Monday, March 27th

16:30-18:00

Oral 7: GVHD (preclinical)

Impact of HLA disparity on GVHD and relapse rate in haploidentical transplants followed by high dose post-transplant cyclophosphamide

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Abstract

Background: By definition “haplo-identical” donor shares genotipically 4/8 antigens with recipient. However because of casual phenotypical homozygosity in the not shared-haplotype in a few couples donor/recipient the degree of disparity is less than standard 4/8 antigens. Aim of the study: In Genoa patients without a HLA identical donor were transplanted from a haplo-identical donor since 2011. This large, single center series offered the opportunity to verify: 1) the effective numbers of antigen disparity between donor and recipient 2) the impact of inferior HLA disparity on outcome parameters. Patients and methods. All haplotransplants performed from August 2010 (n =282) were included in the study. All patients received a myeloablative regimen (MA) followed by unmanipulated BM, and high dose post-transplant cyclophosphamide (PT-CY), combined with cyclosporine and mycophenolate. Donors and recipients were typed, until 31 December 2015, using DNA method (SSO and SBT) for HLA A, B, C, DRB1, DQ and DPB at a high resolution level, as defined by EFI standards and by NGS at allelic level in 2016 for the same loci. When applicable (72,3% of patients) members of the immediate family where typed to definitively establish HLA genotype and haplotype identity. Parameters analyzed were: cumulative incidence of grade II-IV acute GVHD, moderate-severe chronic GVHD, relapse rate and their statistical correlation with real degree of HLA disparity. For this purpose differences for locus A, B, C DRB1 in GVHD “vector” were evaluated. Acute GVHD incidence was calculated at day 100, the other parameters were calculated at the third year of follow up, all by the method of Kaplan and Meier. Differences were analyzed with the log-rank test. Results: Median age of the 283 patient was 48 years (17-74). Diseases were: acute myeloid leukemia: 111, acute lymphoblastic leukemia:56, lymphoproliferative disorders: 41, chronic myeloproliferative diseases: 43 and myelodysplastic syndrome: 31. At transplant time 137 patients were (49%) in advanced phase of disease. With regards to real numbers of mismatched in GVHD “vector” differences (donor versus recipient), among 282 couples: 145 (51%) showed as expected 4 over 8 antigens difference, 86 (30%): 3/8, 33 (11%): 2/8, 9 (3%): 1/8, and no difference: 9 (3%), respectively. For analyses patient population was divided into two groups: 0-1-2 antigens difference (n=49) versus 3-4 antigens difference (n= 233). With the same criteria 236 chronic GVHD evaluable patients were evaluated: 35 (0,1,2 differences) and 201 (3,4 differences). With median follow up of 562 days (range 6-2241 days) overall survival and disease free survival were 55,7% and 47% respectively. The cumulative incidence of grade II-IV aGVHD was 17% (n=49). Cumulative incidence of moderate -- severe cGVHD was 13% (n=39). Ninety-one patients (32%) relapsed. No significant association was found between the number of HLA mismatches and risk of aGVHD grade II-IV (p=ns) and cGVHD (p=ns) (Fig 1). More mismatching also had no effect on relapse rate (p=ns) (Fig 2). Same results are obtained if the analysis is performed only on patients in complete remission at transplant. Conclusions This study shows: 1) about half of HAPLO donor recipient pairs, differ for less than 4/8 HLA antigens. 2) In the setting of a MA conditioning , with PT-CY HLA matching or mismatching had no effect on aGVHD, cGVHD and relapse rate.
Chronic GVHD: green line 3-4 antigens differences 201 patients
blue line: 0-1-2 antigens differences 35 patients

Disclosure of conflict of interest

None
IL-22+γδT17 as the core of cellular crosstalk networks in intestinal acute graft-versus-host disease

