

or deleterious to survival, T- and B-cell reconstitution & clinical outcome after treatment for SCID & what biomarkers are predictive of these outcomes.

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Engraftment Syndrome Has Distinct Biology Compared with Graft Versus Host Disease

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Introduction: The biology of engraftment syndrome (ES) is poorly understood and the degree of overlap with GVHD is unclear.

Methods: To better understand ES, plasma cytokine profiles were evaluated in 52 consecutive pediatric allogeneic bone marrow transplant recipients prior to transplant, on the day of stem cell infusion and weekly until day+100. Patients were divided into three groups, those with isolated engraftment syndrome (n=4), acute graft versus host disease without prior ES (n=12) and with neither engraftment syndrome nor acute graft versus host disease (n=32). Cytokine values were expressed as mean fold increase from pre transplant values.

Results: Median age of recipients was 6.7 years (range 0.6-19.4). ES was observed a median of 12.5 days (range 11-15) after transplant, while aGVHD was diagnosed at median of 55 days (range 19-95 days) after transplant. MCP-1 and MIP1b were significantly elevated in patients with ES during the first two weeks, while remaining unchanged or reduced in either of the other 2 cohorts. Moreover, while various cytokines were found to be elevated in patients who developed aGVHD, the degree of elevation was significantly exaggerated in patients with isolated ES during 4 weeks post-transplant. (See table 1)

Conclusion: MCP-1 and MIP1b are elevated specifically in ES suggesting a separate biology from GVHD. In addition, the degree of elevation of pro-inflammatory cytokines is markedly greater in children with ES compared to those with GVHD.

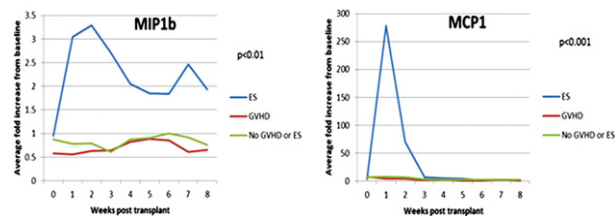


Figure 1. MIP1b and MCP1 in patients with ES, aGVHD and neither GVHD nor ES.

Table 1

Cytokine profiles in ES, aGVHD and patients with neither ES nor GVHD at 4 weeks after transplant

Cytokine	Neither ES nor GVHD (Mean fold increase from pre transplant value)	GVHD (Mean fold increase from pre transplant values)	ES (Mean fold increase from pre transplant values)	P-value (ES vs GVHD)
IL1b	0	2	36	<.01
IL4	2	5	40	<.001
IL7	8	6	138	<.01
IL12	14	4.6	108	<.01
IL13	2.8	3	62	<.01

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Stem Cell Transplantation and Long-Term Survival for Primary Immunodeficiencies: Outcomes Among the Donor Sources and Different Diagnostic Groups

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Matched related hemopoietic stem cell transplantation (MRD-HSCT) for patients with Primary Immunodeficiencies (PIDs) has been life saving. There is less information regarding stem cell transplantation from unrelated donors including umbilical cord blood units. We report the outcome following HSCT (1998-2012) in 69 patients with PIDs: SCID (n=35), WAS (n=9), Phagocytic disorders (CGD (n=17), LAD (n=4)); and other (n=4; one each; Interferon γ receptor deficiency, Hyper IgM syndrome, Autosomal recessive Hyper IgE syndrome (Dock 8 mutation), and reticular dysgenesis). The median age at transplant was 1 year (range, 0.1-17 years). Twenty patients received an MRD graft, 22 patients received a matched unrelated donor graft (MUD), 4 patients received a mismatched unrelated donor graft, 15 patients received a haploidentical related donor graft and 9 patients received a mismatched unrelated cord blood unit (MMUCB). One patient received a MMUCB after a haploidentical graft failure. 58 patients received ablative conditioning regimen with busulfan, cyclophosphamide, and fludarabine or cytarabine. Six patients received reduced intensity conditioning using fludarabine with anti-CD52 or/and anti-CD45. Six SCID patients were not conditioned. 52 patients received anti-CD52; no serotherapy was given for MMUCB grafts. Graft versus host disease (GvHD) prophylaxis combined cyclosporine and methotrexate or cyclosporine and prednisone except for MUCB recipients who were given cyclosporine and MMF as prophylaxis. Engraftment: Forty five of 67 evaluable patients (65%) achieved full donor chimerism (>90%) of all cell lineages including T cells. Twelve patients had primary graft failure. 10 were haploidentical grafts and 2 were MUD grafts. All except one were rescued with a repeat stem cell infusion. Just 3/67 patients developed grade II-IV aGvHD and no patient developed chronic GvHD. Survival. With a median follow up of 4 years (range, 0.3-12 years), overall survival was: 95% and 86%, for phagocytic disorders and SCIDs respectively; and 77% and 75% for WAS and other diseases, respectively. Recipients of MRD and UCB had 100% survival: MUD graft recipients had an 88% survival, while recipients of mismatched unrelated or haploidentical related transplants, had 50% and 71% survival respectively. Infection was the commonest cause of death. Hence excellent overall survival for PID patients may be obtained after unrelated HSCT and results using matched related grafts and mismatched cord blood units are highly comparable.

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Clinical Profile and Outcomes of Patients With α Thalassemia Major and Hepatitis C Virus Infection Undergoing an Allogeneic Stem Cell Transplant

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There is limited data on the prevalence, clinical profile and outcome of patients with β thalassemia major (TM) who was HCV sero-positive (HCV+) prior to an allogeneic stem cell transplant (SCT). From October, 1991 to June, 2012, 370 SCT were done for TM at our center. The median age was 7.5 years (range: 2–24) and there were 232 (62.87%) males, 209 (56.5%) belonged to Lucarelli Class III. There were 44 (11.9%) cases who were HCV+, 6 (1.6%) who were HBsAg positive and 350 (94.6%) who were CMV sero-positive at the time of pre-transplant screening.

