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

*Johnston EE, Muffly L, Alvarez E, et al. End-of-life care intensity in patients undergoing allogeneic hematopoietic cell transplantation: a population-level analysis. *J Clin Oncol*. 2018 Sep 5. [Epub ahead of print]. http://www.ncbi.nlm.nih.gov/pubmed/30183467

- Retrospective, population-based analysis of all patients who died between 2000 and 2013 and underwent an inpatient HCT within 1 year of death as classified by ICD-9 code. This analysis was completed using the California Office of Statewide Health Planning and Development (OSHPAD) Private Patient Discharge Data Database and Vital Statistics Death Certificate Data. All California hospitals are required to report information from all discharges to the OSHPAD database, which ties to California death certificate database.
- For analysis, patients were divided into pediatric (age 0-21 years), young adult (age 22-39 years), and adult (age $\geq$ 40 years). Markers of EOL care intensity were previously defined and included ICU admission, intubation/mechanical ventilation, hemodialysis, CPR within 30 days of death, and hospital death.
- 2135 patients were identified for the study population (337 pediatric, 461 young adults, 1297 adults). Overall, 29.6% of patients died during their allo-HCT admission. The patients in the study population had an average of 105 hospital days (SD 52 days) in their last year of life and were readmitted 1.3 times (SD 0.6 times) after their HCT admission before death. Medical intensity varied according to age (age 15-21 most significant), underlying diagnosis (ALL most significant), and presence of comorbidities at time of HCT.
- In the last 30 days of life, the four most common intensity markers were hospital death (83%), ICU admission (49%), intubation (45%), and hospitalization for the entire last 30 days of life (43%).
- The authors concluded patients dying within 1 year of allo-HCT are receiving medically intense end-of-life care with variations related to several factors. They believe it is necessary to determine of these patients are receiving goal-concurrent care and advocate for beginning to consider what constitutes value-based repayment in HCT end-of-life care.

*Fein JA, Shimoni A, Labopin M, et al. The impact of individual comorbidities on non-relapse mortality following allogeneic hematopoietic stem cell transplantation. *Leukemia*. 2018;32:1787-94. https://www.ncbi.nlm.nih.gov/pubmed/29950692

- Retrospective review of 875 adults who received an allo-HCT to characterize the hazard of individual comorbidities on NRM in a conditioning regimen-specific manner.
- Six conditioning regimens were considered: Flu/Bu2, Flu/Bu4, Flu/Treo, Flu/Mel, Cy/TBI, Bu/Cy.

- In the overall population, renal dysfunction, hypoalbuminemia, and severe hepatic disease were associated with the highest risk of NRM (HR 2.1, HR 1.9, HR 1.7, respectively).
- In those who received Flu/Blu4, NRM risk was increased with cardiac disease (HR 5.54).
- Severe pulmonary disease and a pre-existing infection were associated with increased NRM risk in patients receiving Flu/Mel (HR 4.9) and Flu/Treo (HR 3.6)
- Comorbidities may exert effects unique to certain conditioning regimens; therefore, patient specific comorbidities should contribute to regimen selection

Alternative Donors

**De Latour RP, Chevret S, Jubert C, et al. Unrelated cord blood transplantation in patients with idiopathic refractory severe aplastic anemia: a nationwide phase 2 study. *Blood*. 2018;132:750-54. https://www.ncbi.nlm.nih.gov/pubmed/29760162

- Prospective, multicenter phase 2 study to assess unrelated cord blood transplantation efficacy and safety in refractory SAA patients
- Twenty-six patients (median age, 16 years) who were primary refractory SAA at 6 months after first-line IST with ATG and cyclosporine or in relapse/refractory to a second course of IST without available matched unrelated donor were included
- At a median follow-up of 38.8 months, engraftment occurred in 23 patients (88%); cumulative incidences of grade II-IV acute and chronic GVHD were 45.8% and 36% respectively
- Twenty-three patients were alive at 1 year, with an 88.5% overall survival rate
- CBT after Flu-Cy-ATG-2 Gy TBI conditioning with at least 4 x 10^7 frozen nucleated cells/kg leads to satisfactory OS in refractory SAA and serves as a potential curative option for young adults with no available MUD

