



*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**

\*Epperla N, Ahn KW, Armand P, et al. Fludarabine and busulfan versus fludarabine, cyclophosphamide, and rituximab as reduced-intensity conditioning for allogeneic transplantation in follicular lymphoma. *Biol Blood Marrow Transplant.* 2018;24(1):78-85. <https://www.ncbi.nlm.nih.gov/pubmed/29032272>

- Retrospective analysis using the CIBMTR database of 200 FL patients using the most commonly prescribed RIC regimens of Flu/Bu or FCR during 2008-2014. All patients received peripheral blood grafts, and a CNI-based regimen for GVHD prophylaxis.
- On univariate analysis in the Flu/Bu and FCR groups, there was no significant difference in the rates of 3-year NRM (11% vs 11%, P=0.94), relapse/progression (18% vs 15%, P=0.54), PFS (71% vs 74%, P=0.65), or OS (73% vs 81%, P=0.18)
- On multivariate analysis there was no significant difference in acute GVHD, NRM, relapse/progression, PFS, or OS. However, FCR was associated with a significantly lower risk of chronic GVHD (RR, 0.52; P=0.001).
- The authors conclude that of the two most common RIC regimens for FL, FCR was associated with a lower risk of chronic GVHD, but Flu/Bu and FCR both provide excellent 3-year OS, with acceptable rates of NRM

\*Batalini F, Econimo L, Quillen K, et al. High-dose melphalan and stem cell transplantation in patients on dialysis due to immunoglobulin light-chain amyloidosis and monoclonal immunoglobulin deposition disease. *Biol Blood Marrow Transplant.* 2018;24(1):127-132.

<https://www.ncbi.nlm.nih.gov/pubmed/28865972>

- Retrospective analysis on toxicity, efficacy, and hematologic and renal response of HDM followed by auto-HCT in 32 patients with AL amyloidosis and 4 patients with MIDD who were dialysis dependent for ESRD from 1994-2016
- Ninety-two percent of patients required inpatient admission for management of complications. The most common grade 3/4 non-hematologic toxicities were infections (75%), metabolic abnormalities (56%), mucositis (42%), constitutional symptoms (39%), pulmonary complications (39%), and diarrhea (28%). There were three deaths within the first 100 days post-HCT, conferring an 8% TRM rate
- Seventy percent of evaluable patients achieved a CR at 1 year after HDM and auto-SCT. In the entire cohort, median OS was 5.8 years and was no different among those receiving HDM compared to modified-dose melphalan. Twelve patients (33%) underwent kidney transplantation after successful treatment with HDM followed by auto-HCT at a median of 2.4 years post-SCT.

- The authors conclude that HDM followed by auto-SCT is safe and effective in patients with ESRD from AL amyloidosis and MIDD in inducing hematologic CRs and prolonging survival, allowing these patients to become possible candidates for renal transplantation

\*\* Kennedy V, Chen H, Savani BN, et al. Optimizing antithymocyte globulin dosing for unrelated donor allogeneic hematopoietic cell transplantation based on recipient absolute lymphocyte count. *Biol Blood Marrow Transplant.* 2018;24(1):150-155. <https://www.ncbi.nlm.nih.gov/pubmed/28864139>

- Retrospective analysis of 135 patients who received ATG for GVHD prophylaxis for unrelated donor allo-HCT at doses of 10 mg/kg, 7.5 mg/kg, and 5 mg/kg
- There was no difference in 2-year OS among ATG dosing groups; however, deaths from infectious complications were significantly higher with higher doses of ATG (3.7% vs 19% vs 26.7%; P=0.02), particularly due to fungal infections. The cumulative incidence of extensive chronic GVHD was lower with higher doses of ATG (28% vs 24% vs 4%; P=0.03).
- The ALC did not predict OS; however, in multivariate analysis, the interaction between the median peripheral blood ALC on day of ATG administration and the total amount of ATG dose did predict OS (HR, 0.09; P=0.03). For low recipient ALC (10<sup>th</sup> percentile, or 0.56 × 10<sup>2</sup>/μL), a higher total ATG dose was associated with a greater risk of death, whereas for high recipient ALC (90<sup>th</sup> percentile, or 24.96 × 10<sup>2</sup>/μL), a higher ATG dose was associated with a lower risk of death.
- The authors suggest that the interaction between ATG and recipient ALC may predict OS and could represent a new paradigm for ATG dosing, but a larger retrospective meta-analysis is warranted before dosing nomograms could be developed for prospective studies

\*\*Milone G, Martino M, Leotta S, et al. Cost-effectiveness of on-demand plerixafor added to chemotherapy and granulocyte-colony stimulating factor for peripheral blood stem cell mobilization in multiple myeloma. *Leuk Lymphoma.* 2018;59:42-48. <http://www.ncbi.nlm.nih.gov/pubmed/28573902>

- Phase II/III prospective study that evaluated 111 multiple myeloma patients during peripheral blood stem cell chemo-mobilization with a retrospective control group
- Patients received 4gm/m<sup>2</sup> cyclophosphamide plus G-CSF and were given “on-demand” plerixafor based on a pre-determined algorithm assessing peripheral blood CD34+ counts from days 9-16 after chemotherapy
- Minimum harvest ( $\geq 2.0 \times 10^6$  CD34+ cells/kg) was achieved in 97.2% of patients in the on-demand treatment group, and optimal harvest ( $\geq 4.0 \times 10^6$  CD34+ cells/kg) was achieved in 84.6% of patients
- Multivariate analysis showed that patients in the on-demand plerixafor group had significantly higher likelihoods of successfully achieving both the minimal (P=0.006) and optimal (P= 0.05) harvest
- Compared to the historical control group, the incremental cost-effectiveness ratio for each 1% increase in probability of achieving a successful minimal harvest was determined to be €40.6 per patient

\*Li Z, Wang Y, Wang K, et al. Haploidentical hematopoietic stem cell transplantation for adult patients with Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. *Leuk Lymphoma.* 2018;59:77-84. <http://www.ncbi.nlm.nih.gov/pubmed/28573910>

- Retrospective analysis of 30 cases of EBV-associated HLH who underwent haploidentical HCT after receiving HLH-94 protocol or other salvage therapies. 20 patients (66.7%) had achieved a response from prior treatment at time of HCT.

