

Literature summaries are provided as information only. Please refer to the original published articles for complete details on study methodology, results and discussion.

- *** Must read. Landmark publication that affects practice
- ** Recommend reading. Secondary paper that adds to literature
- * Consider reading. cursory importance to the practice

Hematopoietic Cell Transplantation

***Soiffer RJ, Kim HT, McGuirk J, et al. Prospective, double-blind, phase III clinical trial of anti-T-lymphocyte globulin to assess impact on chronic graft-versus-host disease-free survival in patients undergoing HLA-matched unrelated myeloablative hematopoietic cell transplantation. *J Clin Oncol*. 2017;35(36):4003-4011. <https://www.ncbi.nlm.nih.gov/pubmed/29040031>

- Phase III prospective, double-blind, randomized, multicenter trial of 254 patients (age 18-65 years) with acute leukemia or MDS undergoing myeloablative MUD allogeneic HCT. Patients received either ATLG (n=126) or placebo (n=128) at 20 mg/kg/day on days -3, -2, -1. GVHD prophylaxis consisted of tacrolimus and MTX. The primary endpoint was moderate-severe chronic GVHD-free survival.
- Grade 2-4 acute GVHD was lower in the ATLG group vs placebo (23% vs 40%, P=0.004). Moderate-severe chronic GVHD was also lower in the ATLG group vs placebo (12% vs 33%, P<0.001); however, 2-year moderate-severe chronic GVHD-free survival was not different between the groups (48% vs 44%, P=0.47).
- Both PFS and OS at 2 years was lower with ATLG than placebo (47% vs 65% [P=0.04] and 59% vs 74% [P=0.034], respectively). Multivariate analysis confirmed ATLG was associated with inferior 2-year PFS (HR 1.55 [95% CI, 1.05-2.28; P=0.26]) and OS (HR 1.74 [95% CI, 1.12-2.71; P=0.01]).
- The authors concluded that the use of ATLG in myeloablative MUD allogeneic HCT did not improve chronic GVHD-free survival, despite a reduction in moderate-severe chronic GVHD. Additional analyses are needed to understand the appropriate use of ATLG in HCT.

*Kawamura K, Kako S, Mizuta S, et al. Comparison of conditioning with fludarabine/busulfan and fludarabine/melphalan in allogeneic transplantation recipients 50 years or older. *Biol Blood Marrow Transplant*. 2017;23(12):2079-2087. <https://www.ncbi.nlm.nih.gov/pubmed/28890406>

- Retrospective review of 1607 patients transplanted in Japan aged ≥ 50 years old with AML, ALL, or MDS who underwent allogeneic HCT using FB (intermediate dose, FB2, or high dose, FB4) or FM140 between 2007-2014.
- The clinical outcomes among FB2 (busulfan at 6.4 mg/kg IV, n = 463), FB4 (busulfan at 12.8 mg/kg IV, n = 721), and FM140 (melphalan at 140 mg/m², n = 423) were compared.
- NRM in the FB4 and FM140 groups was higher than that in the FB2 group (HR, 1.63 [P < 0.001]; and HR, 1.71 [P < 0.001], respectively). Conversely, relapse in the FB4 and FM140 groups was less than that in the FB2 group (HR, 0.73 [P = 0.011]; and HR, 0.56 [P<0.001], respectively). There was no significant difference in OS between the FB2, FB4, and FM140 groups. The 3-year OS in patients with high-risk AML and MDS in the FM140 group (37.0% and 60.2%) was superior to

patients in the FB2 group (24.4% and 45.5%) and the FB4 group (24.6% and 40.6%) (P=0.016 and P=0.023).

- The authors conclude while the FB4 and FM140 groups saw a lower relapse rate, they had higher rates of NRM. However, FM140 may be associated with better OS in patients with high-risk AML and MDS. Still, a prospective study is suggested to confirm the results.

**Bhamidipati P, Fiala M, Grossman B, et al. Results of a prospective randomized, open-label, noninferiority study of tbo-filgrastim (Granix) versus filgrastim (Neupogen) in combination with plerixafor for autologous stem cell mobilization in patients with multiple myeloma and Non-Hodgkin lymphoma. *Biol Blood Marrow Transplant*. 2017;23(12):2065-2069.

