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

Allogeneic Transplant

**Malki MM, Nathwani N, Yang D, et al. Melphalan-based reduced-intensity conditioning is associated with favorable disease control and acceptable toxicities in patients older than 70 with hematologic malignancies undergoing allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2018;24:1828-35. https://www.ncbi.nlm.nih.gov/pubmed/29753158.

- Retrospective review of 53 consecutive patients aged 70 years and older who underwent alloHCT with melphalan-based reduced-intensity conditioning regimen
- The median time to engraftment was 15 days (range, 11-29) and more than 95% of patients achieved complete donor chimerism within 6 weeks from HCT
- With a median follow-up of 31.1 months, the 2-year OS, PFS, and NRM were 68.9%, 63.8%, and 17%, respectively
- Cumulative incidences of grade II-IV and III-IV acute GVHD at 100 days were 37.7% and 18.9%, respectively; cumulative chronic GVHD at 1 year and 2 years post-HCT were 54.7% and 61.9%, respectively
- AlloHCT with melphalan-based reduced-intensity regimen is associated with acceptable toxicities and NRM, lower incidence of relapse, and favorable OS and PFS in patients 70 years of age and older

*Kim T, Mooh JH, Ahn JS, et al. Next-generation sequencing-based posttransplant monitoring of acute myeloid leukemia identifies patients at high risk of relapse. *Blood*. 2018;132:1604-1613. https://www.ncbi.nlm.nih.gov/pubmed/30108064.

- This study looked at allelic burden both pre- and post-HCT in 104 AML patients by NGS to investigate the feasibility of post-HCT monitoring using NGS and its prognostic implications on HCT outcomes
- Major inclusion criteria were age <65 years and maintenance of CR before HCT after standard 7+3 induction and consolidation therapy. Samples were obtained at the time of initial diagnosis, pre-HCT (before conditioning), post-HCT (day +21, +90, +180, and yearly thereafter), and at relapse.
- NGS detected 256 mutations in 90/104 patients at diagnosis, which showed stepwise clearances after chemotherapy and HCT; most post-HCT mutations originate from mutations initially detected at diagnosis
- Assessment of VAF revealed that VAF post-HCT is associated with an increased risk of relapse (56.2% vs. 16.0% at 3 years; p<.001) and worse OS (36.5% vs. 67.0% at 3 years; p=0.006). Multivariate analyses confirmed that VAF post-HCT is an adverse prognostic factor for OS (HR,

3.07; p=0.003) and relapse incidence (HR, 4.75; p<0.001) independent of the revised European Leukemia Net risk groups
- The authors concluded that NGS-based post-HCT monitoring in AML patients is feasible and can distinguish high-risk patients for relapse

*Schmid C, Labopin M, Schaap N, et al. Prophylactic donor lymphocyte infusion after allogeneic stem cell transplantation in acute leukaemia – a matched pair analysis by the Acute Leukaemia Working Party of EBMT. *Br J Haematol.* 2018;Nov 22 [Epub ahead of print]. https://www.ncbi.nlm.nih.gov/pubmed/30467839

- Registry-based, matched controls study including patients undergoing allogeneic HCT, in CR without evidence of MRD or relapse, full donor chimerism, received DLI within 1 year of HCT, and no history of higher than grade 1 aGHVD or cGVHD before receiving DLI
- A total of 89 patients were identified as receiving prophylactic DLI between 2000-2011
- Median time to DLI was 163 days and the median number of infusions was 2 with a cell dose of 3x10^6 cells/kg in MRD and 0.5x10^6 cells/kg in MUD
- Only 15% subsequently developed aGVHD (4.5% grade 3-4) and 28% developed cGVHD
- There was no difference between control and DLI in any of the endpoints evaluated for the entire group
- In pre-planned subgroup analysis, no difference between groups remained in standard risk AML or patients with any risk ALL, but a statistically significantly improved 5 year OS was noted in the high-risk AML population (HR, 0.387; p=0.027)
- These data suggest a modest efficacy of prophylactic DLI in patients with acute leukemia with the population most likely to benefit being high-risk AML

Lymphoma

*Sharman JP, Forero-Torres A, Costa LJ, et al. Obinutuzumab plus CHOP is effective and has a tolerable safety profile in previously untreated, advanced diffuse large B-cell lymphoma: the phase II GATHER study. *Leuk Lymphoma*. 2018;Oct 2:1-10. https://www.ncbi.nlm.nih.gov/pubmed/30277102.

