



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

**McCarthy PL, Holstein SA, Petrucci MT, et al. Lenalidomide maintenance after autologous stem-cell transplantation in newly diagnosed multiple myeloma: a meta-analysis. *J Clin Oncol.* 2017;35:3279-3289. <https://www.ncbi.nlm.nih.gov/pubmed/28742454>

- Meta-analysis of three randomized controlled trials (CALGB 100104, GIMEMA RV-MM-PI-209, and IFM 2005-02) of patients with newly-diagnosed multiple myeloma receiving auto-HCT followed by lenalidomide maintenance (N=605) versus placebo/observation (N=603).
- Duration of maintenance therapy varied among the three trials. Mean treatment duration was 28 months with lenalidomide maintenance and 22 months with placebo or observation. Rate of discontinuation due to toxicities was 29% in the lenalidomide maintenance group.
- The primary outcome was OS. At a median of 79.5 years of follow-up, the median OS was not reached in the lenalidomide group compared to 86 months in the placebo group with a 25% reduction in risk of death (P=0.001). OS benefit was not seen in patients with ISS stage III disease or those with high-risk cytogenetics, such as del17p, t(4;14), and t(14;16). PFS benefit was demonstrated across all studies and in all subgroups.
- Cumulative incidence rate of a second primary malignancy before disease progression was higher with lenalidomide maintenance (~5-6% with lenalidomide vs 1-2% with placebo), while cumulative incidence rates of progression, death, or death as a result of myeloma were all higher with placebo or observation.
- This meta-analysis demonstrated a significant OS benefit and confirmed the PFS benefit of lenalidomide maintenance after auto-HCT in patients with newly diagnosed multiple myeloma as compared to placebo or observation.

**Martínez C, Gayoso J, Canals C, et al. Post-transplantation cyclophosphamide-based haploidentical transplantation as alternative to matched sibling or unrelated donor transplantation for Hodgkin Lymphoma: a registry study of the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation. *J Clin Oncol.* 2017;35:3425-32.

<https://www.ncbi.nlm.nih.gov/pubmed/28846465>

- Largest published retrospective study to date comparing outcomes of patients with HL who received haplo transplant with PTCy (N=98) versus HLA-matched sibling (N=338) and HLA-matched MUD (N=273) transplants with a median follow up of 29 months
- Haplo transplants were associated with higher rates of grade II-IV aGVHD compared to MRD (33% vs 18%; P=0.003) but no compared to MUD (33% vs 30%; P=0.36). Grade III-IV aGVHD was not significant between groups (P=0.054).

- Rates of cGVHD were 26%, 25%, and 41% for haplo, MRD, and MUD respectively (P=0.017) with similar results based on stem cell source. On multivariable analysis, relative to MRD, NRM was similar with haplo (P=0.26) and higher with MUD (P=0.003); relapse risk was lower in both the haplo (P=0.047) and MUD (P<0.001) arms.
- The rate of the composite endpoint of extensive cGVHD and RFS was significantly improved in the haplo group (40%) compared with sibling donor (28%; P=0.049) and similar to MUD (38%; P=0.59). There were no significant differences in OS or PFS between haplo and MRD or MUD transplants.
- Haplo HCT with PTCy results in similar survival outcomes compared with MRD or MUD HCT, which supports its use in HL when no conventional donor is available

*Obiozor C, Subramaniam D, Divine C, et al. Evaluation of performance status and hematopoietic cell transplantation specific comorbidity index on unplanned admission rates in patients with multiple myeloma undergoing outpatient autologous stem cell transplantation. *Biol Blood Marrow Transplant.* 2017;23(10):1641-45. <https://www.ncbi.nlm.nih.gov/pubmed/28603071>

- Retrospective analysis of patients with MM undergoing auto-HCT and comparison of inpatients and outpatients in terms of admission rate, transplantation outcome, and OS. Also evaluate if HCT-CI and KPS can predict unplanned admissions in those with planned outpatient auto-HCT.
- Included 448 patients at a single institution between 2009 and 2014. Three cohorts were defined: cohort A, planned inpatient auto-HCT (n = 216); cohort B, unplanned inpatient admissions after outpatient auto-HCT (n = 57); and cohort C, planned outpatient auto-HCT (n = 175).
- One-third of the patients undergoing outpatient transplantation required admission for transplantation-related toxicities, most frequently on day +7. Patients in this group had lower preexisting KPS and higher HCT-CI scores. With a median follow up of 5 years, poor performance status (KPS <70%) appeared to be associated with worse OS (P < 0.002).
- The authors conclude that a prospective study may help determine if planned admission for this group would have prevented the unplanned admissions after outpatient auto-HCT.

