

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**

\*Dhere V, Edelman S, Waller EK, et al. Myeloablative busulfan/cytoxan conditioning versus reduced-intensity fludarabine/melphalan conditioning for allogeneic hematopoietic stem cell transplant in patients with acute myelogenous leukemia. *Leuk Lymphoma*. 2018;59:837-843.

[www.ncbi.nlm.nih.gov/pubmed/28782395](http://www.ncbi.nlm.nih.gov/pubmed/28782395)

- Single-center, retrospective, database review of 156 adult patients with AML comparing MAC Bu/Cy (n=73) to RIC Flu/Mel (n=83) between 2004-2014
- Patients in the RIC were older and more likely to be treated after 2009 when compared to MAC with other demographics being largely similar
- On univariate analysis, OS, RR, RFS, and NRM were similar between Bu/Cy and Flu/Mel. On multivariate analysis Bu/Cy was associated with higher NRM (P<0.001) with similar OS, RR, and RFS
- The regimen selection for the patient population is inherently biased by the retrospective nature and lack of randomization. The clear difference in age groups between MAC and RIC illustrate this bias. However the similar outcomes in terms of OS, RR, RFS, and NRM are encouraging that Flu/Mel is a viable options for patients otherwise ineligible for MAC transplants.

\*Singh AD, Parmar S, Patel K, et al. Granulocyte colony-stimulating factor use after autologous peripheral blood stem cell transplantation: comparison of two practices. *Biol Blood Marrow Transplant*. 2018;24:288-93. <https://www.ncbi.nlm.nih.gov/pubmed/29061534>

- Retrospective, single center study comparing hematologic recovery and transplantation-related outcomes in adult inpatients patients receiving early and those receiving ANC-driven administration of G-CSF after autologous PBSCT between November 2013 and August 2016
- Early group (n=50) received G-CSF empirically starting day +5 after HCT; ANC-driven group (n=50) received G-CSF on day +12 after HCT only if ANC was < 0.5x10<sup>9</sup>/L
- In the ANC-driven group, 24% (n=12) received G-CSF on day +12, 60% (n=30) received G-CSF prior to day +12 due to febrile neutropenia or physician discretion, 10% (n=5) did not receive G-CSF. The median day of initiation of G-SCF was day +10 in the ANC-driven group versus day +5 in the early group. The duration of G-CSF administration was shorter in the ANC-driven group as compared to the early group (3 days versus 6 days; P<0.0001)
- The median time to neutrophil engraftment was 12 days in the early group and 13 days in the ANC-driven group (P=0.07). Febrile neutropenia was more common in the ANC-driven group as compared to the early group (45 patients versus 37 patients, P=0.04); however, there were no significant differences in the incidence of positive bacterial cultures or transfer to the ICU.

No significant differences were found in time to platelet engraftment, duration of post-transplantation hospitalization, 1-year relapse rate or 1-year OS.

- Based on a 300 µg dose, the ANC-driven dosing was associated with a cost savings of \$1078 to \$1168 per patient. With a 480 µg dose, the cost savings was \$1717 to \$1859 per patient. Early initiation of G-CSF (day +5) and ANC-driven initiation following HCT were associated with a similar time to neutrophil engraftment, post-transplantation length of stay, and 1-year OS.

\*Fox T, Chakraverty R, Burns S, et al. Successful outcome following allogeneic hematopoietic stem cell transplantation in adults with primary immunodeficiency. *Blood*. 2018;131:917-931.

[www.ncbi.nlm.nih.gov/pubmed/29279357](http://www.ncbi.nlm.nih.gov/pubmed/29279357)

- Reported outcome of 29 consecutive adult patients with PID who received T-cell depleted RIC regimens. Approximately 80% had PBSC mobilized stem cell source and 60% were MUD transplants.
- Median follow up was 3.5 years with OS at 1 year of 89.2% and 3 years 85.2%. EFS was 89.7% at 1 year and 3 years. No significant difference was identified based on donor source or PID subtype.
- Incidence of acute and chronic GVHD were ~44% and 31% respectively (all grade; grade 3-4 acute GVHD occurred in 6.5%). 42% of patients achieved full donor chimerism with the remainder maintaining stable mixed chimerisms
- The case series illustrates allogeneic HCT can be considered a curative therapy in adult patients who are either refractory to traditional therapies or when conservative management is likely to be insufficient

\*Maziarz RT, Hao Y, Guerin A, et al. Economic burden following allogeneic hematopoietic stem cell transplant in patients with diffuse large B-cell lymphoma. *Leuk Lymphoma*. 2018;59:1133-1142.

