Post ASH 2016: Transplantation

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PLAN

BETTER SELECT PATIENT: Graft and aging

– DECREASE GVHD

- Impact of IEC and microbiome
- Impact of immunosuppressive regimen
 - Use of ATG
 - MMF + CSA vs MMF + Sirolimus + CSA
- Stem cell source and haplo

– New GRFS

Abstract 681: Allogeneic Hematopoietic Cell Transplantation in Elderly Patients Aged 65 and Older: A Retrospective Analysis By the Complications and Quality of Life Working Party of the EBMT

Basak et al.

Number of alloHSCTs/year in patients aged > 65 in EBMT transplant centers

 A total of 6046 alloHCT, including 214 second or subsequent procedures, from 270 EBMT centers in 32 countries were identified



AlloHCT activity in elderly patients in EBMT transplant centers: 37 out of 6413 in 2000 (<1%) 1057 out of 15765 in 2014 (6,7% ; p<0.001)

Non-relapse mortality (NMR) after alloHCT



NRM	All (n=6046)	65-69 y (n=4914)	>70 y (n=1132)	р
1 year	27% (95%CI 26-28)	26% (25-28)	29% (27-36)	0.001
3 years	35% (95%Cl 33-36)	34% (33-36)	39% (36-42)	

Overall Survival after alloHCT



OS	All (n=6046)	65-69y (n=4914)	>70y (n=1132)	р
1 year	57% (95%Cl 55-58)	57% (56-59)	53% (50-57)	<0.0001
3 years	39% (95%Cl 37-40)	39% (38-41)	35% (31-38)	

Outcomes in patients >75 years old at alloHCT

	1 year	3 years
Non relapse mortality	26% (95%Cl 16-38)	34% (95%Cl 21-47)
Overall survival	57% (95%CI 45.5-70)	38.5 (95%CI 27-56)
Relapse incidence	25% (95%Cl 15-36)	32% (95%CI 18-46)

Educational: biologic versus physiologic age in the transplant candidate

Andrew S. Artz

Survival from allogenic recipients > 70 years in US



Muffy BMT Tandem 2016 abstracts

Multiple comorbidity influences non relapse mortality and survival (HCT-CI)



Sorror et al, BBMT 2015

Pronostic influence on survival of GA in patients 50+ after allograft

Variable	Total p	population	(n=203)		50-59 year (n=124)	S		60-73 years (n=79)	
	HR	95%CI	р	HR	95%CI	р	HR	95%Cl	р
GA variable									
IADL impairment	2.38	1.59-3.56	<0.001	1.86	1.07-3.24	0.03	3.25	1.75-6.05	<0.001
Slow walk speed	1.80	1.14-2.83	0.01	1.16	0.60-2.28	0.66	3.27	1.68-6.39	0.001
Reduced mental health	1.67	1.13-2.48	0.01	1.55	0.92-2.62	0.10	1.87	1.01-3.49	0.04
Low albumin	1.52	0.94-2.46	0.09	1.23	0.57-2.63	0.60	2.63	1.26-5.47	0.01
High CRP	2.51	1.54-4.09	<0.001	1.89	0.94-3.79	0.07	3.13	1.52-6.46	0.002

Muffly et al. 2014

High comorbidity and functional limitation influence overall survival



Muffly et al, Haematologica 2014

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Educational: Role of the intestinal mucosa in acute gastrointestinal GVHD

Robert R. Jenq

Change in Intestinal bacteria during GVHD

- Obligate anaerobes, in particular clostridium species, are important mediators for intestinal homeostasis and prevent inflammation by upregulating intestinal T Reg (Atarashi et al, 2013)
- GVHD leads to change in the microbiota composition
 - Expansion of G- enterobacteriales and G+ lactobacillus
 Loss of obligate anaerobes
- GVHD induce changes in the metabolites produced by these bacteria (Butyrate)

Potential targets of butyrate that ameliorate GVHD

• <u>T cells</u>

- Induce FOXP3 expression (Arpaia et al. 2013, Furusawa et al. 2013)

- Induce colonic homing of regT cells (Smith et al. 2013)

Macrophage

- Reduced response to LPS (Chang et al. 2014)

- Epithelial cells (Mathewson 2016)
 - Improved IEC junctional integrity
 - Decreased apoptosis by alloreactive T cells

