



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

**Alatrash G, Thall PF, Valdez BC, et al. Long-term outcomes after treatment with clofarabine ± fludarabine with once-daily intravenous busulfan as pretransplant conditioning therapy for advanced myeloid leukemia and myelodysplastic syndrome. *Biol Blood Marrow Transplant.* 2016;22:1792-1800. <https://www.ncbi.nlm.nih.gov/pubmed/27377901>

- Single-center, Bayesian model of the long-term safety and efficacy of clofarabine and busulfan (6000 $\mu\text{Mol}\cdot\text{min} \pm 10\%$ /day), with or without fludarabine, as myeloablative allogeneic HCT conditioning for 70 high-risk AML, CML, or MDS patients.
 - Arm 1 (n=18): fludarabine 30 mg/m²/day + clofarabine 10 mg/m²/day
 - Arm 2 (n=7): fludarabine 20 mg/m²/day + clofarabine 20 mg/m²/day
 - Arm 3 (n=29): fludarabine 10 mg/m²/day + clofarabine 30 mg/m²/day
 - Arm 4 (n=16): clofarabine 40 mg/m²/day
- There were no deaths reported at day +30, whereas the 100-day NRM was 4% (n=3).
- Engraftment was achieved in all patients with a median time of 12 days (range, 10-22).
- 31% of patients (n=22) developed grades II-IV acute GVHD, 6% (n=4) developed grades III-IV acute GVHD, and 40% (n=28) developed chronic GVHD; no significant renal and hepatic toxicities were reported.
- Median OS was 2.4 years (Arm 1: not reached; Arm 2: 0.4 years; Arm 3: 2.2 years; Arm 4: not reached); median PFS was 0.9 years (Arm 1: 2.0 years; Arm 2: 0.2 years; Arm 3: 0.8 years; Arm 4: not reached).
- Better OS and PFS was seen in patients who received higher doses of clofarabine, irrespective of the disease status at the time of allogeneic HCT, and warrants further investigation from larger randomized trials.

*Xu LP, Wang SQ, Wu DP, et al. Haplo-identical transplantation for acquired severe aplastic anaemia in a multicentre prospective study. *Br J Haematol.* 2016;175:265-274. <https://www.ncbi.nlm.nih.gov/pubmed/27352174>

- Multicenter, prospective trial of 101 patients with SAA who received a HID HCT compared contemporaneously to 48 patients who received a MRD stem cell transplant
- There was no difference in the primary endpoint of cumulative incidence of myeloid engraftment by day +28. HID patients experienced a significantly higher rate of grades II-IV acute GVHD compared to MRD patients (33.7% vs. 4.2%, $p < 0.001$); however there was no difference in grades III-IV acute GVHD ($p=0.157$).

- Secondary endpoint of 3-year OS and PFS did not differ between the HID and MRD/MUD groups (OS: 89% vs. 91%, $p = 0.555$ and 3-year PFS: 86.8% vs. 80.3%, $p = 0.659$, respectively)
- The two groups significantly differed in proportion of adults, prior therapies, sex matching, and graft source
- Early trials of HID HCT for SAA patients showed unfavorable outcomes due to unacceptable graft failure and acute GVHD. Due to advances in HID transplantation, this trial adds to the recent literature suggesting that when compared to the standard MRD/MUD, there are similar rates of engraftment, survival outcomes and severe acute GVHD. Further studies are needed.

**Herrera AF, Mei M, Low L, et al. Relapsed or refractory double-expressor and double-hit lymphomas have inferior progression-free survival after autologous stem cell transplantation. *J Clin Oncol*. 2016 Oct 17. [Epub ahead of print]. <http://ascopubs.org/doi/pdf/10.1200/JCO.2016.68.2740>

- Retrospective, multi-center study of 144 patients with chemosensitive relapsed/refractory DLBCL and unclassifiable DLBCL who received an autologous HCT to evaluate the prognostic impact of double-expressor lymphoma (DEL) or double-hit lymphoma (DHL).
- The 4-year PFS and OS in patients with DEL was inferior to those without coexpression: PFS: 48% (95% CI, 34-61%) versus 59% (95% CI, 45-70%; $P=0.049$) and OS: 56% (95% CI, 40-69%) versus 67% (95% CI, 53-79%; $P=0.1$), respectively.
- Similarly, the 4-year PFS and OS in patients with DHL were worse compared to those without DHL: PFS: 28%, (95% CI, 6% to 57%) versus 57% (95% CI, 46% to 66%; $P=0.013$), and 25% (95% CI, 5% to 54%) versus 66% (95% CI, 55% to 75%; $P<0.001$), respectively.
- Patients with DHL had worse 4-year PFS and OS compared to patients with DEL without DHL and compared to patients without either DEL or DHL (three-way P value for PFS, $P=0.013$; OS, $P=0.002$).
- Though already known to be associated with inferior outcomes after R-CHOP induction therapy, DHL or DEL relapsed/refractory DLBCL was shown in this study to carry poor prognosis even after autologous HCT. These results are similar to, but more robust than the previously reviewed study by Puvvada et al. last month. Alternative transplant and post-autologous HCT strategies should be studied, particularly in patients with isolated DHL who had the lowest survival rate.