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Abstract

Introduction: Acute graft-versus-host disease (aGVHD) is the major complication and cause of mortality after allogeneic hematopoietic stem cell transplantation (allo-HSCT), in which the intestine is a particularly serious organ leading to significant morbidity and poor prognosis. Interleukin-17 (IL-17) producing γδT (γδT17) cells plays an important role in intestinal regeneration during injury, while it has both protective and inflammatory properties and its mechanism is unclear. The aim of this study is to explore the role of γδT17 cells in the intestine during aGVHD. Material (or patients) and Methods: Lethally irradiated host BALB/c(H-2kb) mouse were injected with T cell depleted bone marrow (non-aGVHD group) plus splenic T cells (aGVHD group) from C57BL/6 mice (H-2kd). The intestine were cut and digested into single cells and mononuclear cells from lamina propria were isolated by centrifugation on a Percoll gradient. γδT cells were sorted by Microbeads and then single-cell gene profiling was performed using BioMark 96.96 Dynamic Arrays (Fluidigm) as described in the manufacturer’s protocol. Phenotypic analysis was performed by Flow Cytometry. Results: Single-cell gene profiling reveals higher expression of epithelium-reconstruction-related genes, including Il17a, Il17ra, Il17rc and Ocnn.(Figure 1) In the early phrase the proportion of γδT17 cells in the intestine from aGVHD group is lower than that from non-aGVHD group (5.9% v.s. 35.3%, p=0.0001), while in the late phrase γδT17 cells proportion from aGVHD group is higher than that from non-aGVHD group (44.5% v.s. 33.6%, p=0.0068). Interestingly, there are more IL-22+ γδT17 cells in non-GVHD group than in aGVHD group. After improving the ratio of IL-22+ cells in donor γδT cells in transplantation, we observed greater survival in the higher IL-22 group compared with normal aGVHD group.(Figure 2) Moreover, Myeloid-Derived Suppressor Cells (MDSCs) changes in consistent with IL-22+γδT17 cells and Innate Lymphoid Cells (ILCs) decrease during aGVHD, and IL-22+γδT17 can also secret GM-CSF to recruit MDSCs. Conclusion: IL-22+γδT17 cells is the key and specific cellular group contributing to the protective property in intestinal aGVHD. IL-22+γδT17 cells may support the survival of Intestinal Stem Cells (ISCs) and promote Epithelial regeneration via secreting IL-22 in place of ILC3. Meanwhile, they can also recruit MDSCs to negatively regulate the immune system and reducing intestinal damage.
Disclosure of conflict of interest

None declared
Oral Syk inhibitor, Entospletinib (GS-9973), controls disease and enhances survival in a mouse model of chronic graft-versus-host disease (cGVHD)

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Abstract

Introduction. Chronic graft-versus-host disease (cGVHD) is a major complication of hematopoietic stem cell transplantation (HCT). The tyrosine kinase Syk is required for B cell hyper-responsiveness in cGVHD patients (1, 2) and for cGVHD development in mice (2). Syk inhibition in vivo also reduces established lung pathology in a cGVHD model of bronchiolitis obliterans (2). Whether Syk blockade early after HCT attenuates cGVHD development and affords immune recovery is unknown. In this study entospletinib (ENTO), a specific oral Syk inhibitor (3), was administered early after HCT in a mouse model of cGVHD to test these possibilities. Materials and Methods. Lethally-irradiated (8.5 Gy) BALB/c recipient mice (n=10 per treatment group) were transplanted i.v. with 1 x 10⁷ T cell-depleted C57BL/6 bone marrow cells alone (Control), or with 1 x 10⁷ T cell-depleted C57BL/6 bone marrow cells plus 1 x 10⁶ C57BL/6 splenocytes (cGVHD). 12 days post-transplant, recipient mice were started on chow formulated with ENTO at a concentration of 0.06% or 0.02%, or with placebo. Pharmacokinetic (PK) studies to assess plasma ENTO concentrations were performed 7 days after ENTO initiation to estimate Syk target coverage. Mice were evaluated over time for weight loss, eye pathology†, alopecia†, lymphocyte reconstitution (by flow cytometry), immunohistochemistry, and survival.

†Measurements were performed by a masked investigator. P-values were determined by unpaired, two-tailed Mann-Whitney test. Duke University IACUC approved all studies. Results. PK analysis revealed dose-dependent plasma ENTO concentrations based on diet, with Syk target pharmacodynamics (PD) coverage of P high/P average = 85%/66% for the 0.06% dose and 62%/32% for the 0.02% dose. cGVHD mice receiving ENTO at either dose developed dramatically reduced clinical eye symptoms (Figure 1 and data to be shown), including chemosis (P < 0.001), conjunctiva redness (P < 0.001), eyelid edema (P < 0.001) blepharitis (P < 0.001), and mucoid discharge (P < 0.001). cGVHD mice receiving placebo developed severe total body alopecia, while alopecia was nearly absent in the ENTO cGVHD groups (P < 0.001). Survival of cGVHD mice in both ENTO groups was significantly improved vs. placebo (70% alive in each ENTO group through day 72, compared to 20% alive in the placebo group). Lymphocytes reconstituted to a greater degree in each ENTO cGVHD group relative to the placebo cGVHD group (P < 0.01 for B cells, P < 0.05 for T cells), supporting the hypothesis that specific inhibition of Syk activity affords recovery of immune homeostasis after HCT. Figure 1. ENTO improves clinical eye scores in cGVHD mice. (A) Representative mice from the cGVHD groups on day 33 post-HCT. (B) Eye chemosis scores for all HCT groups 4 weeks post-HCT performed in a masked fashion by Duke Eye Center investigators. Age-matched normal BALB/c mice were included as reference healthy controls. ***, P < 0.001; *, P < 0.05.