Gut microbiome-derived metabolites modulate intestinal epithelial cell damage and mitigate graft-versus-host disease



Butyrate induce Treg, and inhibit histone deacetylase \rightarrow Oral feeding with butyrate or introduction of butyrate producing clostridium \rightarrow improved survival in mice with acute GVHD

Mathewson et al, Nat immunology 2016

Effect of frequently administred antibiotics on GVHD mortality



- Retrospective analysis, n=857 alloHCT
- Neutropenic fever
- Treatment with imipenem or pip-tazo:
 - Increase grade II-IV aGVHD (p=0.0167 and p=0.0165)
 - Increase upper GI aGVHD (p=0.002 and p=0.045)
 - Increase lower GI aGVHD (p=0.019 and p=0.036)
 - Increase GVHD mortality (p=0.02 and p=0.007)
 - No change in OS

Shono at al, Sci Trans Med 2016

Evaluating the effect of antibiotics on murine GVHD



Shono et al, Sci Transl Med, 2016

TRANSPLANTATION

CME Article

Fecal microbiota transplantation for patients with steroid-resistant acute graft-versus-host disease of the gut

Kazuhiko Kakihana,^{1,*} Yuki Fujioka,^{2,3,*} Wataru Suda,^{4,5,*} Yuho Najima,¹ Go Kuwata,⁶ Satoshi Sasajima,⁷ Iyo Mimura,⁸ Hidetoshi Morita,⁸ Daisuke Sugiyama,² Hiroyoshi Nishikawa,² Masahira Hattori,^{4,9} Yutaro Hino,¹ Shuntaro Ikegawa,¹ Keita Yamamoto,¹ Takashi Toya,¹⁰ Noriko Doki,¹ Koichi Koizumi,⁶ Kenya Honda,^{5,7,11} and Kazuteru Ohashi¹

- 3 patients with steroid refractory and 1 with steroid-dependent GVHD
- Treated with FMT from a spouse of relative administred by NJ tube
- Appeared to be safe
- 3 CRs and 1 PR

Developing strategies to address intestinal mucosa injury in GVHD

Epithelial regeneration

Growth factors Cellular therapies

Probiotics

Fecal microbiota transplant Introducing rationaly selected cultured bacteria

Postbiotics

Identifying and introducing bacterial metabolites that mediate the anti-inflammatory effects

Prebiotics

Encouraging eating Gastric nutritional supplementation Flora-targetted nutritionnnal supplementation

Antibiotics

Selecting antibiotics that spare bacterials with beneficial potential

Alternatively, target potentialy harmfull bacteria

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Abstract 505: A Prospective Randomized Double Blind Phase 3 Clinical Trial of Anti- T Lymphocyte Globulin (ATLG) to Assess Impact on Chronic Graft-Versus-Host Disease (cGVHD) Free Survival in Patients Undergoing HLA Matched Unrelated Myeloablative Hematopoietic Cell Transplantation (HCT). Soiffer et al.

- Trial design and Eligibility
 - Design:
 - Placebo controlled double blind randomized trial
 - ATG (n=128) versus placebo (n=132)
 - In addition to standard tacro/Mtx GVHD prophylaxis
 - ATG dose: 20 mg/kg iv on Days -3, -2, -1
 - Eligibility:
 - Patients 18-65 ys with ALL/AML in remission or MDS (<10% blasts) undergoing MA 8/8 matched UD allo-HCT

Engraftment, Infusion reactions, Viral infections

	ATG (n=128)	Placebo (n=132)	р
Graft failure	3.4%	0.8%	0.029
Engraftment ANC>500 Plt > 30000 Day30 ANC recovery Day 100 Plt recovery	24 (5-45) 28 (6-205) 85% (77-90) 79% (71-86)	19 (8-41) 19 (5-45) 95% (89-97) 94% (88-97)	P<0.001 P<0.001 P<0.001 P<0.001
CMV reactivation	32%	28%	
EBV PTLD	1.6%	0%	

Chronic GVHD

Mod-severe cGVHD





ATLG 16% vs placebo 38%, p<0.00002

ATG 12% vs placebo 33%, p<0.000007

NRM

Relapse









OS



Abstract 666: The Use of Anti-Thymocyte Globulin Is Associated with Increased Chance of Survival Free from Relapse and Graft-Versus-Host Disease after Allogeneic Peripheral Blood Stem Cell Transplantation for Adults with Philadelphia-Negative Acute Lymphoblastic Leukemia: An Analysis By the Acute Leukemia Working Party of the EBMT.

