

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

***LeGouill S, Thieblemont C, Oberic L, et al. Rituximab after autologous stem-cell transplantation in mantle-cell lymphoma. *New Engl J Med*. 2017;377:1250-60.

<https://www.ncbi.nlm.nih.gov/pubmed/28953447>

- Phase III trial randomized 240 patients to rituximab maintenance vs observation after R-DHAP for 4 cycles followed by R-BEAM conditioning and autologous HCT
- Rituximab maintenance was dosed at 375 mg/m² every 2 months for 3 years
- Median EFS, PFS, and OS from randomization were not reached in either group. A significant increase noted in 4-year EFS (79% vs 61%; P= 0.001), 4-year PFS (83% vs 64%; P<0.001), and 4-year OS (89% vs 80%; P=0.04) with rituximab vs observation, respectively
- There was no difference in rate of infection between study groups
- Rituximab maintenance therapy after HCT prolonged EFS, PFS, and OS among patients with mantle-cell lymphoma who were younger than 66 years of age at diagnosis

** Berro M, Arbelbide JA, Rivas MM, et al. Hematopoietic Cell Transplantation-Specific Comorbidity Index Predicts Morbidity and Mortality in Autologous Stem Cell Transplantation. *Biol Blood Marrow Transplant*. 2017;23:1646-1650. <https://www.ncbi.nlm.nih.gov/pubmed/28669923>

- Retrospective review of 1730 medical records from 10 Argentinean centers evaluating impact of HCT-CI on 100-day morbidity, long-term NRM, and OS
- Patients had median age of 53 year with 48% MM, 27% NHL, and 17% HL; HCT-CI scores were low-risk in 60%, intermediate in 29%, and high-risk in 13%
- 100-day NRM was significantly higher with high-risk HCT-CI (6.1% vs 3.2% vs 1.8%; p=0.002) as was early composite morbidity-mortality (13% vs 9% vs 4.7%; p<0.001). No significant impact was found in OS.
- The use of HCT-CI has been established in allogeneic transplants but has been limited in autologous HCT. This study found significant association between high-risk HCT-CI and NRM that appeared to be driven by early composite morbidity-mortality including intubation, shock, and dialysis

*Burroughs LM, Shimamura A, Talano JA, et al. Allogeneic hematopoietic cell transplantation using treosulfan-based conditioning for treatment of marrow failure disorders. *Biol Blood Marrow Transplant*. 2017;23:1669-77. <https://www.ncbi.nlm.nih.gov/pubmed/28602958>

- Prospective, phase II multicenter trial of 14 patients with marrow failure disorders (Shwachman-Diamond syndrome, n=3; Diamond-Blackfan anemia, n=4; GATA2 deficiency, n=2; paroxysmal nocturnal hemoglobinuria, n=4; and an undefined marrow failure disorder, n=1) undergoing HCT

with HLA-matched related (n=2) or unrelated (n=12) grafts after conditioning with treosulfan 42 mg/m² and fludarabine 150 mg/m², with or without thymoglobulin 6 mg/kg

- At median follow up of 3 years, 13 patients are alive with complete correction of underlying disease; all patients engrafted. No grade III-IV GVHD or infection-related deaths in patients receiving thymoglobulin (n=11).
- Treosulfan, fludarabine, and thymoglobulin conditioning is effective at establishing donor engraftment with a low toxicity profile and DFS in patients with marrow failure disorders

*Jakubowski AA, Petrlik E, Maloy M, et al. T cell depletion as an alternative approach for patients 55 years or older undergoing allogeneic stem cell transplantation as curative therapy for hematologic malignancies. *Biol Blood Marrow Transplant*. 2017;23:1685-94.

<https://www.ncbi.nlm.nih.gov/pubmed/28734876>

- Retrospective single-center study of 214 patients aged ≥ 55 years (median age 61 years) to determine efficacy and tolerability of *ex-vivo* T-cell depleted myeloablative allogeneic HCT for hematologic malignancies
- Most patients had myeloid diseases (70%); high risk features (84%); poor-risk disease (73%); acute leukemias in remission (88%); and unrelated donors (57%). Peripheral blood stem cell (97%) and bone marrow sources were utilized, without pharmacologic GVHD prophylaxis.
- After median follow up of 70 months, 4-year overall and relapse-free survival rates were 44% and 41%, respectively with relapse rate of 25%. Incidence of grades II-IV aGVHD was 9% at day 100 and for cGVHD was 7% at 2 and 4 years.
- Non-relapse mortality was 10% at day +100 and 30% at 2 years with 63% of deaths attributed to non-relapse causes (primarily infection and GVHD)
- The authors concluded that using this T cell depleted graft approach an older, high-risk patient population was associated with minimal GVHD, similar to that observed in a younger population

**Li Z, Wang Y, Wang J, et al. Haploidentical hematopoietic stem cell transplantation for adult patients with Epstein–Barr virus-associated hemophagocytic lymphohistiocytosis. *Leuk Lymphoma*.