Conclusions. Oral ENTO administration early after HCT in mice ameliorated clinical manifestations of cGVHD, enhanced survival, and improved immune cell recovery. These data support the potential for oral ENTO in the treatment of cGVHD patients. Phase II clinical trials are currently underway (ClinicalTrials.gov identifier: NCT02701634).

References

A. cGVHD model

Placebo  ENTO 0.02%  ENTO 0.06%

B. Chemosis

Control HCT  cGVHD model

Disclosure of conflict of interest

Azacytidine prevents experimental xenogeneic graft-versus-host disease without abrogating graft-versus-leukemia effects

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Abstract

Introduction: The demethylating agent 5-azacytidine (AZA) has proven its efficacy as treatment for myelodysplastic syndrome and acute myeloid leukemia. In addition, AZA can demethylate FOXP3 intron 1 (FOXP3i1) leading to the generation of regulatory T cells (Tregs). Here, we investigated the impact of AZA on xenogeneic graft-versus-host disease (xGVHD) and graft-versus-leukemia (GVL) effects in a humanized murine model of transplantation, and described the impact of the drug on human T cells in vivo. Material and methods: In order to induce xGVHD, human peripheral blood mononuclear cells (huPBMC) were administered intravenously in NOD-scid IL-2Rnull (NSG) mice. Mice were treated or not with AZA 5mg/kg s.c. every 48h and were either monitored for survival and xGVHD score or were sacrificed at day 28 to perform various analyzes (flow cytometry, RT-qPCR, ELISA, ...). For GVL assessment, NSG or NSG-HLA-A2/HHD mice were transplanted with 3x10^6 THP-1 cells, transfected to express luciferase, and/or 20x10^6 human PBMCs and were treated or not with AZA. Imaging of luciferase-generated bioluminescence was performed at indicated time points. Results: AZA improved both survival and xGVHD scores. Further, AZA significantly decreased human T-cell proliferation as well as IFN-γ and TNF-α serum levels, and reduced the expression of GRANZYM E B and PERFORIN 1 by cytotoxic T cells. In addition, AZA significantly increased the frequency of Tregs through hypomethylation of FOXP3i1 as well as through increasing their proliferation, assessed by KI67 expression. This increased proliferation was subsequent to higher STAT5 signaling in Tregs, which resulted from a higher secretion of IL-2 by conventional T cells, induced by demethylation of IL-2 gene promoter by AZA. Interestingly, among AZA-treated mice surviving the acute phase of xGVHD, there was an inverse correlation between the frequency of Tregs and signs of chronic GVHD. Tregs harvested from AZA-treated mice were suppressive and stable over time since they persisted at high frequency in secondary transplant experiments. Finally, we found that graft-versus-leukemia (GVL) effects were not abrogated by AZA as mice having received THP-1 cells + AZA presented a higher tumor burden than mice having received THP-1 cells + PBMCs + AZA (figure 1). Figure 1. AZA do not abrogate GVL effects. NSG-HLA-A2/HHD mice were transplanted with THP-1-luciferase cells alone or in combination with human PBMC and were administered or not with Azacytidine (AZA). Bioluminescence imaging was performed at day 28 post transplantation and showed a complete eradication of THP-1 cells by AZA. Conclusions: The present study shows that AZA successfully mitigates GVHD without abrogating GVL effects and suggest that AZA promotes Tregs not only through demethylation of FOXP3i1 but also through increasing indirectly their proliferation. Our findings could serve of basis of further studies of GVHD prevention by AZA in acute myeloid leukemia patients offered an allogeneic transplantation.

Disclosure of conflict of interest

None
Safety and Efficacy of Placenta derived Decidua Stroma cells in experimental studies and in clinical settings