<https://www.ncbi.nlm.nih.gov/pubmed/28933643>

- Database review of commercially insured patients from the US who underwent allogeneic HCT for DLBCL between 2008-2015. A total of 101 adult patients were identified via ICD9 code for both DLBCL and a hospitalization coded with allogeneic HCT. Patients were required to be continuously enrolled in their insurance plan for 90 days prior and at least 30 days after transplant. Patients with no cost associated with transplant were excluded.
- Healthcare resource utilization included inpatient days, DME, ER care, days with outpatient services (office visits, SNF days, home care, etc.), lab/imaging services, and days with drug administration-related medical services. Healthcare costs were defined as the sum of the above costs plus prescription medications from a payer perspective. Out-of-pocket costs were also reported.
- Costs were assessed over six periods: baseline (90 days prior to transplant), day 0 to discharge, through day +100, through day +364, from day +365 to +729, and day +730 to 1094. For the above time periods, average payer costs per patient were \$132,249, \$248,390, \$355,115, \$455,741, \$92,720, and \$72,957 respectively. Out-of-pocket costs for year 1, 2, and 3 were \$8,371, \$15,904, and \$6,733 respectively.
- This review illustrates the significant cost burden of allogeneic HCT in DLBCL. However, this remains the only potentially curative options in this particular subset of patients. This review also likely underestimates the total economic burden as only patients alive and continuously enrolled on insurance plans were included (less than half the patients were evaluable by the end of year 1) while excluding all Medicare and Medicaid patients. The review also does not reflect the total charges associated with allogeneic HCT but rather paid claims from a payers' perspective.

## **Pediatrics**

\*Sano H, Hilinski J, Qayed M, et al. Early blood stream infection following allogeneic hematopoietic stem cell transplantation is a risk factor for acute grade III–IV GVHD in children and adolescents. *Pediatr Blood Cancer*. 2018;65(2). <https://www.ncbi.nlm.nih.gov/pubmed/28921804>

- Retrospective review of 293 pediatric patients between 2005 and 2014 to assess if early BSI (before day +30) predisposes allogeneic HCT patients to severe acute GVHD
- GVHD prophylaxis included a calcineurin inhibitor and methotrexate or mycophenolate mofetil, and prophylactic antibiotics were not routinely used
- The cumulative incidence of grade III–IV acute GVHD by day +100 was 17.1%. In multivariate analysis, HLA-mismatched donor (hazard ratio [HR]=4.870, P<0.001), and BSI between day 0 and +30 (HR=3.010, P=0.002) were associated with grade III-IV acute GVHD.
- The authors conclude that early BSI is a risk factor for grade III–IV acute GVHD, especially when it is mucosal barrier injury associated

## **Chimeric Antigen Receptor (CAR) T-Cell Therapy**

\*\*\*Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. *New Engl J Med*. 2018;375(5):439-49. <https://www.ncbi.nlm.nih.gov/pubmed/29385370>

- Phase 2, single-cohort, 25-center, global study of tisagenlecleucel in 75 pediatric and young adults (age 3-21) with CD-19+ relapsed/refractory B-cell ALL who received a median of 3 previous therapies, range 1-8). Patients who received previous CD-19 directed therapy were excluded.
- Overall remission rate at 3 months was 81%, with all patients who had an initial response to therapy being negative for MRD by flow cytometry. EFS and OS were 73% and 90%, respectively. The rates at 12 months were 50% and 76%, respectively. The median duration of remission was not reached.
- Grade 3/4 adverse effects suspected to be related to tisagenlecleucel occurred in 73% of patients. CRS occurred in 77% of patients, with 44% receiving tocilizumab. Neurological adverse effects occurred in 40% of patients, with 13% being grade 3 and no grade 4 neurological toxicity.
- Despite transient high grade toxicities, a single infusion of tisagenlecleucel provided durable remission with long-term persistence in pediatric and young adult patients with relapsed or refractory B-cell ALL.