- Phase II, open-label, multicenter, single-arm study in previously untreated patients with CD20-positive advanced DLBCL who received obinutuzumab (G) plus CHOP to assess impact of cell-of-origin (COO) on patient outcomes
- Eligible patients were aged ≥18 years with: measurable disease; Ann Arbor stage II with bulky disease (mass >7.5 cm), stage III, or stage IV; IPI 1 (low risk) with bulky disease or IPI 2-5 (low-intermediate, high-intermediate, or high risk)
- Patients (n=100) received eight 21-day cycles (10 doses) of obinutuzumab (1000 mg on days 1, 8, and 15 of C1, and day 1 of C2-8) plus CHOP (cyclophosphamide 750 mg/m2 IV day 1; doxorubicin 50 mg/m2 IV day 1; vincristine 1.4 mg/m2 (that could be capped at 2 mg) IV day 1; and prednisone 100 mg oral days 1-5 on C1-6
- ORR and CR rates, as determined according to the Cheson et al. criteria by investigators/independent radiological facility, were 82.0/75.0% and 55.0/58.0%, respectively
- This study indicates that G-CHOP is effective and can be administered with a tolerable safety profile, including the ability to administer obinutuzumab as a short 90 minute infusion after the initial cycle.

Pediatrics

*Diorio C, Robinson PD, Ammann RA, et al. Guidline for the management of clostridium difficile infection in children and adolescents with cancer and pediatric hematopoietc stem-cell transplantation recipients. *J Clin Oncol.* 2018 Sept 14 [Epub ahead of print]. https://www.ncbi.nlm.nih.gov/pubmed/30216124

- Multicenter, multidisciplinary panel recommendations for managing C-diff infection in pediatric patients. Reportedly the first C-diff related guideline specific to pediatric cancer or HCT patients
- Recommendations include:
    - Avoid probiotics for prevention or treatment of C-diff
    - Use vancomycin for severe C-diff infection
    - Clinical cure rates of metronidazole or oral vancomycin appear equivalent in nonsevere infection. Vancomycin presents better palatability and fewer drug interactions but metronidazole may present a reduced cost
    - Consider fidaxomicin for recurrent infection
    - Currently not enough evidence to support FMT or monoclonal therapy in pediatrics

*Wallace G, Jodele S, Myers K, et al. Single ultra-high-dose cholecalciferol to prevent vitamin D deficiency in pediatric hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2018;24:1856-60. https://www.ncbi.nlm.nih.gov/pubmed/29782992.

- Prospective, pilot study to evaluate the safety and efficacy of ultra-high dose vitamin D in 10 patients preparing to undergo HCT within 14 days and had a 25-OH vitamin D level < 50 ng/mL
- A single enteral vitamin D dose (maximum 600,000 IU) was administered to each patient based on weight and pre-transplantation vitamin D level from the day before HCT; patients were not allowed to receive additional supplementation during 8-week observation window
- The mean age of the study was 5.8 ± 4.9 years and the mean pre-transplantation vitamin D level was 28.9 ± 13.1 ng/mL
- All patients achieved a therapeutic vitamin D level of > 30 ng/mL with mean peak serum level of 80.4 ± 28.6 ng/mL being reached at median of 9 days after the dose
- Mean vitamin D levels were sustained at or above 30 ng/mL during the 8-week observation period and there were no electrolyte abnormalities observed
- This pilot suggests that single ultra-high-dose oral vitamin D treatment just before HCT is safe and well tolerated in children, but larger prospective studies are needed to address impact on outcomes

*Rasche M, Zimmermann M, Borschel L, et al. Successes and challenges in the treatment of pediatric acute myeloid leukemia: a retrospective analysis of the AML-BFM trials from 1987 to 2012. *Leukemia*. 2018;32:2167-2177. https://www.ncbi.nlm.nih.gov/pubmed/29550834.

- Retrospective analyses of outcomes and clinical data of 1940 pediatric de novo AML patients enrolled in 4 consecutive AMLBFM trials (AML-BFM 87, AML-BFM 93, AML-BFM 98, and AML-BFM 04 from 1987 and 2012
- Five-year probability of OS (pOS) increased from 49 ± 3% (1987-1992) to 76 ± 4% (2010-2012; p < 0.0001), probability of EFS only improved from 41 ± 3% (1987-1992) to 50 ± 2% (1993-1998; p=0.02) after introduction of high-dose cytarabine/mitoxantrone, but remained stable since then
- Non-response and relapse rates stayed constant despite intensified first-line therapy (p= 0.08 and p=0.17). After 1999, more relapsed or refractory patients underwent HCT with increased pOS after HCT (29 ± 5% (1993-1998) vs. 50 ± 4% (2005-2010); p<0.0001).
- Intensification of first-line therapy translated into an unsteady and insignificant improvement of

pEFS over the past 25 years, which is mainly explained by a failure to significantly reduce the relapse or non-response rate