Other

***Corbacioglu S, Carreras E, Mohty M, et al. Defibrotide for the treatment of hepatic veno-occlusive disease: final results from the international compassionate use program. *Biol Blood Marrow Transplant*. 2016;22:1874-82. <https://www.ncbi.nlm.nih.gov/pubmed/27397724>

- Open-label multicenter program which provided defibrotide on a compassionate-use basis or via single-patient emergency IND for hepatic VOD/SOS either after HCT or after nontransplantation-associated chemotherapy/radiotherapy treatment.
- Efficacy and safety analyses were performed using the data received for 710 treated patients, who were given a median daily dose of 25 mg/kg of defibrotide (range, 10-80 mg/kg/day), given for a median of 15 days (range, 1-119).
- Across all doses, the Kaplan-Meier estimate of 100-day survival after HCT or nontransplantation-associated chemotherapy/radiotherapy was 54% (95% CI, 50.2-58.0), and for the 25 mg/kg/day dose, was 58% (95% CI, 51.1-63.5).
- A total of 53% of patients ($n=378$) reported AEs, 51% reported serious AEs ($n=364$), and 49% ($n=350$) experienced fatal AE. Hemorrhage occurred in 12% ($n=85$) of patients.

- The authors concluded that these safety and efficacy results are consistent with prior studies of defibrotide treatment in patients with VOD/SOS, and subgroup analyses support the use of 25 mg/kg/day dose.

*Della Porta MG, Galli A, Bacigalupo A, et al. Clinical effects of driver somatic mutations on the outcomes of patients with myelodysplastic syndromes treated with allogeneic hematopoietic stem-cell transplantation. *J Clin Oncol*. 2016 Sept 6. [Epub ahead of print].

<https://www.ncbi.nlm.nih.gov/pubmed/27601546>

- Retrospective review of 401 tumor samples from patients with MDS or AML who underwent an allogeneic HCT reported between 1997 and 2013 to the Italian Transplant Registry to determine the effect of independent mutations on post-transplant outcome
- Of the 401 patients, 318 had at least one oncogenic mutations and the greater the number of mutations, the greater the effect on the probability of relapse and OS after HCT ($p < 0.001$ and $p = 0.017$, respectively).
- In patients with MDS and AML, mutations independently associated with predicting relapse and overall survival after allogeneic HCT were ASXL1, RUNX1, and TP53 (p values ranging from 0.003 to 0.035). The effect these mutations had on survival after allogeneic HCT were independent of the revised International Prognostic Scoring System (IPSS-R).
- This review found somatic mutations, ASXL1, RUNX1, and TP53, to be independent predictors of survival. Taken together with the IPSS-R, it may improve identifying prognosis and clinical options for patients with MDS and AML.

*Green DJ, Bensinger WI, Holmberg LA, et al. Bendamustine, etoposide, and dexamethasone to mobilize peripheral blood hematopoietic stem cells for autologous transplantation in patients with multiple myeloma. *Bone Marrow Transplant*. 2016;51:1330-1336.

<http://www.ncbi.nlm.nih.gov/pubmed/27214069>

- Single-center, open-label prospective trial of 34 patients with multiple myeloma
- Compared hematopoietic stem cell collection with bendamustine, etoposide, and dexamethasone (BED) to historical mobilization success rates of 80%
- All 34 patients were successfully mobilized with a median number of CD34+ cells of $21.6 \times 10^6/\text{kg}$
- Grade 3 or 4 thrombocytopenia, leukopenia, and lymphopenia were seen in most patients
- 31/34 patients had undergone autologous HCT with neutrophil engraftment at a median of 15 days (range 7-19) and platelet engraftment at a median of 11 days (range 8-15)

AE, adverse events; AML, acute myelogenous leukemia; CI, confidence interval; CML, chronic myeloid leukemia; DLBCL, diffuse large B cell lymphoma; GVHD, graft-versus-host disease; HCT, hematopoietic stem cell transplantation; HID, haploidentical; IND, investigational new drug; MDS, myelodysplastic syndrome; MRD, matched related donor; MUD, matched unrelated donor; NRM, non-relapse mortality; OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; SAA, severe aplastic anemia; SOS, sinusoidal obstruction syndrome; VOD, veno-occlusive disease