- All patients underwent myeloablative conditioning with TBI, etoposide, cyclophosphamide, and rabbit ATG and received peripheral blood stem cells from related, haploidentical donors. GVHD prophylaxis consisted of IV cyclosporine, oral mycophenolate, and IV methotrexate x4 doses. No post-transplant cyclophosphamide was utilized.
- Twenty-six patients (86.7%) achieved donor cell engraftment, with 23 achieving complete donor chimerism while three others demonstrated mixed chimerism.
- Acute GVHD occurred in 69.2% patients, with grade I-II in 11 patients and grade III-IV in 7 patients. Chronic GVHD occurred in 23.1% of patients.
- Nineteen patients survived until the end of follow-up, with 3-year overall survival of 63.3%.

### **Graft-versus-Host Disease**

\*\* Zeiser R, Blazar BR. Pathophysiology of chronic graft-versus-host disease and therapeutic targets. *N Engl J Med* 2017;377:2565-79. <http://www.ncbi.nlm.nih.gov/pubmed/29281578>

- Comprehensive review of the incidence and risk factors of chronic GVHD, as well as the use of the NIH consensus criteria in the diagnosis and scoring of chronic GVHD
- The review outlines the different phases of the pathophysiology of chronic GVHD: early inflammation caused by tissue injury, chronic inflammation leading to adaptive activation of immune system effector cells, and aberrant tissue repair with fibrosis
- A review of current therapeutic strategies is provided, along with a discussion of novel agents undergoing testing and potential therapeutic targets
- Although glucocorticoids are still considered standard front-line therapy, other central therapeutic strategies focus on impeding B-cell signaling and germinal-center formation, eliminating B cells, or increasing Treg cells
- The review acknowledges several biomarkers that are being investigated for their usefulness in predicting prognosis and therapeutic response, as well as aiding in the identification of new therapeutic targets

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

\*\*Hill JA, Li D, Hay KA, et al. Infectious complications of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy. *Blood*. 2018;131(1):121-30.

<http://www.ncbi.nlm.nih.gov/pubmed/29038338>

- Phase 1/2 study that evaluated infections that occurred in 133 patients treated with CD19 CAR-T cells in a variety of hematological malignancies (ALL n = 47, CLL n = 24, NHL n = 62)
- There were 43 infections in 30 of the 133 patients (23%) within 28 days after CAR-T-cell infusion with an infection density of 1.19 infections for every 100 days at risk. There was a lower infection density of 0.67 between days 29 and 90 (P= 0.02). Six patients (5%) developed invasive fungal infections and 5 patients (4%) developed life-threatening or fatal infections.
- An adjusted model of baseline characteristics showed patients with ALL,  $\geq 4$  prior antitumor regimens, and higher CAR-T-cell dose ( $2 \times 10^7$  cells/kg) had a higher infection density within 28 days. CRS severity was the only factor after CAR-T-cell infusion associated with infection.
- According to the authors, the incidence of infections was comparable to other salvage chemoimmunotherapies observed in clinical trials

## **Other**

\*Sweiss K, Anderson J, Wirth S, et al. A prospective study of intravenous pentamidine for PJP prophylaxis in adult patients undergoing intensive chemotherapy or hematopoietic stem cell transplant. *Bone Marrow Transplant*. 2017 Dec 21. [Epub ahead of print].

<https://www.ncbi.nlm.nih.gov/pubmed/29269796>

- Prospective trial of 50 patients undergoing intensive chemotherapy or HCT assigned to receive pentamidine 4 mg/kg (max. dose 300mg) IV q28 days
- Patients received a median 2 doses of pentamidine (range 1-9). Five (10%) had prior inhaled pentamidine while nine (18%) had prior IV pentamidine.
- No cases of PJP were documented during the study. Most common adverse events included nausea (n=4), hypotension during or at the end of infusion (n=6), and acute kidney injury (n=2). Engraftment was not delayed.
- Overall, patients reported satisfaction with IV pentamidine (n = 43, 86%, P <0.01)

## **Abbreviations**

AL: immunoglobulin light-chain

TBI: total body irradiation

ALL: acute lymphoblastic leukemia

Treg: regulatory T-cells

ALC: absolute lymphocyte count

TRM: transplant-related mortality

ATG: anti-thymocyte globulin

CIBMTR: Center for International Blood and Marrow Transplant Research

CLL: chronic lymphocytic leukemia

CNI: calcineurin inhibitor

CR: complete response

CRS: cytokine release syndrome

EBV: Epstein-Barr virus

ESRD: end-stage renal disease

FCR: fludarabine, cyclophosphamide, and rituximab

FL: follicular lymphoma

Flu/Bu: fludarabine and busulfan

G-CSF: colony growth stimulating factor

GVHD: graft-versus-host disease

HCT: hematopoietic cell transplantation

HDM: high-dose melphalan

HLH: hemophagocytic lymphohistiocytosis

MIDD: monoclonal immunoglobulin deposition disease

NHL: non-Hodgkin lymphoma

NIH: National Institutes of Health

NRM: non-relapse mortality

OS: overall survival

PFS: progression-free survival

PJP: *Pneumocystis jirovecii* pneumonia

RIC: reduced-intensity conditioning

RR: relative risk

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