## **Other**

\*Farowski F, Bucker V, Vehreschild J, et al. Impact of choice, timing, sequence and combination of broad-spectrum antibiotics on the outcome of allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2018;53(1):52-57. <https://www.ncbi.nlm.nih.gov/pubmed/29131156>

- Review to assess the relevance of timing, duration, sequence and combination of antibiotic treatment in 399 patients of the Cologne Cohort of Neutropenic Patients who underwent allogeneic HCT from January 2007 to April 2013. All patients received fluoroquinolone prophylaxis at the beginning of conditioning, unless contraindicated.
- Cumulative antibiotic exposure >100 days (HR 2.46; P=0.001) and exposure to sequential treatment with penicillin derivatives followed by carbapenems (HR 6.22, 95% CI 1.28–30.31), but not to the individual classes, were associated with intestinal GVHD at day 100. Glycopeptides were identified as a risk factor (HR 3.73, 95% CI 1.51–9.19), but not considered independent,

since their use was dependent on prior exposure to penicillin derivatives and carbapenems. Patients with intestinal GVHD experienced higher NRM at 1 year (HR 3.51; P=0.001).

- The authors conclude that sequential exposure to penicillin derivatives followed by carbapenems and overall exposure to antibiotics are independent risk factors for intestinal GVHD, although larger studies are warranted.

\*Shanis D, Anandi P, Grant C, et al. Risks factors and timing of genital human papillomavirus (HPV) infection in female stem cell transplant survivors: a longitudinal study. *Bone Marrow Transplant.* 2018;53(1):78-83. <https://www.ncbi.nlm.nih.gov/pubmed/29035398>

- Combined retrospective (1994–2005) and prospective (2005 onward) long-term study evaluating gynecologic history and assessment, cervical cytology and HPV testing in a cohort of 82 female HCT survivors transplanted between 1994-2014 at the National Institutes of Health Clinical Center, who survived at least 1 year after transplant and completed a gynecologic exam
- All patients received an HLA-identical sibling HCT, and 93% received a MAC regimen with TBI. The cumulative proportions of any genital HPV infection at 1, 3, 5, 10 and 20 years were 4.8%, 14.9%, 28.1%, 36.7% and 40.9%, respectively.
- In multivariate analysis, a history of pre-transplant HPV disease (OR=6.5, P=0.008) and experiencing either extensive or genital chronic GVHD (OR=5.7, P=0.002) was associated with increased risk of any HPV disease post-transplant. Extensive or genital chronic GVHD was also associated with an increased risk for severe HPV-related dysplasia (OR=13.1, P=0.017), although no patient developed HPV-related genital cancer.
- The authors note that women with extensive chronic GVHD, genital chronic GVHD, or pre-transplant HPV are at greatest risk for post-transplant HPV disease. Early initiation of annual screening, comprehensive genital tract assessment and aggressive management are essential to their post-transplant care.

## Abbreviations

ALL: acute lymphoblastic leukemia

AML: acute myeloid leukemia

ANC: absolute neutrophil count

BSI: blood stream infection

Bu/Cy: busulfan and cyclophosphamide

CRS: cytokine release syndrome

DLBCL: diffuse large B-cell lymphoma

DME: durable medical equipment

EFS: event-free survival

ER: emergency room

Flu/Mel: fludarabine and melphalan

G-CSF: granulocyte colony stimulating factor

GVHD: graft-versus-host disease

HCT: hematopoietic cell transplant

HLA: human leukocyte antigen

HPV: human papilloma virus

OS: overall survival

ICU: intensive care unit

MAC: myeloablative conditioning

MRD: minimal residual disease

MUD: matched unrelated donor

NRM: non-relapse mortality

OS: overall survival

PBSCT: peripheral blood stem cell transplant

PID: primary immunodeficiency

RFS: relapse-free survival

RIC: reduced intensity conditioning

RR: response rate

SNF: skilled nursing facility

TBI: total body irradiation

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