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

** Dhakal B, Szabo A, Chhabra S, et al. Autologous transplantation for newly diagnosed multiple myeloma in the era of novel agent induction: a systematic review and meta-analysis. *JAMA Oncol.* 2018;4:343-50. http://www.ncbi.nlm.nih.gov/pubmed/29302684

- Systematic review, conventional meta-analysis and network meta-analysis of all phase 3 RCTs evaluating the role of high-dose therapy with melphalan followed by autologous stem cell transplant (HDT/ASCT) in MM
- Four RCT's comparing HDT/ASCT with SDT (n=2421) were included in the conventional meta-analysis; 5 RCT's (n = 3171) were selected for network meta-analysis. The combined OR for CR was 1.27 (95% CI, 0.97-1.65; P=0.07) with HDT/ASCT compared with SDT. The combined HR was 0.55 (95% CI, 0.41-0.74, P=0.004) for PFS, indicating a statistically significant benefit with HDT/ASCT. For OS, the combined HR was 0.76 (95% CI, 0.42-1.36, P=0.20) for HDT/ASCT. Of note, significant heterogeneity was present for PFS and OS (P=0.01 for both).
- Meta-regression showed that longer median follow-up was associated with a larger beneficial effect of HDT on PFS (HR/mo 0.98; 95%CI 0.96-0.99, P=0.03) and OS (HR/mo 0.90; 95% CI 0.84-0.96, P=0.002)
- Compared to SDT, tandem transplantation showed the most favorable PFS (HR, 0.49; 95% CI, 0.37-0.65), followed by HDT/ASCT plus consolidation with VRD (HR, 0.53; 95% CI, 0.37-0.76). None of the transplantation-based approaches had a significant impact on OS as compared to SDT.
- The authors concluded that HDT followed by ASCT was associated with superior PFS with minimal toxic effects compared with SDT. Both tandem transplantation and single transplantation with VRD were superior to single HDT/ASCT alone and SDT for PFS, but OS was similar across the 4 approaches.

*Avivi I, Boumendil A, Finel H, et al. Autologous stem cell transplantation for primary mediastinal B-cell lymphoma: long-term outcome and role of post-transplant radiotherapy. A report of the European Society for Blood and Marrow Transplantation. *Bone Marrow Transplant.* 2018 February. doi: 10.1038/s41409-017-0063-7. [Epub ahead of print]. https://www.ncbi.nlm.nih.gov/pubmed/29463854

- Retrospective registry study of adult patients with PMBCL who received autologous HCT between 2000 and 2012, to investigate outcomes in the rituximab era, including effects of post-transplant RT consolidation
- Eighty six patients registered with the EBMT were included. At the time of HCT, 16 patients were in remission after first-line therapy (CR/PR1), 44 patients had chemo-sensitive relapsed or primary refractory disease (CR/PR >1), and 24 patients were chemo-refractory.

- After a median follow-up of 5 years, 3-year estimates of relapse incidence, PFS, and OS were 6%, 94%, and 100% for CR/PR1; 31%, 64%, and 85% for CR/PR >1; and 52%, 39%, and 41% for chemo-refractory disease, respectively
- The authors conclude that despite no clear benefit of adding consolidating RT, autologous HCT is associated with excellent outcomes in chemoimmunotherapy-sensitive PMBCL; however, whereas its benefits seem to be limited in chemoimmunotherapy-refractory disease, especially if post-transplant RT cannot be administered

Graft-versus-Host Disease

*Magenau JM, Goldstein SC, Peltier D, et al. α_1-Antitrypsin infusion for treatment of steroid-resistant acute graft-versus-host disease. *Blood*. 2018;131:1372-79. http://www.ncbi.nlm.nih.gov/pubmed/29437593

