GvHDHub

ASH 2018

Practice changing abstracts in graft-versus-host disease

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Scientific Education Support

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Novel Treatment Strategies

#601: Results from REACH1, a single-arm phase II study of ruxolitinib in combination with corticosteroids for the treatment of steroid-refractory acute graft-vs-host disease

http://www.gvhdhub.com/medical-information/ash-2018-ruxolitinib-plus-corticosteroids-in-patients-with-steroid-refractory-acute-graft-versus-host-disease-the-reach1-trial

#602: KD025-208: A phase IIa study of KD025 for patients with chronic graft versus host disease (cGVHD) - pharmacodynamics and updated results

http://www.gvhdhub.com/medical-information/ash-2018-pharmacodynamics-and-updated-data-from-the-phase-iia-kd025-208-trial

#605: A phase Ib study of intravenous vedolizumab plus standard of care for graft-versus-host disease prophylaxis in subjects undergoing allogeneic hematopoietic stem cell transplantation for hematologic malignancies: 6-month results

http://www.gvhdhub.com/medical-information/ash-2018-vedolizumab-plus-standard-of-care-to-prevent-graft-versus-host-disease-a-phase-ib-study

Comments provided by Robert Zeiser and Bipin Savani

- aGvHD patients who are refractory to standard steroid treatment have a dismal long-term prognosis
- This year at ASH, promising new therapeutic and prophylactic concepts were presented, including JAK1/2 inhibition for SR-GvHD (**#601**), ROCK2 inhibition with KD025 for chronic GvHD (**#602**) and blockade of α4β7-integrin (vedolizumab) for GvHD prophylaxis (**#605**)
- These novel concepts are exiting because they translate findings made in preclinical models into early clinical trials
- REACH1 showed that ruxolitinib led to a 54.9% ORR at d28 and the best ORR at any time was 73.2% (CR = 56.3%). These results are encouraging but will need confirmation in the ongoing phase-III trial
- In patients with cGvHD, KD025 demonstrated an ORR of 65% which is impressive and should be the basis for a following phase III trial
- Prophylaxis with vedolizumab treatment in the phase 1b trial was connected to low GvHD rates (no GvHD in cohort 1, 19% GVHD in cohort 2) which is very promising

Mesenchymal Stromal Cells

#603: Children and adults with steroid-refractory acute graft-versus-host disease respond to treatment with the mesenchymal stromal cell preparation "MSC-Ffm": treatment results for 92 consecutive patients

http://www.gvhdhub.com/medical-information/ash-2018-msc-ffm-for-the-treatment-of-pediatric-and-adult-patients-with-steroid-refractory-graft-versus-host-disease

Comments provided by Florent Malard

- aGvHD patients who are refractory to standard steroid treatment have a dismal long-term prognosis
- The usefulness of mesenchymal stroma cells (MSCs) in refractory aGvHD remain open for discussion
- This year at ASH, promising results with MSCs in refractory aGvHD were reported, both in children and adults with an ORR > 80% at day 28
- 6-month overall survival rates for children and adults were 68% and 54%, respectively
- These results are promising in patients with severe steroid refractory aGvHD

Microbiome

#69: Metabolomics profiling after allogeneic hematopoietic stem cell transplantation unravels a specific signature in human acute Gvhd

http://www.gvhdhub.com/medical-information/ash-2018-the-role-of-metabolomics-profiling-in-acute-graft-versus-host-disease

#359: Pre-transplant and peri-d100 gastrointestinal dysbiosis is associated with the subsequent development of chronic graft-versus-host disease

http://www.gvhdhub.com/medical-information/kate-a-markey-ash-2018-pre-transplant-and-peri-d100-gastrointestinal-dysbiosis-in-chronic-gvhd

Comments provided by Takanori Teshima

- Tissue microenvironment and microbiota of the transplant recipients are topical areas of research in GvHD
- Most studies have been focusing on acute GvHD using fecal samples
- This year, the Paris group presented the potential roles of metabolomics alterations in the patients' blood regarding pathogenesis and biomarker of acute GvHD **(#69)**
- The Sloan Kettering group presented intestinal microbial signature before chronic GvHD onset was predictive of chronic GvHD **(#359)**
- Although it remains to be elucidated if such changes were causes or effects of GvHD, such studies on host and microbial homeostasis will open a new avenue of research on GvHD pathophysiology that could be targeted for prophylaxis or treatment in the future

