

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

*Bashey A, et al. Mobilized Peripheral Blood Stem Cells Versus Unstimulated Bone Marrow As a Graft Source for T-Cell-Replete Haploidentical Donor Transplantation Using Post-Transplant Cyclophosphamide. *J Clin Oncol*. 2017 June 23. Doi: 10.1200/JCO.2017.72.8428.
<https://www.ncbi.nlm.nih.gov/pubmed/28644773>

- Study of data reported to the CIBMTR to evaluate outcomes after T-cell replete haploidentical transplantation of PB (n=190) compared with BM (n=481) for hematologic malignancies.
- The reduced-intensity conditioning regimen was uniform for both graft types (TBI 2 Gy, cyclophosphamide 29 mg/kg, fludarabine 150 mg/m²). Myeloablative regimens included TBI (≥ 10 Gy with fludarabine or cyclophosphamide) or busulfan and cyclophosphamide with or without fludarabine. All received BM or PB from haploidentical related donors with a uniform GVHD prophylaxis regimen (tacrolimus or cyclosporine with mycophenolate and post-transplant cyclophosphamide).
- There was no difference in OS by graft type (HR 0.99; p = 0.98) or hematopoietic recovery (28-day neutrophil recovery 88% BM vs. 90% PB; p=0.07). Risks of grade 2-4 acute GVHD (HR 0.45; p <0.001) and chronic (HR 0.35; p <0.001) GVHD were significantly lower with BM compared with PB, but this was not the case in grade 3-4 acute GVHD (HR 0.61; p=0.06). There were no differences in NRM but relapse risk were higher after BM (HR 1.49; p = 0.009), however, after additional analysis the high relapse risk was limited to patients with leukemia (HR 1.73; p=0.002) and not lymphoma (HR 0.87; p=0.64).
- PB and BM grafts are suitable for haploidentical transplantation with the post-transplant cyclophosphamide approach but with differing patterns of treatment failure.

*Kasenda B, Ihorst G, Schroers R, et al. High-dose chemotherapy with autologous haematopoietic stem cell support for relapsed or refractory primary CNS lymphoma: a prospective multicenter trial by the German Cooperative PCNSL study group. *Leukemia*. 2017 Jun 16. [Epub ahead of print].
<https://www.ncbi.nlm.nih.gov/pubmed/28559537>.

- Prospective multicenter single-arm phase II trial of 32 patients with relapsed or refractory PCNSL who failed prior HD-MTX based chemotherapy that received conditioning chemotherapy comprised of rituximab, carmustine, and thiotepa following a short 2 course induction regimen of rituximab, HiDAC, and thiotepa.
- 22 patients (56.4%) achieved the primary endpoint of CR at 30 days post-autologous transplant.
- Overall survival at 1 and 2 years was 61.5% and 56.4%, respectively. Main grade III toxicities were hematologic with 2 treatment-related deaths recorded.

- The authors concluded that short-induction followed by autologous HCT is an effective treatment option for PCNSL patients who failed prior HD-MTX based chemotherapy.

*Sezer O, et al. Effects Of Single-Agent Bortezomib As Post-Transplant Consolidation Therapy On Multiple Myeloma-Related Bone Disease: A Randomized Phase II Study. *British Journal of Haematology*. 2017;178(1):61-71. <https://www.ncbi.nlm.nih.gov/pubmed/28382618>.

- Phase II randomized, open label, multi-center study comparing bortezomib consolidation to observation alone on multiple myeloma related bone disease in patients who had undergone frontline auto-HCT with at least a PR or better.
- Patients (n=104) were randomized 1:1 [stratified by age (<65 vs. ≥65 years) and baseline bisphosphonate use (yes or no)] to receive four 35-day cycles of bortezomib 1.6 mg/m² IV on days 1, 8, 15 and 22, or observation alone.
- No meaningful differences were noted in the primary endpoint of change from baseline to end of treatment in bone mineral density. End of treatment CR rates were 22% vs. 11% (p=0.19), and progressive disease 8% vs. 23% (p=0.06) with a median PFS of 44.9 vs. 21.8 months (p=0.22) for bortezomib and observation, respectively. Adverse events observed ≥ 15% more frequently with bortezomib were diarrhea (37% vs. 0), peripheral sensory neuropathy (20% vs. 4%), nausea (18% vs. 0) and vomiting (16% vs. 0).
- The authors concluded that bortezomib compared to observation had little impact on bone metabolism/health but was associated with a trend in improved myeloma response and survival.

*Hamilton BK, Rybicki L, Abounader D, et al. Allogeneic Hematopoietic Cell Transplantation for Adult T-Cell Acute Lymphoblastic Leukemia. *Biol Blood Marrow Transplant*. 2017;23(7):1117-21. <https://www.ncbi.nlm.nih.gov/pubmed/28396160>.

- Multicenter, retrospective cohort study using data from 208 adult patients who underwent HCT between 2000 and 2014 to describe outcomes of HCT.
- Median age at HCT was 37 years and the majority of patients were in CR. The majority of patients received a TBI-based myeloablative conditioning regimen. 25% of patients received transplants from an alternative donor source.
- With a median follow up of 38 months, OS at 1 year was 58% and at 5 years was 34%. Cumulative incidence of NRM and relapse were 26% and 41%, respectively.
- A multivariate analysis showed that factors significantly associated with OS were use of TBI in conditioning regimen (HR 0.57, p=0.021), age >35 years (HR 1.55, p=0.025), and relapsed/refractory disease status at time of transplant (HR 1.98, p=0.005). Relapse remains the main cause of treatment failure following HCT for ALL.