<https://www.ncbi.nlm.nih.gov/pubmed/28797783>

- This is the first prospective, randomized (1:1), non-inferiority, phase II trial comparing the safety and efficacy of tbo-filgrastim plus plerixafor to filgrastim plus plerixafor for stem cell mobilization in patients with MM and NHL undergoing autologous HCT.
- 97 patients were included, receiving tbo-filgrastim or filgrastim 10 µg/kg/day SQ on days 1 to 5. Around 6pm on day 4, plerixafor 0.24 mg/kg SQ was given. Apheresis was initiated on day 5 with a target cumulative collection goal of at least 5.0×10^6 CD34+ cells/kg.
- Tbo-filgrastim was not inferior to filgrastim in the primary endpoint of day 5 CD34+ cell collection (mean, 11.6 ± 6.7 CD34+ cells/kg vs. 10 ± 6.8 CD34+ cells/kg). While multivariate analysis revealed a trend toward improved mobilization in the tbo-filgrastim arm, this was not statistically significant. There were no differences in secondary endpoints between the two groups.
- The authors conclude that tbo-filgrastim has non-inferior efficacy and similar safety profile compared to filgrastim when used for stem cell mobilization in patients with MM and NHL.

*Rondon G, Saliba R, Chen J, et al. Impact of fluid overload as new toxicity category on hematopoietic stem cell transplantation outcomes. *Biol Blood Marrow Transplant*. 2017;23(12):2166-2171.

<https://www.ncbi.nlm.nih.gov/pubmed/28844946>

- Retrospective study describing the prevalence, severity, and prognostic value of fluid overload in 2 separate cohorts of allogeneic HCT recipients based on a proposed grading system.
- The study cohort (n=145) included all recipients of an HCT from an HLA-haploidentical donor following a FM-based regimen with PT-Cy, tacrolimus and MMF for GVHD prophylaxis treated at a single institution between 2010 and 2015 for a hematologic malignancy. The validation cohort (n=449), included all recipients of an HCT from an HLA-MRD or MUD following a FB-based regimen with tacrolimus and mini-MTX for GVHD prophylaxis for the treatment of AML or MDS during the same period.
- According to univariate analysis, factors associated with day +100 NRM were fluid overload grade ≥ 2 (HR, 15; 95% CI, 4.2 to 55; P<0.001), creatinine >1 mg/dL (HR, 4.7; 95% CI, 1.6 to 14; P = 0.005), and age >55 years (HR, 4.5; 95% CI, 1.5 to 13; P=0.008). In multivariate analysis, factors associated with day +100 NRM were fluid overload grade ≥ 2 (HR, 13.1; 95% CI, 3.4 to 50; P<0.001) and creatinine level >1 mg/dL at transplantation admission (HR, 3.5; 95% CI, 1.1 to 11; P=0.03). These findings were verified in the validation cohort.
- A higher NRM translated to significantly poorer 1-year OS rates for patients with fluid overload grade ≥ 2 than for patients without fluid overload (70% vs. 42%, P<0.001 in the study cohort and 64% vs. 38%, P<0.001 in the validation cohort).

- The authors concluded fluid overload and should be considered an important prognostic factor in allogeneic HCT, as grade ≥ 2 fluid overload is strongly associated with higher NRM and lower OS.

Graft-versus-Host Disease

** Zeiser R, Blazar BR. Acute graft-versus-host disease- biologic process, prevention, and therapy. *N Engl J Med* 2017;377:2167-79. <http://www.ncbi.nlm.nih.gov/pubmed/29171820>

- Comprehensive review of the clinical presentation, risk factors, pathogenesis, and biology of acute GVHD.
- The review outlines the early pathophysiological events of acute GVHD, neoangiogenesis and intestinal tract infiltration with innate myeloid cells, which cause activation and production of reactive oxygen species in the gastrointestinal tract. These inflammatory triggers play a role in both innate and adaptive immune responses.
- T-cell activation and co-stimulation pathways are discussed, as well as the role of cytokines in T-cell activation and survival. The review also discusses the high metabolic demands that are required during the processes of T-cell differentiation and proliferation in GVHD and the energy sources used to meet these demands.
- The review acknowledges several biomarkers that have been investigated which could not only predict the risk of GVHD among allogeneic HCT recipients, but also predict the response to IST. The use of biomarkers could allow an individualized approach to GVHD prophylaxis.
- A review of current preventative and therapeutic strategies, including calcineurin inhibitors, folate antagonists, mTOR inhibitors, cyclophosphamide, T-cell depletion, glucocorticoids, and monoclonal antibodies is included. Potential preventative and therapeutic options as well as those in preclinical studies are also discussed.