Risk factors

#357: Genetic risk of severe chronic graft-versus-host disease defined by host-derived CXCR3 ligands

https://gvhdhub.com/medical-information/prediction-of-severe-chronic-graft-versus-host-disease-by-host-derived-cxcr3-ligand-genes

Comments provided by Arnon Nagler

- A very interesting and novel study by Dr Sivaramakrishna and colleagues from two transplant centers in Heidelberg and Berlin Charité, Germany, assessing the role of the CXCR3 signaling pathway in cGvHD
- The very well designed and executed study included training and validation cohorts, and compared the chemokine profiling between patients that received or did not receive statin-based endothelial prophylaxis (SEP)
- The study results demonstrated that in the no-SEP training cohort, higher serum CXCL9 levels at day +28 were significantly associated with a higher risk of severe cGvHD, while no significant association was found for serum CXCL10 and CXCL11 pre- or post-transplant with severe cGvHD
- Furthermore, the rs884304 SNP in the CXCL9-11 locus showed a significant association with severe cGvHD. Then the authors dissected the risk of severe cGvHD based on several specific SNPs in the CXCL9-11 and CXCL4 loci. Based on this genetic profiling the authors were able to allocate high-risk patients. Patients in the high-risk group that have not received statins had significantly higher serum CXCL9 levels at day +28 and a significantly higher risk of severe cGvHD. In contrast, in patients receiving statins the adverse effect of high risk genotypes was not observed
- The authors concluded that the risk of severe cGvHD in patients not receiving statin prophylaxis could be predicted by a genetic score. Importantly, the results suggest that in high-risk patients, host-derived CXCR3 ligands are upregulated early after transplantation and may promote the development of severe cGvHD. Endothelial prophylaxis may reduce the risk of severe cGvHD by regulating serum CXCL9 levels and, thus, warrants further study
- Overall, this is an important study that speaks to the role of chemokines and may be endothelial cells in GvHD, and most importantly the ability to predict GvHD by genetic profiling in agreement with our study published a few years ago (Ostrovsky Olga *et al.*, Blood. 2010 Mar 18; 115(11): 2319-28)

Biomarkers

#356: Serial biomarker monitoring early after HCT identifies different risks for relapse and graft-vs-host disease

https://gvhdhub.com/medical-information/james-ferrara-ash-2018-how-biology-drives-acute-gvhd-biomarkers

Comments provided by Arnon Nagler

- This is additional important work from Professor Ferrara's group, one of the pioneers and leaders, if not the leader, in the field of biomarkers in GvHD. In this study, the authors were able to show that biomarker assessment and monitoring, as early as one month post-allogeneic transplantation, can predict the risk of developing GvHD
- This is an extremely important achievement in the long path to overcome GvHD, the major obstacle for successful transplantation, with major clinical applications and I would dare to predict that it may revolutionize the field. Specifically, the study included 1608 patients (702 in the training set and 906 in the validation set)
- Biomarkers (ST2 and REG3α) were analyzed on days 7, 14, 28, or at GvHD onset (if onset occurred within the first 28 days). This method was able to predict GvHD risk. Patients with low probability for GvHD experienced significantly better relapse free survival (69%) compared to patients in the high probability group (53%), $P < 0.001$. Furthermore, incidence of lethal GvHD were significantly higher in the high probability group
- There was also correlation between the predictive risk groups, lethal GvHD, relapse rate and disease risk index (DRI). The probability of relapse was three fold higher than lethal GvHD in malignancies with a low DRI (12%), six fold higher for intermediate DRI (20%), and eleven fold higher for high/very high DRI (33%). Overall patients with low predictive risk for GvHD based on the two biomarker profiles had exceptionally low risk of lethal GvHD, and, thus, they relapsed (25%) much more often than they died from GvHD (3%)
- In summary, this important study speaks again for the validity of DRI, the inverse correlation between relapse and GvHD, namely the graft-versus-tumor effect, but most importantly for the ability to predict GvHD early on