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

*Srour SA, Li S, Popat UR, et al. A Randomized Phase II Study of Standard-Dose Versus High-Dose Rituximab with BEAM in Autologous Stem Cell Transplantation for Relapsed Aggressive B-cell Non-Hodgkin Lymphomas: Long-Term Results. British Journal of Haematology. 2017 May 9. DOI: 10.1111/bjh.14731. https://www.ncbi.nlm.nih.gov/pubmed/28485023.

- Randomized, open-label prospective, single center, phase 2 clinical trial comparing the efficacy and safety of high dose rituximab (HD-R; 1000 mg/m2) versus standard-dose rituximab (SD-R; 375 mg/m2) on day +1 and +8 after stem cell infusion combined with BEAM in relapsed and refractory B-cell NHL.
- Patients (n=93) aged ≤80 years with histologically proven DLBCL, transformed follicular lymphoma, or CD20 positive B-cell NHL that relapsed after conventional chemotherapy but have chemo-sensitive disease and less than 5% bone marrow involvement were included. All patients had prior rituximab exposure, either as frontline and/or with salvage chemotherapy.
- The 5-year DFS (36% with HD-R vs. 43% with SD-R; p = 0.205) and 5-year OS (43% with HD-R vs. 52% with SD-R; p = 0.392) were not statistically significant. No differences in engraftments or adverse events were noted between arms.
- The authors conclude HD-R did not provide a DFS or OS advantage over SD-R. In patients who have been exposed to rituximab in the frontline or salvage setting, the addition of rituximab in the peri-transplant setting remains controversial.

*Weil E, Zook F, Oxencis C, et al. Evaluation of the Pharmacokinetics and Efficacy of a Busulfan Test Dose in Adult Patients Undergoing Myeloablative Hematopoietic Cell Transplantation. *Biol Blood Marrow Transplant*. 2017;23(6):952-57. https://www.ncbi.nlm.nih.gov/pubmed/28288949.

- A case-control observational study of 60 patients undergoing a myeloablative HCT with a busulfan-containing conditioning regimen. 30 control (pre-test) patients were included prior to the start of test dosing, with PK monitoring performed on the first dose of 0.8 mg/kg conditioning busulfan, and dose adjustments were made on the final 10 doses to achieve a goal steady state concentration (Css) of 900 ng/mL. 30 post-test patients received a 0.9 mg/kg test dose of busulfan 1 week prior to the start of conditioning with PK dose adjustments made for all 16 doses of the conditioning busulfan. Additional PK monitoring was also performed on the first conditioning dose to assess the primary objective.
- The primary objective for this study was the percentage of patients whose first conditioning dose of busulfan was within 10% of the desired Css of 900 ng/mL. The pre-test group had 10% of

patients within the desired Css range, compared to 73.3% of the post-test group (p<0.001). The average Css in the pre-test and post-test groups were 660 ng/mL and 879.9 ng/mL, respectively (p<0.001).

- Secondary objectives included toxicity measurements (TPN and/or PCA use for severe mucositis, veno-occlusive disease, or seizures) as well as treatment outcomes (mortality, disease relapse, incidence of GVHD). Use of a busulfan test dose did not significantly change any of these secondary objectives compared to the pre-test group. There were numerically higher rates of acute GVHD in the pre-test group, but this was not statistically significant, and the authors suggest this could be due to institutional implementation of ursodiol prophylaxis in between the two study groups.

Other

*Webb BJ, Healy R, Majers J, et al. Prediction of bloodstream infection due to vancomycin-resistant *Enterococcus* in patients undergoing leukemia induction or hematopoietic stem-cell transplantation. *Clin Infect Dis*. 2017;64:1753-9. https://www.ncbi.nlm.nih.gov/pubmed/28369204

- Single-center, retrospective cohort study evaluating a clinical predictive score for VRE bloodstream infection (BSI) based on specific risk factors in 650 patients receiving leukemia induction therapy or HCT (664 admissions from 2006-2014)
- Overall, 41.3% had VRE colonization (53.9% in allo HCT). Anti-VRE therapy was used in 31.9%, while VRE BSI incidence was 6.5% of admissions (8.3% in allo HCT)
- One-year mortality (46.5% vs 31.8%; p=0.046) and length of stay (28 days vs 36 days; p <0.0001) were significantly higher in patients with VRE BSI whereas 30 day mortality was similar
- The VRE scoring system assigned 2 points for VRE colonization and 1 point for severe neutropenia, gastrointestinal disturbance, renal insufficiency, antianaerobic antibiotic use, carbapenem use, aminoglycoside use, and cephalosporin use
- The VRE score effectively stratified risk of VRE BSI, demonstrated by an area under the operating curve of 0.84 (95% CI 0.79-0.89)
- VRE colonization, renal insufficiency, aminoglycoside use, and antianaerobic antibiotic use were most closely correlated with VRE BSI
- At a threshold of ≥5 points, per day probability of VRE BSI was increased nearly 4-fold
- Utilizing this predictive scoring model may help guide decisions regarding use of empiric anti-VRE antimicrobial therapy in patients with hematologic malignancy. Validation of this novel predictive score is needed to confirm clinical utility and generalizability

**Richardson PG, Smith AR, Triplett BM, et al. Defibrotide for Patients with Hepatic Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome: Interim Results from a Treatment IND Study. *Biol Blood Marrow Transplant*. 2017;23(6):997-1004. https://www.ncbi.nlm.nih.gov/pubmed/28285079.

- Interim results from this multicenter, single-arm, open label, expanded-access study assessed the safety, tolerability, and survival benefit of defibrotide following HCT patients with VOD/SOS with or without multi-organ dysfunction (MOD) or patients without MOD, non-HCT VOD/SOS, VOD/SOS diagnosed by Modified Seattle criteria, and VOD/SOS diagnosed after day +35. Patients received defibrotide dosed at 6.25 mg/kg IV every 6 hours for a minimum of 21 days or until symptom resolution.
- The primary outcome was OS at day +100. Safety outcomes included reporting of significant treatment-related adverse effects. Subgroup analysis included patients +/- MOD, type of transplant (auto vs. allo), pediatric vs. adult HCT patients, and cases that were before or after day +35.

- A total of 573 patients that underwent HCT received at least one dose of defibrotide. Day +100 OS was 50.3% (95% CI 46.2%-54.4%). Day +100 OS in pediatric and adult HCT patients was 54.5% and 44.9%, respectively. Patients with MOD had a day +100 OS of 45.3% compared to 58.1% in patients without MOD. The day +100 OS was lower (34.2%) in patients diagnosed with late-onset VOD/SOS. A post-hoc analysis also showed a statistically significant improvement in day +100 OS the quicker that defibrotide was initiated after diagnosis of VOD/SOS.
- This study demonstrated day +100 survival rates similar to that of previous, smaller defibrotide trials. The data also suggests that there is benefit from defibrotide both in severe VOD/SOS cases with MOD as well as mild cases that may present without MOD.

Abbreviations
BSI: bloodstream infection
DFS: disease free survival
DLBCL: diffuse large B-cell lymphoma
GVHD: graft-versus-host disease
HCT: hematopoietic cell transplantation
NHL: non-Hodgkin lymphoma
MOD: multi-organ dysfunction
OS: overall survival
PCA: patient-controlled analgesia
PK: pharmacokinetic
TPN: total parenteral nutrition
VRE: vancomycin-resistant *Enterococcus*
VOD/SOS: veno-occlusive disease/sinusoidal obstruction syndrome

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