* Eichler F, Duncan C, Musolino PL, et al. Hematopoietic stem-cell gene therapy for cerebral adrenoleukodystrophy. *N Engl J Med.* 2017;377(17):1630-8. <http://www.ncbi.nlm.nih.gov/pubmed/28976817>

- Cerebral adrenoleukodystrophy is an X-linked genetic disease in which mutations in *ABCD1* gene lead to a dysfunctional ALD protein. The disorder is characterized by demyelination and neurodegeneration. Allo-HCT has been used to halt disease progression and is the only effective therapy that has been identified to date.
- The STARBEAM study was a multicenter, single-group, open-label, phase 2-3 safety and efficacy study of gene therapy with the Lenti-D drug product in 17 males with early-stage disease.
- All 17 patients received conditioning with busulfan and cyclophosphamide followed by gene therapy with the Lenti-D drug product, which involved infusion of autologous CD34+ hematopoietic stem cells that have been transduced ex vivo with the elivaldogene tavalentivec (Lenti-D) lentiviral vector containing *ABCD1* cDNA.
- The primary endpoint was being alive and having no major functional disability at 24 months after infusion; patients were also assessed for the occurrence of GVHD, death, major functional disabilities, changes in neurologic function, and extent of lesion on MRI.

- At median follow-up of 29.4 months, 15 of 17 patients (88%) were alive with no major functional disability, and had only minimal clinical symptoms. Measurable ALD protein was observed in all patients. There were no reports of treatment-related death or GVHD. Most adverse events occurred during conditioning and were consistent with the adverse events associated with myeloablative chemotherapy.
- Early results from this study suggest that for males with early-stage cerebral adrenoleukodystrophy, Lenti-D gene therapy may be a safe and effective alternative to allo-HCT. Additional follow-up is needed to long-term safety and efficacy.

Graft-versus-Host Disease

***Miklos D, Cutler CS, Arora M, et al. Ibrutinib for chronic graft-versus-host disease after failure of prior therapy. *Blood*. 2017;130(21):2243-50. <https://www.ncbi.nlm.nih.gov/pubmed/28924018>

- Multicenter, prospective, open-label study of 42 patients with active cGVHD who had failed 1 to 3 separate lines of therapy including corticosteroids. Patients received ibrutinib 420mg once daily until progression.
- Primary efficacy endpoint was cGVHD response based on 2005 National Institutes of Health criteria
- At median follow-up of 13.9 months, best overall response rate was 67%, with 71% of those responding having a sustained response of >20 weeks. Responses were seen across all involved organs that were evaluated for GVHD, and patients with multi-organ cGVHD also had multi-organ responses.
- Median corticosteroid dose in responders decreased from 0.29 mg/kg/day at baseline to 0.12 mg/kg/day at week 49, with 5 patients discontinuing corticosteroids completely.
- Most common adverse effects were fatigue (57%), diarrhea (37%), muscle spasms (28%), nausea (26%), and bruising (24%).
- Based on these results, ibrutinib was approved in the United States for treatment of adult patients with cGVHD after failure of 1 or more lines of systemic therapy.

Pediatrics

*Ivaturi V, Dvorak C, 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(10):1701-13. <https://www.ncbi.nlm.nih.gov/pubmed/28684371>

- Prospective multicenter PK study to evaluate patient specific factors that influence variability in fludarabine exposure in children undergoing HCT for malignant and nonmalignant diseases, with an evaluation of clinical outcomes. Plasma and PBMCs were collected throughout conditioning for quantification of f-ara-a and f-ara-ATP.
- Data from 133 children were included in the PK and PD analysis. Patient variability was successfully predicted using a covariate model, incorporating patient weight and CrCl, as these were identified to be significant factors influencing f-ara-a clearance.
- No association with f-ara-a exposure and TRM was identified. However, in patients with malignant disease, DFS was highest at 1 year after SCT in those achieving a systemic f-ara-a cAUC greater than 15 mg*hour/L compared to patients with a cAUC less than 15 mg*hour/L (82.6% vs. 52.8% P = 0.04).
- The authors conclude that individualized model-based dosing of fludarabine in infants and young children may reduce morbidity and mortality through improved rates of DFS and minimizing toxicity.

*Rotz SJ, Ryan TD, Hlavaty J, et al. Cardiotoxicity and cardiomyopathy in children and young adult survivors of hematopoietic stem cell transplant. *Pediatr Blood Cancer*. 2017;64:e26600.

<https://www.ncbi.nlm.nih.gov/pubmed/28453909>

- Long-term HCT survivors have elevated cardiac risk due to pre-HCT therapies, HCT itself, and other adult-onset risk factors. Varying recommendations suggest survivors should have a cardiovascular assessment at least yearly after HCT.
- Combined long-term data from Pediatric Oncology Group (POG) studies 9404, 9425, and 9426 suggest dexrazoxane could be used more frequently to prevent cardiotoxicity with pediatric chemotherapy without adversely affecting overall mortality, relapse-free survival, or death from second cancers.
- Treatment of LVEF dysfunction after anthracyclines with ACE/ARB therapy is likely beneficial. Statins are beneficial for dyslipidemia, and may have a protective effect without dyslipidemia.