2018;59(1):77-84. <https://www.ncbi.nlm.nih.gov/pubmed/28573910>

- Retrospective analysis of 30 patients with EBV-HLH that underwent a haploidentical HCT from peripheral blood at a single institution
- At the time of HSCT, 20 patients (66.7%) had achieved a response after receiving HLH-94 therapy or salvage therapies. The median age was 32 years old
- 26 patients (86.7%) achieved donor cell engraftment; the remaining 4 died of conditioning regimen related toxicity. EBV reactivation occurred in 25 patients (96.2%); 3 developed PTLD. aGVHD occurred in 18 (69.2%), with grade I–II in 11 patients and grade III–IV in 7 patients. cGVHD occurred in six (23.1%). The 3-year OS was 63.3%.
- The authors conclude that haploidentical HCT is a feasible and effective treatment for adult patients with EBV-HLH

*Miot C, Imai K, Imai C, et al. Hematopoietic stem cell transplantation in 29 patients hemizygous for hypomorphic *IKBKG*/NEMO mutations. *Blood*. 2017;130(12):1456-1467.

<https://www.ncbi.nlm.nih.gov/pubmed/28679735>

- X-linked recessive ectodermal dysplasia with immunodeficiency is a rare primary immunodeficiency caused by hypomorphic mutations of the *IKBKG* gene, encoding nuclear factor κB (NF-κB) essential modulator (NEMO).
- This is the largest international retrospective series of 29 NEMO-deficient patients with 23 different hypomorphic *IKBKG* mutations who underwent HCT. HCT type included MRDs (n=7), MUDs (n=12), MMUDs (n=8), and haploidentical donors (n=2).
- Median age was 3.35 years and OS was 74% at 108 months after HSCT. Engraftment was documented in 24 patients, and aGVHD occurred in 13 patients. Preexisting mycobacterial infection and colitis were found to be associated with poor HSCT outcome.
- The authors conclude that HSCT can cure most clinical features of patients with a variety of *IKBKG* mutations.

Graft-versus-Host Disease

*Michallet M, Sobh M, Garban F, et al. Extracorporeal photopheresis for GVHD prophylaxis after reduced intensity conditioning allogeneic hematopoietic stem cell transplantation: a prospective multicenter phase 2 study. *Leuk Lymphoma*. 2018;59(2):372-380.

<https://www.ncbi.nlm.nih.gov/pubmed/28587506>

- Prospective multicenter phase II study to evaluate the safety and efficacy of prophylactic ECP in adult patients with hematological malignancies early after allo-HSCT with RIC of busulfan, fludarabine, and ATG.
- 20 patients received ECP therapy starting on day +21 twice per week during the first two weeks and then once per week for the next four weeks for a total of eight sessions.
- All patients engrafted and 17 (85%) received the total eight ECP courses. There were no adverse effects related to ECP. Seven patients developed aGVHD, all resolved with steroids and 15% were between grades II-IV GVHD at day 100. 4 patients developed cGVHD; the 3 with limited were steroid sensitive and one with extensive resolved after reinitiating ECP. Two-year OS and PFS was 84 and 74%, respectively.
- The authors conclude that this study demonstrates the safety of early ECP and encouraging results with low acute and chronic GVHD incidence and no evident interference with graft-versus-leukemia effect

Pediatrics

*Ivaturi V, Dvorak CC, Chan D, et al. Pharmacokinetics and model-based dosing to optimize fludarabine therapy in pediatric hematopoietic cell transplant recipients. *Biol Blood Marrow Transplant*.