Pediatrics

**Heimall J, Logan BR, Cowan MJ, et al. Immune reconstitution and survival of 100 SCID patients post-hematopoietic cell transplant: a PIDTC natural history study. *Blood*. 2017;130(25):2718-27.

<https://www.ncbi.nlm.nih.gov/pubmed/29021228>

- Prospective natural history study analyzing 100 children with SCID treated with allogeneic HCT. 68 patients had typical SCID and 32 had leaky SCID, Omenn syndrome, or reticular dysgenesis.
- The 2-year OS was 90%, but was 95% for those that were infection-free at time of HCT vs 81% for those with active infection (P=0.009).
- Diagnosis of typical SCID versus leaky SCID/Omenn syndrome, diagnosis via family history versus newborn screening, preparative regimen, or type of donor did not have an impact on survival.
- Although post-transplant CD4 counts and freedom from need of IVIG infusions were improved after HCT, other immunologic reconstitution parameters were not affected.
- The authors conclude that in the modern era, active infection poses the greatest threat to survival of SCID patients, and while newborn screening has been effective in diagnosing early in life, additional prospective trials to identify additional approaches for early-in-life diagnosis are needed to ensure children are infection-free when undergoing HCT.

*Hashem H, Kumar AR, Muller I, et al. Hematopoietic stem cell transplantation rescues the hematological, immunological, and vascular phenotype in DADA2. *Blood*. 2017;130(24):2682-88. <https://www.ncbi.nlm.nih.gov/pubmed/28974505>

- Deficiency of DADA2 is an autoimmune condition caused by mutations in CECR1 and results in autoinflammation and vasculopathies, including fevers, ischemic strokes, intracranial hemorrhages, immunodeficiencies, and bone marrow failure.
- Tumor necrosis factor alpha blockade has been the treatment of choice for inflammatory and vascular manifestations, but HCT represents potential definitive treatment.
- A cohort of 14 patients from 6 different countries who had previous immunodeficiency or bone marrow failure (median age - 7.5 years) were given HLA-matched sibling (n=1), HLA-matched unrelated donor (n=9), HLA-mismatched unrelated (n=3), or haploidentical sibling (n=1) HCT.
- With a median follow up of 18 months, all patients are alive resolution of hematological and immunological phenotype and no new vascular events.
- Plasma ADA2 enzyme activity normalized in all 7 patients tested post-HCT as early as day +14
- Post-HCT hematological autoimmunity (cytopenias) occurred in 4 patients, grade 1 acute GVHD occurred in 1 patient, grade 2 acute-GVHD in 3 patients, grade 3 acute-GVHD in 1 patient, and moderate chronic-GVHD occurred in 1 patient.

Chimeric Antigen Receptor (CAR) T-Cell Therapy

**Pan J, Yang JF, Deng BP, et al. High efficacy and safety of low-dose CD-19-directed CAR-T cell therapy in 51 refractory or relapsed B acute lymphoblastic leukemia patients. *Leukemia*. 2017;31:2587-93. <https://www.ncbi.nlm.nih.gov/pubmed/28490811>

- Prospective, single-arm cohort of 51 patients with primary relapsed/refractory (R/R, n=42) or MRD-positive (n=9) ALL treated with optimized second-generation CD19-directed CAR-T cells.
- CAR-T infusion doses initially ranged from 0.05 to 14 x 10⁵/kg but eventually settled at 1 x 10⁵/kg for the last 20 cases in cohort.
- 36/40 (90%) of the evaluated R/R patients achieved CR or CR with incomplete count recovery (CRi), and 9/9 (100%) of MRD-positive patients achieved MRD-negative status. All cases that received at least 1 x10⁵/kg dosing achieved CR.
- Nearly all patients experienced CRS, with a median severity grade 2. MRD-positive patients had significantly less severe CRS than R/R patients (P=0.0044). Two patients died from grade 5 CRS with intracranial hemorrhage and heart failure, respectively. 8/51 patients experiences seizures, and all regained consciousness quickly with early intervention.
- 23/27 patients that were CR/CRi and proceeded to HCT remained MRD-negative with a median follow-up of 206 days. 9/18 patients that were CR/CRi and did not proceed to HCT relapsed.