Pediatrics

*Gassas A, Sivaprakasam P, Cummins M, et al. High transplant-related mortality associated with haematopoietic stem cell transplantation for paediatric therapy-related acute myeloid leukaemia (t-AML). A study on behalf of the United Kingdom Paediatric Blood and Bone Marrow Transplant Group. *Bone Marrow Transplant*. 2018;53:1165-1169. https://www.ncbi.nlm.nih.gov/pubmed/29545594.

- Multi-center retrospective pediatric study for 36 children with t-AML who received FLAG with or without idarubicin (FLAG-Ida) for salvage therapy prior to HCT
- With a median follow up of 7.3 years, 12 patients are long term survivors (OS=34%), and 23 patients died. Thirteen out of the 23 patients (56%) died from TRM and 10 patients (44%) died from disease relapse given an overall TRM rate of 37% and a relapse rate of 29%. All patients who relapsed died, therefore EFS and OS was the same
- TRM is the main cause of death in this very high risk pediatric malignancy and potential measures such as reduction of salvage chemotherapy after achieving remission and a careful choice of the conditioning regimen may be helpful in reducing TRM. Larger prospective studies are required

Supportive Care

*Malek E, Gupta V, Cregar R, et al. Amifostine reduces gastro-intestinal toxicity after autologous transplantation for multiple myeloma. *Leuk Lymphoma.* 2018;59:1905-12. https://www.ncbi.nlm.nih.gov/pubmed/29295650

- Case control study of 107 patients who underwent auto-HCT using pre-transplant amifostine at the University Hospitals Seidman Cancer Center in Cleveland, OH were compared to 114 patients treated at the MD Anderson Cancer Center in Houston, TX, without amifostine

- All patients had multiple myeloma and were receiving auto-HCT with high-dose melphalan conditioning; patient characteristics were similar between both groups
- Amifostine 740 mg/m^2 was administered as a bolus infusion at 24 hours and 15 minutes prior to high-dose melphalan
- Grade II or greater oral mucositis (27.1% vs 47.4%, p=0.002), nausea (31.8% vs 86.0%, p=0.0001), vomiting (18.7% vs 52.6%, p=0.0001), and diarrhea (56.1% vs 72.7%, p=0.006) occurred less frequently in the amifostine-treated group
- There was no discernable effect of amifostine on engraftment, PFS, or OS
- Amifostine decreases GI toxicity while preserving anti-myeloma efficacy of high-dose melphalan and auto-HCT

Infectious Diseases

*Cesaro S, Tridello G, Blijlevens N, et al. Incidence, risk factors, and long-term outcome of acute leukemia patients with early candidemia after allogeneic stem cell transplantation: A study by the Acute Leukemia and Infectious Diseases Working Parties of European Society for Blood and Marrow Transplantation. *Clin Infect Dis*. 2018;67:564-72. https://www.ncbi.nlm.nih.gov/pubmed/29481599

- EBMT study with outcome analysis of 28,542 acute leukemia patients who underwent HCT from 2000 to 2012
- Incidence of candidemia by day +100 was 1.2% (347/28542) and occurred at a median of 22 days after HCT (range 1-100)
- A higher 100-day NRM (HR 3.0, p < 0.0001), and a lower 100-day OS (HR 2.5, p < 0.0001) were observed in patients with candidemia. The case fatality rate by day +100 in patients with candidemia was 22% (76/347)
- Factors associated with candidemia occurrence were gender female, bone marrow or cord blood stem cell source, T-cell depletion, use of total body irradiation, and acute graft versus host disease
- Among patients alive at day 100, the 5-year NRM and OS for patients with and without candidemia were 22.5% vs. 13.5% (p <0.001) and 45.6% vs. 53.4% (p = 0.0003), respectively
- In multivariate analysis, occurrence of candidemia was identified as an independent risk factor for higher NRM (HR 1.7, p = 0.001) and lower OS (HR 1.4, p = 0.001)

