MYELOABLATIVE CONDITIONING REGIMEN INCORPORATING DAILY INTRAVENOUS BUSULFAN, FLUDARABINE, 400 cGy TOTAL BODY IRRADIATION AND LOW-DOSE ANTITHYMOCYTE GLOBULIN

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Intravenous (IV) busulfan (BU) gives more predictable exposure than the oral form and is easier to administer once daily than the conventional four times daily schedule. Fludarabine is immunosuppressive, antileukaemic and perhaps better tolerated than cyclophosphamide. Low-dose pretransplant ATG appears to reduce morbidity and mortality of graft-versus-host disease (GVHD). A conditioning regimen incorporating these agents appears well tolerated and adding a low dose of total body irradiation (TBI) does not seem to increase non-relapse mortality. This regimen was given to a total of 64 acute leukemia patients (pts) aged 18-63 (median 40) years of whom 28 (44%) had ALL or lymphoblastic lymphoma (n = 2) in CR1 (n = 22) or CR2 (n = 6), and 36 (66%) had AML (25 CR1, 11 CR2). Donors were matched siblings (MRD) for 31 (48%) and alternate donors (AD, 28 unrelated and 5 mismatched related) for 33 (52%). Cell source was blood in all MRD and 26 (76%) AD pts. All pts received fludarabine 50 mg/m^2 on days −6 to −2 and IV BU (Busulfex, ESP Pharma) at a "myeloablative" dose of 3.2 mg/kg daily days −5 to −2 inclusive and TBI 200 cGy × 2 on day −1 or 0. Prophylaxis for GVHD was cyclosporine A, "short course" methotrexate with folinic acid and Thymoglobulin (Genzyme) 4.5 mg/kg in divided doses over 3 consecutive days pretransplant finishing day 0. Follow-up of survivors is 3-64 months, median 20. After MRD and AD transplants the incidence of acute GVHD grade II-IV was 11 ± 6% vs 35 ± 9% (P = .047), acute GVHD grade III-IV was 0% vs 10 ± 6% (P = .09) and chronic GVHD was 46 ± 10% vs 73 ± 9% (P = ns) respectively. There were 3 transplant-related deaths, only in ALL patients, one each from acute GVHD, pneumonitis and PTLD giving an overall TRM of 5 ± 3%. Of 6 relapsing pts with ALL 4 are in a further remission after a second myeloablative transplant (3) or chemotherapy and DLI (1), all have chronic GVHD. Four AML pts died from relapse. Projected 2-year disease-free survival and survival respectively is 72 ± 9% and 80 ± 8% for ALL, 87 ± 6% and 87 ± 6% for AML. For the combined group the corresponding figures are 80 ± 8% and 89 ± 6% for MRD and 78 ± 8% and 78 ± 8% for AD transplants respectively (P = ns). This regimen appears relatively well tolerated and gives equivalent final outcomes from MRD and AD. If these results can be confirmed the combination deserves study in children with acute leukemia in whom the toxicity of higher doses of TBI could be avoided.

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COMPARISON OF METHOTREXATE- VERSUS SIROLIMUS-CONTAINING GRAFT-VERSUS-HOST DISEASE PROPHYLAXIS REGIMENS AFTER MYELOABLATIVE STEM CELL TRANSPLANTATION