Other

**Marty FM, Ljungman P, Chemaly RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. *New Engl J Med*. 2017 Dec 6. [Epub ahead of print] doi:10.1056/NEJMoa1706640. <https://www.ncbi.nlm.nih.gov/pubmed/29211658>

- Phase III, multicenter, randomized, double-blind, placebo-controlled, superiority trial in 565 CMV-seropositive patients randomized in a 2:1 ratio to letermovir 480 mg daily (or 280 mg daily with concomitant CsA use) or placebo through week 14 post-HCT.
- Letermovir or placebo was initiated a median of 9 days (range 0-28) after transplant and the median duration of therapy was 82 days (range 1-113) and 56 days (range 4-115) in the letermovir and placebo groups, respectively.

- The primary endpoint was the proportion of patients that experienced clinically significant CMV infection through week 24 post-transplantation. Patients who discontinued the trial before week 24 for any reason or who had missing data at week 24 were input as having a primary endpoint event.
- Of the 495 evaluable patients, fewer patients in the letermovir group vs the placebo group had clinically significant CMV infection or were input as having a primary end-point event by week 24 post-HCT (37.5% vs 60.6%, $P < 0.001$).
- At 14 weeks post-HCT, fewer patients had clinically significant CMV infection or were input as having a primary endpoint event in the letermovir group as compared to the placebo group (19.1% vs 50%, $p < 0.001$). The Kaplan-Meier event rate of clinically significant CMV infection was also lower in the letermovir group as compared to the placebo group at 24 weeks post-HCT (18.9% vs 44.3%, $P < 0.001$). At week 24 post-transplantation, all-cause mortality was lower among patients receiving letermovir (10.2%) vs placebo (15.9%) (95% CI 10.2 – 21.6, $P = 0.03$).
- Adverse events were similar between the groups. While not statistically significant, there was a higher incidence of vomiting and edema in the letermovir group. There was also a higher frequency of atrial fibrillation and flutter events with letermovir but further analysis did not show a relationship with letermovir exposure. This will require further evaluation in future studies.
- The authors concluded that letermovir prophylaxis was highly effective, led to minimal side effects, and was associated with lower all-cause mortality than placebo through week 24 after post-HCT.

Abbreviations

ALL: acute lymphoblastic leukemia

AML: acute myeloid leukemia

ATLG: anti-T-lymphocyte globulin

CMV: cytomegalovirus

CR: complete response

CRi: CR with incomplete hematologic recovery

CRS: cytokine release syndrome

CsA: cyclosporine

DADA2: adenosine deaminase 2

FB: fludarabine/busulfan

FM: fludarabine/melphalan

GVHD: graft-versus-host disease

HCT: hematopoietic cell transplantation

HLA: human leukocyte antigen

IST: immunosuppressive therapy

IVIg: intravenous immunoglobulin

MDS: myelodysplastic syndrome

MM: multiple myeloma

MMF: mycophenolate mofetil

MRD: minimal residual disease or matched related donor

MTX: methotrexate

MUD: matched unrelated donor

mTOR: mechanistic target of rapamycin

NHL: Non-Hodgkin lymphoma

NRM: non-relapse mortality

OS: overall survival

PFS: progression-free survival

PT-Cy: post-transplant cyclophosphamide

R/R: relapsed/refractory

SCID: severe combined immunodeficiency

ASBMT Pharmacy SIG Communications Working Committee:

Brandi Anders, Morgan Belling, David Eplin, Katie Gatwood, Suzanne Gettys, Teresa (Kam) Thakrar, Scott Lanum, Stephanie (Malenfant) Willenbring, Shreya Shah, Ryan Shaw