Infectious Diseases

*Ganetsky A, Han J, Hughes ME, et al. Oral vancomycin prophylaxis is highly effective in preventing *Clostridium difficile* infection in allogeneic hematopoietic cell transplant recipients. *Clin Infect Dis.* 2018 Sep 26. [Epub ahead of print]. http://www.ncbi.nlm.nih.gov/pubmed/30256954

- Retrospective cohort study to examine the effectiveness of CDI prophylaxis with oral vancomycin compared to no prophylaxis in 145 consecutive adult alloHCT recipients at the University of Pennsylvania between April 2015 and November 2016.
- Those patients receiving prophylaxis were given oral vancomycin (125 mg twice daily) from day of admission until discharge.
- Primary outcome was the association between oral vancomycin prophylaxis and CDI diagnosis. Secondary outcomes included VRE bloodstream infections, acute GVHD, NRM, GRFS, relapse, and OS. No routine screening for VRE colonization was performed during the study period.
- There were no significant differences in patient, disease, and transplant characteristics between intervention and control group. Gram-negative and gram-positive antibiotic exposure within 30 days prior to alloHCT were similar between groups, but metronidazole use was greater in the control group (7% vs 0%, *P*=0.02).
- There were no cases of CDI in patients receiving prophylaxis (0/90; 0%) whereas 20% (11/55) of patients not receiving prophylaxis developed CDI (*P*<0.001). Oral prophylaxis was not associated with higher risk of acute grade 2-4 (*P*=0.12), grade 3-4 (*P*=0.36), or grade 2-4 gastrointestinal (*P*=0.08) GVHD at day 180 post-transplant. No associations between oral vancomycin prophylaxis and relapse or survival were observed in this cohort.
- The authors concluded that prophylaxis with oral vancomycin is highly effective in preventing CDI in alloHCT recipients without increasing risk of GVHD or relapse and further prospective studies are warranted.

*Scordo M, Morjaria SM, Littmann ER, et al. Distinctive infectious complications in patients with central nervous system lymphoma undergoing thiotepa, busulfan, and cyclophosphamide-conditioned autologous stem cell transplantation. *Biol Blood Marrow Transplant.* 2018;24:1914-19. https://www.ncbi.nlm.nih.gov/pubmed/29679773

- Single center retrospective review of the incidences of viral, fungal, bacterial, and parasitic infections in 57 patients undergoing TBC-conditioning ASCT versus 79 patients undergoing BEAM-conditioning ASCT
- 20 of 57 (35%) TBC-ASCT patients had detectable viremia with human herpesvirus 6, cytomegalovirus (CMV), adenovirus, or BK virus, versus 9 of 79 (11%) BEAM-ASCT patients
- 8 TBC-ASCT patients had clinically relevant viral infections (4 human herpesvirus 6, 2 CMV, 1 adenovirus, 2 BK virus), versus 0 in the BEAM-ASCT group
- 4 TBC-ASCT patients suffered infections from either a fungal or parasitic pathogen versus 1 BEAM-ASCT patient
- TBC-ASCT patients have a higher risk of DNA virus infections compared with BEAM-ASCT; fungal and parasitic infections appear more common after TBC-ASCT; prolonged lymphopenia and steroid use did not explain the observed differences between the two groups

Abbreviations

ALL: acute lymphoblastic leukemia
aGVHD: acute graft versus host disease
alloHCT: allogeneic hematopoietic stem cell transplantation
AML: acute myeloid leukemia
ASCT: autologous stem cell transplant
BEAM: carmustine, etoposide, cytarabine, melphalan
BK-HC: BK virus-associated hemorrhagic cystitis
CDI: *Clostridium difficile* infection
cGVHD: chronic graft versus host disease
CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone
CR: complete response
DLBCL: diffuse large B-cell lymphoma
DLI: donor lymphocyte infusion
DNA: deoxyribonucleic acid
EFS: even free survival
FMT: fecal microbiota transfer
GRFS: GVHD-free, relapse-free survival
GVHD: graft-versus-host disease
HCT: hematopoietic cell transplant
HDM/SCT: high dose melphalan/stem cell transplant
IPI: International Prognostic Index
IU: international units
MRD: matched related donor
MUD: matched unrelated donor
NGS: next-generation sequencing
NRM: non-relapse mortality
ORR: overall response rate
OS: overall survival
pEFS: probability of event-free survival
PFS: progression-free survival
pOS: probability of overall survival
TBC: thiotepa, busulfan, cyclophosphamide
VAF: variant allele frequency
VRE: vancomycin-resistant enterococcus

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