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Background: Graft-versus-host disease (GvHD) is a serious complication after allogeneic hematopoietic stem cell transplantation (HSCT). Methotrexate in combination with a calcineurin inhibitor (CM) is considered standard GvHD prophylaxis. Studies suggest that sirolimus in combination with a calcineurin inhibitor (SC) is effective in preventing GvHD and minimizing transplant-related morbidity and mortality. **Method:** A total of 159 patients with hematological diseases underwent myeloablative HLA-matched HSCT with either CM (n = 97) or SC (n = 62) as GvHD prophylaxis at the Dana-Farber Cancer Institute between June 2000 and December 2004 using Cytoxan and TBI conditioning. Inpatient costs for the first transplant year of 94 CM and 47 SC recipients were obtained. We compared inpatient costs and clinical outcomes for the first transplant year between the two different GvHD prophylaxis groups by use of univariate and multivariate analyses. **Results:** CM recipients were more likely to have unrelated donors, BM grafts, and to be transplanted in earlier years than SC recipients. In univariate analysis, the SC regimen was associated with faster engraftment (13 days vs 17 days, $P < .01$), less grade II to IV acute GvHD (18% vs 37%, $P = .01$) and better DFS (71% vs 52%, $P < .01$) and OS (72% vs 53%, $P = .01$). Days of initial hospitalization and costs within the first year were lower for SC in the univariate analysis (27 days vs 33 days, $P < .01$, $101697 vs $110081, $P = .03$, respectively) but not in the multivariate analysis (ratio (CM vs SC) 0.99, $P = .91$, ratio 1.14, $P = .30$, respectively). Use of an unrelated donor was the only significant predictor of high costs considering baseline patient characteristics. In contrast, grade II to IV aGvHD, late engraftment, and in-hospital death were the significant factors associated with high costs considering both baseline patient characteristics and post-transplant events. **Conclusion:** Both OS and DFS in the SC group were higher in the multivariate analysis, probably due to early engraftment and reduced incidence of grade II to IV aGvHD seen in SC group. However, we could not detect the impact of GvHD prophylaxis on inpatient costs for the first transplant year. The SC regimen is a promising alternative to CM and larger multi-center randomized trial is planned through the NIH-funded Clinical Trials Network.

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VALIDATION OF THE PREDICTIVE POWER OF THE HEMATOPOIETIC CELL TRANSPLANTATION-COMORBIDITY INDEX (HCT-CI) FOR NON-RELAPSE MORTALITY (NRM) AND SURVIVAL AFTER ALLOGENEIC HCT

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The HCT-CI proved to be a sensitive tool to capture pretransplant comorbidities among patients (pts) given allogeneic HCT at FHCRC (*Blood* 2005;106:2912). We sought to validate the effectiveness of the HCT-CI in predicting NRM and survival at another institution (MDACC) and compare its performance to those of other comorbidity indices. For this purpose, pretransplant comorbidities were assessed in pts with acute myeloid leukemia in first remission from FHCRC (n = 137) and MDACC (n = 70) by two independent investigators. Comorbidities were scored using HCT-CI, Charlson comorbidity index (CCI), and the adult comorbidity evaluation (ACE-27, a recent modification of the Kaplan-Feinstein Index). Conditioning included myeloablative (78% and 69% of FHCRC and MDACC pts, respectively) or reduced intensity regimens. Donor grafts were from related (66% and 86% of FHCRC and MDACC pts, respectively) or unrelated donors. Stem cell source was marrow (28% and 60% of FHCRC and MDACC pts, respectively) or G-PBMC. Among the 207 pts, 35%, 29%, and 36%, respectively, had HCT-CI scores of 0 vs 1-2 vs ≥3; 83%, 9%, and 8%, respectively, had CCI scores of 0 vs 1 vs ≥2; and 56%, 28%, and 16%, respectively, had ACE-27 scores of 0 vs 1 vs ≥2. HCT-CI scores of 1-2 and ≥3 were found in 33% and 25% FHCRC pts and 20% and 59% MDACC pts. Cumulative incidences of 2-year NRM were 5%, 7%, and 24%, respectively, among FHCRC pts with HCT-CI scores of 0 vs 1-2 vs ≥3 and 7%, 14%, and 31% among their MDACC counterparts. Unadjusted hazard ratios (HR) for NRM were 1.11 and 4.3 for HCT-CI scores of 1-2 and ≥3 among FHCRC pts compared to 2.41 and 5.72 among MDACC pts. Similarly, HR for worse survival were 2.47 and 6.21 for HCT-CI scores of 1-2 and ≥3 among FHCRC pts compared to 2.18 and 2.73 among MDACC pts. In multivariable regression analyses, HCT-CI scores showed the highest prediction for NRM (HR 5.13, $P = .001$) and worse survival (HR 4.96, $P < .0001$) compared to CCI scores ($P = .2$ and .05, respectively) and ACE-27 scores ($P = .03$ and .002, respectively). These results were further validated separately at each institution (Table 1), where higher HCT-CI scores showed the highest HR predicting of NRM and worse survival among FHCRC and MDACC pts compared to other risk factors. Results confirm the ability of HCT-CI to predict post-HCT outcomes. The HCT-CI identified more pts with co-