- Phase II prospective, multicenter trial to determine safety and efficacy of the protease inhibitor, AAT 60 mg/kg given twice weekly as an IV infusion for 4 weeks in adult patients with SR-acute GVHD. The primary endpoint was ORR at day 60 or the number of patients who achieved CR or PR by day 28 without need for further immunosuppression.
- 40 patients with a median age of 59 years received ≥2 doses of AAT and were included in the study. 70% had grade III-IV acute GVHD at enrollment. ORR and CR rates by day 28 were 65% and 35%, respectively, in the 26 evaluable patients and responses were noted in all target organs. Median time to PR was 16 days and to CR was 24 days. Responses were sustained in 73% of patients by day 60.
- An increase in the ratio of active Treg to Teff as well as a significant increase in serum AAT levels were noted following treatment (197 vs 147 mg/dL, P=0.004).
- No significant drug-related adverse events were observed and infectious-related mortality was 10% at 6 months and 2.5% within 30 days of AAT infusion. One death occurred within 30 days of AAT infusion related to Gram-negative bacteremia.
- This study suggests that AAT is safe and may be efficacious in treating SR-acute GVHD

Chimeric Antigen Receptor T-Cell Therapy

** Cirillo M, Tan P, Sturm M, Cole C. Cellular immunotherapy for hematologic malignancies: beyond bone marrow transplantation. *Biol Blood Marrow Transplant.* 2018;24:433-42. http://www.ncbi.nlm.nih.gov/pubmed/29102721

- Comprehensive review discussing the advances in cellular immunotherapy, beyond HCT, and the current applications for patients that have hematologic malignancies
- The review includes a discussion on the interplay between GVHD and the GVL effect and ways in which the management of GVHD has been influenced by cellular immunotherapy
- The role of dendritic cells in triggering T-cell mediated cytotoxicity, which can be monitored in response to vaccine-based therapy, is discussed. Tumor antigens can be used to stimulate expanded dendritic cells leading to a cytotoxic T-cell response to malignant cells.
- The review includes a section on the use of DLI to increase donor chimerism and treat early relapse, as well as reports of DLI with lymphocytes manufactured from NK cells.
- Cytokine-induced killer lymphocytes are cytotoxic lymphocytes (T and NK cells) that are selectively collected from blood and stimulated and primed for killing of tumor cells. This is an expanding area of cancer immunotherapy that may offer additive efficacy and acceptable toxicity.
- The review concludes with a discussion on CAR T-cells, including the disease states in which it is used, evolving technology and a list of currently recruiting clinical trials utilizing CAR technology

Other

*Khosla J, Yeh AC, Spitzer TR, and Dey BR. Hematopoietic stem cell transplant-associated thrombotic microangiopathy: current paradigm and novel therapies. *Bone Marrow Transplant*. 2018;53(2):129-137. https://www.ncbi.nlm.nih.gov/pubmed/28967899

- Comprehensive review of the pathophysiology, management, and new treatment options of TA-TMA highlighting the risk factors leading to endothelial injury and the pathophysiological cascade leading up to TA-TMA, as well as various diagnostic criteria and biomarkers that can enable early intervention
- A review of current first-line management including discontinuation or alteration of the immunosuppressive regimen, treatment of co-existing infections and GVHD, aggressive hypertension control and supportive therapy
- Lastly, the authors review the current pharmacological options and include newer agents that target the complement cascade and nitric oxide pathways, including eculizumab, rituximab and defibrotide.

Abbreviations:

AAT: α_1-Antitrypsin
CAR: chimeric antigen receptor
CR: complete response
DLI: donor lymphocyte infusion
EBMT: European Society for Blood and Marrow Transplantation
GVHD: graft-versus-host disease
GVL: graft-versus-leukemia
HCT: hematopoietic cell transplantation
HDT/ASCT: high-dose therapy followed by autologous stem cell transplant
MM: multiple myeloma
NK: natural killer
OS: overall survival
PFS: progression-free survival
PMBCL: primary mediastinal B-cell lymphoma
PR: partial response
RCT: randomized controlled trial
RT: radiotherapy
SDT: standard dose therapy
SR: steroid-refractory
TA-TMA: transplant-associated thrombotic microangiopathy
Teff: effector T-cells
Treg: regulatory T-cells
VRD: bortezomib, lenalidomide, and dexamethasone

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