2017;23:1701-13. <https://www.ncbi.nlm.nih.gov/pubmed/28684371>

- Prospective, multicenter, PK-PD study of plasma (f-ara-a) and intracellular (f-ara-ATP) fludarabine in children undergoing fludarabine-based conditioning in 133 children with malignant (n=59) and non-malignant (n=74) disorders
- No association between f-ara-a exposure and the primary endpoint of TRM was found however lower exposure was noted compared to adult studies which correlated TRM. Covariate analysis demonstrated actual body weight and creatinine clearance are significant patient-specific factors affecting f-ara-a clearance

- In the malignant setting, 1 year DFS was highest in patients achieving a systemic f-ara-a cumulative AUC greater than 15 mg*hr/L compared to patients with a cumulative AUC less than 15 mg*hr/L (82.6% vs 52.8%, P=.04). Non-malignant conditions were more variable with no observable trend in OS.
- Authors suggest achieving exposure over 4-5 days for malignant indications to avoid higher daily exposures that have been associated with TRM in other adult studies. Individualized model-based dosing of fludarabine in infants and young children may reduce morbidity and mortality through improved DFS rates and by limiting drug-related toxicity.

Other

*Milone G, Martino M, Leotta S, et al. Cost-effectiveness of on-demand plerixafor added to chemotherapy and granulocyte-colony stimulating factor for peripheral blood stem cell mobilization in multiple myeloma. *Leuk Lymphoma*. 2018;59(1):42-48.

<https://www.ncbi.nlm.nih.gov/pubmed/28573902>

- Prospective phase II/III trial evaluating the utility of on-demand PLX given per algorithm for patients showing predictive signs of mobilization failure. This was a subgroup of MM patients undergoing chemomobilization.
- A total of 111 MM patients were evaluated and received cyclophosphamide 4 g/m² and G-CSF.
- A successful CD34+ cell mobilization was achieved in 97.2% (108/111) of patients. Compared to a historical control group (no PLX), patients who received on-demand PLX treatment had significantly higher likelihoods of successfully achieving both the minimal (p=0.006) and optimal harvest (p=0.05) goals. The incremental cost-effectiveness ratio was 40.6 EUR per patient for each 1% increase in probability of achieving a successful minimal harvest.
- The authors conclude that cyclophosphamide plus G-CSF and on-demand PLX, used according to a validated algorithm, is an effective and economically advantageous method for mobilizing PBSC in MM patients

*Kennedy LB, Li Z, Savani BN, et al. Measuring immune response to commonly used vaccinations in adult recipients of allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*.

2017;23:1614-21. <https://www.ncbi.nlm.nih.gov/pubmed/28624476>

- Review article evaluating available studies and providing guidance on measurement of specific antibody titers, definition of an immune response, and durability of response in HCT recipients
- Discusses pneumococcal, influenza, hepatitis B, tetanus, diphtheria, pertussis, *Haemophilus influenzae*, polio, meningococcal, human papillomavirus, and live attenuated vaccines
- Studies of vaccine immunogenicity demonstrate that more immunogenic vaccines (i.e. protein-polysaccharide conjugates compared with pure polysaccharide antigens) and higher dose vaccines elicit a more robust immune response in HCT recipients
- Questions for future research include: Can more immunogenic vaccines be developed? What is the most accurate definition of appropriate response to vaccination? How should durability of immune response be followed over time? Should all patients be immunized according to the same schedules, or are there special considerations for haploidentical transplant, cord blood transplant, and elderly patients?

Abbreviations

ATG: anti-thymocyte globulin

CI: comorbidity index

CR: complete response

DFS: disease-free survival

EBV: Epstein-Barr virus

ECP: extracorporeal photopheresis

EFS: event-free survival

G-CSF: granulocyte-colony stimulating factor

GVHD: graft-versus-host disease

HCT: hematopoietic stem cell transplant

HL: Hodgkin lymphoma

HLH: hemophagocytic lymphohistiocytosis

MM: multiple myeloma

NHL: non-Hodgkin lymphoma

NRM: non-relapse mortality

ORR: overall response rate

OS: overall survival

PBSC: peripheral blood stem cells

PFS: progression-free survival

PLX: plerixafor

PR: partial response

PTLD: post-transplant lymphoproliferative disorder

R-BEAM: rituximab, carmustine, etoposide, cytarabine, melphalan

R-DHAP: rituximab, dexamethasone, high-dose cytarabine, platinum

RIC: reduced intensity conditioning

TRM: transplant-related mortality

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