Cellular Therapy

*Park JH, Romero FA, Taur Y, et al. Cytokine release syndrome grade is a predictive marker for infections in patients with relapsed or refractory B-cell acute lymphoblastic leukemia treated with chimeric antigen receptor T cells. *Clin Infect Dis.* 2018;67:533-40. https://www.ncbi.nlm.nih.gov/pubmed/29481659

- Infectious complications following CD19 CAR T-cell therapy were analyzed in 53 adults (relapsed ALL enrolled in a phase I clinical trial at Memorial Sloan Kettering Cancer Centre)
- 22 patients (42%) experienced 26 infections (17 bacterial, 4 fungal, 5 viral) within the first 30 days of CAR T-cell infusion
- In general, bacterial, fungal, and viral infections were detected at a median of 18, 23, and 48 days, respectively, after CAR T-cell infusion
- Grade 3 or higher CRS was independently associated with increased risk of subsequent infection (HR: 2.67, P = 0.05); in particular bloodstream infection (adjusted HR: 19.97, P < 0.001). Three of 53 (6%) patients died due to infection-related cause

Mobilization

*Chua CC, Lim HY, Chai KL, et al. Peripheral blood stem cell mobilisation with G-CSF alone versus G-CSF and cyclophosphamide after bortezomib, cyclophosphamide and dexamethasone induction in multiple myeloma. *Bone Marrow Transplant*. 2018;53:1116-1123. https://www.ncbi.nlm.nih.gov/pubmed/29523889.

- Study assessing the efficacy of G-CSF alone (G-alone) vs. G-CSF and cyclophosphamide (G-cyclo: standard dose: 1.5-2 g/m^2; high dose: 3-4 g/m^2) PBSC mobilization strategies in 288 patients who only received bortezomib, cyclophosphamide and dexamethasone induction prior to autograft across six apheresis centers
- Success rates were 84% in G-cyclo standard dose (6% FN rate), 64% in G-cyclo high dose (18% FN rate) and 69% in G-alone (plerixafor successfully salvaged 8/9 patients).
- Median total stem cell yield was significantly higher with G-cyclo, but not different between the two cyclophosphamide doses. Age >61 years was associated with higher failure rates (22 vs 11%, p = 0.01) and lower PBSC yield, especially in the G-alone group.
- Both G-cyclo standard dose and G-alone are reasonable mobilization strategies, though the former may be preferred if salvage plerixafor is unavailable

Abbreviations

ALL: acute lymphomblastic leukemia
allo-HCT: allogeneic hematopoietic stem cell transplant
ATG: antithymocyte globulin
auto-HCT: autologous hematopoietic cell transplantation
CAR: chimeric antigen receptor
CBT: cord blood Transplanation
CPR: cardiopulmonary resuscitation
CRS: cytokine release syndrome
EBMT: European Society for Blood and Marrow Transplantation
EFS: event-free survival
EOL: end-of-life
FLAG: fludarabine, high-dose cytarabine, and granulocyte colony stimulating factor
Flu-Cy-ATG-2 GY TBI: fludarabine, cyclophosphamide, antithymocyte globulin, and 2-Gy total body irradiation
FN: febrile neutropenia
G-CSF: granulocyte colony stimulating factor
GI: gastrointestinal
GVHD: graft-versus-host-disease
HCT: hematopoietic stem cell transplant
HR: hazard ratio
IST: immunosuppressive therapy
MUD: matched unrelated donor
NRM: non-relapse mortality
OS: overall survival
PBSC: peripheral blood stem cell
PFS: progression free survival
SAA: severe aplastic anemia
SD: standard deviation
TBI: total body irradiation
TRM: treatment-related mortality

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