HCV+ cases were significantly older ($P = .000$) and had a significantly larger liver size ($P = .001$). There were significantly more number of HCV+ cases who were Lucarelli Class III (84% Vs. 52.8%; $P = .000$). The number of graft rejections was significantly higher in the HCV+ group (22.7% Vs. 10.4%; $P = .025$) while the treatment related mortality was comparable between the two groups. It is well recognized that patients with TM are at a high risk of developing sinusoidal obstruction syndrome (SOS) post SCT. In this series, 165 (44.6%) patients developed SOS. HCV+ cases did not have a significantly higher incidence of SOS compared to those that were HCV negative (47.7% Vs. 44.3%; $P = .747$). Among the 15 (34%) of HCV+ cases that died, the major contributory cause of death was infection (40%), graft failure (20%) and SOS (20%). The overall and event free survival among those that were HCV+ve Vs. those that were negative was $63.7 \pm 8.1\%$ Vs. $75 \pm 2.5\%$ and $47.4 \pm 8.1\%$ Vs. $70 \pm 2.7\%$; P -value = 0.158 and 0.019 respectively. On a univariate cox regression analysis, HCV+ had an adverse impact on EFS (RR=1.710; 95%CI 1.066–1.744; $P = .026$). However, on a forward stepwise multivariate analysis after adjusting for conventional risk factors HCV+ status did not confer an independent adverse risk factor. Of the 29 HCV+ patients who are surviving, at a median follow up of 25 months, none have had progression to chronic liver disease. 20 (69%) had a normal liver function test at last follow up while only 3 have had HCV directed therapy post transplant.

From August, 2009 at our center we have been using a treosulfan based conditioning regimen for our Class III patients. Among the 44 HCV+ patients 10 were conditioned with this regimen. This regimen was well tolerated with 100% engraftment. Two patients died, one due to sepsis and the other to GVHD. This compared favorably with the historical control of HCV+ cases conditioned with a conventional busulfan based regimen.

In conclusion HCV+ status is a surrogate risk factor for other adverse risk factors such as older age, increased liver size and inadequate medical therapy prior to SCT. After adjusting for such risk factors HCV+ cases with TM undergoing an allogeneic SCT transplant have comparable outcomes to HCV negative cases. Use of a treosulfan based regimen is well tolerated in the HCV+ group and could potentially improve the outcome in this high risk group.

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Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for Juvenile Myelomonocytic Leukemia (JMML) in France: A Retrospective Study of Société Française De Greffe De Moelle Et De Thérapie Cellulaire

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Juvenile myelomonocytic leukemia (JMML) is a rare and aggressive childhood haematological malignant disorder. Allogeneic HSCT is the only proven curative therapy. This study reports more than 20 years (1986–2011) of French experience in HSCT for children with JMML.

Outcome of 107 HSCT (91 children) performed between March 1986 and November 2011 in 18 French centres was retrospectively studied. Overall Survival (OS), Non Relapse Mortality (NRM), Graft Versus Host Disease (GVHD) and relapse cumulative incidences were analyzed per patient from the first transplantation. Multivariate analyses were performed to assess risk factors. Statistical analyses were carried out according to guidelines of European group for Blood and Marrow Transplantation (EBMT).

Ninety-one children (58 males), median age 1.4 yrs (range 0.0–15.7 yrs) with JMML underwent 107 allogeneic HSCT (14 second graft and a third one). The median follow-up was 47 months (1–166). At 72 months, OS was 59% (95% CI: 47–74). Cumulative incidence of aGVHD was 48% (95% CI: 37–58). The 6-year cumulative incidence of relapse and NRM was 34% (95% CI: 23–44) and 21% (95% CI: 13–32), respectively. The median delay of relapse was 80 days (range 15–1096). In multivariate analysis, age at HSCT older than 2 years, female donor to male recipient sex-mismatch, matched unrelated or mismatched non cord donor, total body irradiation and no serotherapy in conditioning regimen predicted poorer outcomes. Age at HSCT older than 2 years was an increased risk of relapse whereas Busulfan/Cyclophosphamide/Melphalan conditioning regimen was a decreased risk. Serotherapy was associated with a decreased risk of NRM. Age at HSCT older than 2 years and male recipient were associated with higher probability of dying of NRM causes.

Our results show that allogeneic HSCT may cure approximately 60% of patients with JMML and are similar to best results published by other groups. Relapse represents the main cause of treatment failure and a second HSCT should be proposed. Novel strategies to decrease the risk of relapse are needed.

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Hematopoietic Cell Transplantation for Acute Leukemia and Advanced Myelodysplastic Syndrome in Fanconi Anemia

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The presence of acute leukemia or advanced myelodysplastic syndrome (MDS with 5% blasts or more) in Fanconi Anemia (FA) patients is associated with very poor prognosis. The experience of hematopoietic cell transplantation (HCT) in these patients is limited, and the question of pre-transplant chemotherapy remains. We report 21 FA patients with acute myeloid leukemia, acute lymphoblastic leukemia, or advanced MDS who underwent HCT at the University of Minnesota from 1988–2009. 6 patients had biallelic BRCA2 mutations (29%). Median age at transplant was 15.5 years (range 1.1–48.5). 7 patients (33%) received chemotherapy before HCT, with 4 achieving complete remission. HCT