Other

**Tzannou I, Papadopoulou A, Naik S, et al. Off-the-shelf virus-specific T cells to treat BK virus, human herpesvirus 6, cytomegalovirus, Epstein-Barr virus, and adenovirus infections after allogeneic hematopoietic stem-cell transplantation. *J Clin Oncol*. 2017;35(31):3547-57.

<https://www.ncbi.nlm.nih.gov/pubmed/28783452>

- Phase II trial evaluating the effects of banked VSTs that recognized five common viral pathogens (i.e. pentavalent T cells) in 37 patients with 45 infections refractory to drug therapy
- Single infusion produced a cumulative clinical response rate of 92% by week 6 (95% CI 78.1% - 98.3%) overall and the following rates by virus:
 - BKV: 100% (N=16)
 - CMV: 94% (N=17)
 - AdV: 71% (N=7)
 - EBV: 100% (N=2)
 - HHV-6: 67% (N=3)
- Of the 18 patients screened but did not receive VSTs, 12 (67%) developed progressive disease
- Clinical benefit was achieved in 31 patients treated for one infection and in seven patients treated for multiple concomitant infections. 15 patients required a second infusion of the same (N=8) or different (n=7) VSTs VST persistence was confirmed at up to 12 weeks in 69% of evaluable patients (N=16) and declined with immune reconstitution.
- Infusions were safe; two cases of de novo grade I GVHD were observed
- The use of banked VSTs is a feasible, safe, and effective approach to treat severe and drug-refractory viral infections after HCT. The multi-specificity of the VSTs promotes extensive antiviral coverage, making treatment of patients with multiple concomitant infections possible.

**Alvarnas JC, Zaia JA, Forman SJ. How I treat patients with HIV-related hematological malignancies using hematopoietic stem cell transplantation. *Blood*. 2017;130(18):1976-84.

- Auto-HCT for HRL has been shown to be safe and effective in several retrospective trials and one prospective trial, with outcomes similar to non-HIV-infected patients. It is standard of care for patients with HRL and treatable HIV infections that otherwise meet transplant eligibility criteria.
- The authors recommend a planned interruption cART during the period of transplant-related mucositis/enteritis to avoid subsequent starting and stopping of cART therapy that might infer HIV resistance.

- Patients should be monitored closely for opportunistic infections after AHCT due to increased risk for CMV reactivation, and pre-emptive treatment should be initiated for CMV viral loads >1000 copies/mL. Patients should also receive prophylaxis for PJP, herpes viruses, and *Mycobacterium avium* complex until they receive adequate CD4 T-cell recovery.
- Most trials report a peri-transplant spike in HIV viral load and a decrease in CD4 T-cell counts, but is rarely associated with clinical sequelae. The goal after re-initiation of cART after AHCT should be an undetectable viral load within 3 months of resuming cART, with viral load assessments every 2-4 weeks post-transplant.
- While there is less data on utilizing allogeneic stem cell transplants in HRL patients, it is generally an acceptable option given the patient otherwise meets organ-specific criteria and has treatable HIV infection.
- There are more considerations with drug interactions with cART and concomitant transplant medications in allogeneic stem cell transplant such as immunosuppression. Myelotoxic drugs such as zidovudine and proteasome boosters should be avoided.
- Consideration should be made for enrolling allogeneic stem cell transplant candidates on clinical trials that offer access to CCR5Δ32 homozygous donors or gene-modified hematopoietic stem cells to confer resistance to HIV infection.

Abbreviations

ACE: angiotensin converting enzyme	MRD: matched related donor
aGVHD: acute graft-versus-host disease	MUD: matched unrelated donor
ARB: angiotensin II receptor blocker	NRM: non-relapse mortality
ALD: adrenoleukodystrophy	OS: overall survival
Allo-HCT: allogeneic hematopoietic stem cell transplant	OTI: orotracheal intubation
Auto-HCT: autologous hematopoietic stem cell transplant	PBMC: peripheral blood mononuclear cell
cART: combination anti-retroviral therapy	PD: pharmacodynamics
cAUC: cumulative area under the curve	PFS: progression-free survival
cDNA: complementary DNA	PK: pharmacokinetics
CI: comorbidity index	PTCy: post-transplant cyclophosphamide
CrCl: creatinine clearance	PR: partial remission
cGVHD: chronic graft-versus-host disease	TRM: treatment-related mortality
CR: complete remission	VSTs: virus-specific T cells
DFS: disease-free survival	
f-ara-a: fludarabine plasma	
f-ara-ATP: fludarabine intracellular triphosphate	
GVHD: graft-versus-host disease	
HCT: hematopoietic stem cell transplant	
HL: Hodgkin lymphoma	
HLA: human leukocyte antigen	
HRL: HIV-related lymphomas	
ISS: International Staging System	
KPS: Karnofsky Performance Status	
LVEF: left ventricular ejection fraction	
MM: multiple myeloma	

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