Giebel et al.

- Design:
 - 682 ALL patients in CR 1
 - between 1997-2014
 - PBSC
 - MA 81%
 - 339 sibling, 343 8/8 UD
 - ATG used in 22% of siblings, 78% of UD

Multivariate analysis - Use of ATG associated with:

- Reduced risk of grade II-IV aGVHD (HR=0,64, p=0.007)
- Reduced risk of grade III-IV aGVHD (HR=0;52, p=0;03)
- Reduced risk of overall cGVHD (HR=0.61, p=0.001)
- Reduced risk of extensive cGVHD (HR=0.4, p<0.0001)
- No effect on relapse (p=0.27), LFS (p=0.7) and OS (p=0.16)
- Increased GRFS (HR=0.74, p=0.009)

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Abstract 506: Sirolimus Combined with Mycophenolate Mofetil (MMF) and Cyclosporine (CSP) Significantly Improves Prevention of Acute Graft-Versus-Host-Disease (GVHD) after Unrelated Hematopoietic Cell Transplantation (HCT): Results from a Phase III Randomized Multi-Center Trial

Sandmaier et al



Grade II-IV aGVHD



Grade III-IV aGVHD

cGVHD









NRM

Survival

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Abstract 683 Comparison of Peripheral Blood Stem Cells (PBSC) to Bone Marrow (BM) for T-Replete HLA-Haploidentical Donor Transplantation Using Post-Transplant Cyclophosphamide.

Bashey et al.

- Selection criteria:
 - First allogeneic HCT (Haplo-HCT with ptCy), US
 - 2009-2014
 - AML, ALL, MDS, NHL, HL
 - Myeloablative and RIC
 - GVHD prophylaxis: post-transplant Cy + CNI + MMF
 - N=671 eligible
 - BM (n=481) and PBSC (n=190)



Chronic Graft vs. Host Disease Adjusted for age and performance score



Non-relapse Mortality Adjusted for age, regimen intensity, CMV serostatus







Overall Survival Adjusted for age, disease risk index, CMV serostatus



Abstract 1165 Use of Bone Marrow or Peripheral Blood Stem Cell Grafts in Non T Cell Depleted Haploidentical Transplants Using Post-Transplant Cyclophosphamide, an ALWP-EBMT Analysis. Ruggeri et al.

- Design:
 - Retrospective registry-based
 - 451 patients
 - BM in 260 pts, PBSC in 191
 - MAC in 61% of patients receiving BM versus in 49% of PBSC pts
 - GVHD prophylaxis: CNI + MMF + Cy

Multivariate analysis – PB associated with:

- Increased grade II-IV aGVHD (HR=2.2, p=005)
- No association with:
 - Grade III-IV aGVHD (HR=2.5, p=0.07)
 - cGVHD (HR=1, p=0.88)
 - Relapse (HR 0.7, p=0.21)
 - NRM (HR 0.80, p=0.4)
 - GRFS (HR 0.90, p=0.56)
 - LFS (HR 0.73, p=0.08)
 - OS (HR 0.79, p=0.23)

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Abstract 1170 Current Graft-Versus-Host Disease (GVHD), Relapse-Free Survival – a Novel, Dynamic Composite Endpoint to Better Define Effectiveness Following Allogenic Hematopoietic Cell Transplantation. Solomon et al.

New statistical method to determinate the probability of being alive, in remission and without moderatesevere cGVHD

- Death and relapse = terminal event
- cGVHD= dynamic event
- Grade 3-4 aGVHD not included

Gain in GRFS due to the treatment of cGVHD as a dynamic event



Take home messages

- Age is no longer a CI to transplantation but GA mandatory
- Gut GVHD: importance of microbiota and intestinal cells and we can impact with food or antibiotics
- ATG still controversial: reduction in aGVHD, cGVHD but decrease DFS and OS? (Soiffer). Increased GRFS in EBMT study
- Addition of sirolimus to CSP-MMF in minitransplant decrease aGVHD and TRM and increase OS
- Haplo: use of BM decrease acute and chronic GVHD but concern about relapse in myeloablative conditioning
- New **GRFS** as a new endpoint

Thank you for your attention!