Other

*Richardson PG, et al. Earlier Defibrotide Initiation Post-Diagnosis Of Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome Improves Day +100 Survival Following Hematopoietic Stem Cell Transplantation. *British Journal of Haematology*. 2017;178(1):112-118. <https://www.ncbi.nlm.nih.gov/pubmed/28444784>.

- Post-hoc analysis to determine optimal timing to initiate defibrotide and its potential impact on outcomes from the defibrotide expanded-access treatment protocol for hepatic VOD/SOS.
- Defibrotide was administered to 573 adult and pediatric transplant patients at 25 mg/kg/day in 4 divided doses for at least 21 days for the treatment of VOD/SOS, with and without MOD. Overall, 61.3% had MOD and 87.8% received allogeneic transplants.

- Approximately 30% of patients received defibrotide on the day of diagnosis, and 93% started by day 7. The relationship between Day +100 survival and treatment initiation before/after specific days post-diagnosis showed superior survival when treatment was initiated closer to VOD/SOS diagnosis with a statistically significant trend over time for better outcomes with earlier treatment initiation ($p < 0.001$). Similar improvement with earlier treatment initiation was shown for the subgroup of patients with MOD ($p < 0.001$).
- The authors suggest that initiation of defibrotide should not be delayed after diagnosis of VOD/SOS.

*Heo ST, Tataru AM, Jiménez-Ortigosa C, et al. Changes in in vitro susceptibility patterns of *Aspergillus* to triazoles and correlation with aspergillosis outcome in a tertiary care cancer center, 1999-2015. *Clin Infect Dis*. 2017;65:216-25. <https://www.ncbi.nlm.nih.gov/pubmed/28379304>.

- Retrospective, single-center case-control study analyzed *Aspergillus* respiratory isolates for changes in triazole antifungal MICs from 2 non-overlapping periods: 1999-2002 (before voriconazole and posaconazole availability) and 2003-2015. Azole susceptibility was based on MIC values and referred to as non-WT (azole resistant) versus WT (azole susceptible).
- 290 isolates were evaluated for changing resistance patterns. The number of pan-susceptible isolates between the time periods decreased (91.3% vs 80.4%, $p=0.0102$) and multi-resistant isolates increased (7.7% vs 19.6%, $p=0.004$).
- Azole resistance was found in 13% of isolates; all of these were low level (MIC < 8 mg/L) for any azole. Higher MICs were more frequent in the second period and only seen with *A. fumigatus*.
- 107 adult patients with hematologic malignancy and/or HCT with proven or probable invasive pulmonary aspergillosis were reviewed for clinical outcomes.
- Neutropenia, lymphopenia, ICU stay at diagnosis, and time period of 1999-2002 were independent prognostic factors of 42-day mortality but no correlation was found based on in-vitro susceptibility.
- Azole resistance was associated with Asian race (OR 20.9, 95% CI 2.5-173.5, $p=0.005$) and azole exposure in the previous 3 months (OR 9.6, 95% CI 1.9-48.5, $p=0.006$).
- Azole resistance aspergillus rates are increasing, but no correlation of MIC to outcome of aspergillosis was observed. Environmental vs. drug selection process cannot be determined and the study was limited by the number of isolates collected.

**Sanchez L, Sylvester M, Parrondo R, et al. In-Hospital Mortality and Post-Transplantation Complications in Elderly Multiple Myeloma Patients Undergoing Autologous Hematopoietic Stem Cell Transplantation: A Population-Based Study. *Biol Blood Marrow Transplant*. 2017;23(7):1203-7. <https://www.ncbi.nlm.nih.gov/pubmed/28286198>.

- Retrospective analysis of MM patients undergoing autologous HCT using the Nationwide Inpatient Sample database with primary aim to characterize and compare in-hospital complications and mortality in younger (age < 65) vs. elderly (age > 65) patients.
- Over a 3-year period (2008 to 2010), 2209 patients with MM were admitted to US hospitals for autologous HCT. Median age was 59 years, with 74.7% of patients < 65 years and 25.3% of patients > 65 years.
- In-hospital mortality was rare (1.5%) and there was no significant difference in mortality between younger and older patients.
- Elderly patients had a significantly increased mean LOS (18.6 days vs. 16.8 days, $p < 0.001$), mean total hospital charges (\$161,117 vs. \$151,192, $p=0.018$), and significantly more likely to develop major in-hospital post-HCT complications such as severe sepsis (OR 3.10, $p=0.001$), septic shock

(OR 3.10, p=0.004), pneumonia (OR 1.62, p=0.024), acute respiratory failure (OR 3.44, p=0.001), endotracheal intubation and mechanical ventilation (OR 2.19, p=0.035), acute renal failure (OR 2.14, p=0.001), and cardiac arrhythmias (OR 2.06, p <0.001).

Abbreviations

BM: bone marrow

CIBMTR: Center for International Blood and Marrow Transplant Research

CR: complete response

GVHD: graft-versus-host disease

HCT: hematopoietic cell transplantation

HD-MTX: high-dose methotrexate

HiDAC: high-dose cytarabine

ICU: intensive care unit

LOS: length of stay

MIC: minimum inhibitory concentration

MM: multiple myeloma

MOD: multi-organ dysfunction

NRM: non-relapse mortality

OS: overall survival

PB: peripheral blood

PCNSL: primary central nervous system lymphoma

PFS: progression-free survival

SOS: sinusoidal obstruction syndrome

TBI: total body irradiation

VOD: veno-occlusive disease

WT: wild type

ASBMT Pharmacy SIG Communications Working Committee:

*Brandi Anders, Morgan Belling, David Eplin, Katie Gatwood, Suzanne Gettys, Teresa Kam, Scott Lanum,
Stephanie Malenfant, Shreya Shah, Ryan Shaw*