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Abstract

Safety and efficacy of placenta derived decidua stroma cells in experimental studies and clinical settings We introduced bone marrow derived mesenchymal stromal cells (BM-MSCs) as novel therapy for acute GVHD. Not all patients responded to MSC therapy and some of them died due to invasive fungal infection. Decidua stromal cells (DSCs) are isolated from the fetal membrane and showed stronger immunosuppression compared to other MSCs. Toxicity was investigated in Balb/c mice. Human DSCs were infused IV in doses of 4, 20 and 40×10^6/kg. None of the animals died or showed acute toxicity or adverse reaction related to cell infusion both in short (+3 day) and long (+30 day) follow up. Blood biochemistry profiles related to liver, kidney, heart and blood were not influenced by DSC infusion. Coagulation factors as well as inflammatory indices were not affected. We also applied DSCs to treat GVHD in a full MHC mismatched model (B6 to Balb/c). Recipient mice were conditioned with 950cGy TBI and received DSCs. All mice receiving 40x10^6 DSC/kg died from pulmonary embolism. However, those receiving lower doses had a lower GVHD score and a better weight compared to controls. We also evaluated stromal cell infusion on fungal infection in a pig model of septicemia. Pigs tolerated 1×10^6/kg DSCs or BM-MSCs well with no side effects and no enhanced risk of candida septicemia. In clinical settings, patients were treated with DSCs for severe acute GVHD (n=40), hemorrhagic cystitis (11), chronic GVHD (4), polyneuropathies (2), ARDS (1). Median dose was 1,5 (0,7-2,8)×10^6/kg, given from 1 up to 15 doses. DSCs were well tolerated and only three patients had transient infusion related toxicity. Adverse events using DSC were similar to retrospective controls, but with less death from acute GVHD. One-year survival for severe acute GVHD using DSCs was 76%, which was similar to 78% in all patients (n=453) undergoing HSCT during 2010-2015. We conclude that DSCs is a promising therapy for acute GVHD and toxicity/inflammation after allogeneic stem cell transplantation with almost no side effects.

Disclosure of conflict of interest

None
METABOLIC SERUM PROFILES AND CHRONIC GRAFT VERSUS HOST DISEASE AMONG PATIENTS RECEIVING ALLOGENEIC STEM CELL TRANSPLANTATION

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Abstract

INTRODUCTION Metabolic regulation is important for immune reconstitution, and the aims of the present study were to investigate serum metabolic profile among patients one year after transplantation, and comparing patients with and without cGVHD. PATIENTS AND METHODS The study included 51 consecutively allotransplanted adult patients (29 men and 22 women; median age 44 years, range 16-69) transplanted with peripheral blood stem cells derived from HLA-matched family donors. Majority of patients received GVHD prophylaxis with cyclosporine A and methotrexate. All samples were collected one year after the allo-HSCT (median 358 days), and global metabolomic profiling analysis in serum were investigated. RESULTS 31 of the 51 patients (61 %) had signs of cGVHD at the one year post-allo-HSCT control. The affected organ systems were (number of patients); liver/bile duct (23), eyes (15), gastrointestinal tract (14), skin (13), mouth (10), lungs (3) and urogenital tract (1). 67% of the patients used cyclosporine A either as a prophylaxis or treatment for GVHD, and 11 patients (22 %) used systemic steroid therapy as treatment for GVHD. Using the primary groupings of cGVHD and no cGVHD subjects, Random Forrest classification analysis of serum metabolites resulted in 75% accuracy in differentiating the two groups. This indicating difference in serum biochemical profiles between the two groups was quite evident, and cGVHD appeared to have profound impact on the serum metabolome. (i) First, bile acid metabolites contained four of the top 30 ranked metabolites; including glycochenodeoxycholate sulfate, taurocholate, hyocholate and glycohyocholate. All these potential markers of bile acid metabolism were increased among cGVH patients. (ii) The metabolic signatures of inflammation associated with cGVHD were evident. A significant increase in lipid mediators such as 1-linoleoyl-GPC (18:2), 1-oleoyl-GPC (18:1), 1-palmitoleoyl-GPC (16:1)*, 12-HETE and sphingosine was exhibited by cGVH patients. (iii) Changes in phenylalanine and tyrosine metabolism were prominent in cGVH subjects. A significant increase in microbial flora-derived phenyllactate, phenylacetate, 3-(4-hydroxyphenyl) lactate and phenylalanine in serum of cGVH patients could indicate alterations in microbial composition and/or activity in response to cGVHD. (iv) We detected potential evidence of proteolysis and oxidative stress in cGVH subjects. A profound increase in proteolysis markers including was noted in the serum of cGVH patients, indicating accelerated protein catabolism in cGVH patients. Consistent with an oxidative stress phenotype, increased activity of γ-glutamyl cycle, was apparent in cGVH subjects as evidenced by elevations in γ-glutamyl amino acids; e.g. gamma-glutamylglutamate, gamma-glutamylvaline, gamma-glutamylphenylalanine, gamma-glutamyltryptophan and gamma-glutamylthreonine. Similarly, a significant increase in other oxidative stress markers including 2-hydroxypalmitate, alpha-tocopherol, cysteine sulfonic acid and methionine sulfoxide was also observed. (v) Finally we detected an altered complex lipid composition in cGVH subjects. Serum levels of several phospholipids, plasmalogens, lysolipids, lysoplasmodogen and sphingolipids were elevated in cGVH subjects, reflecting elevated membrane breakdown and remodeling activity in cGVH subjects. CONCLUSION The findings in this study suggest cGVH patients may exhibit a unique metabolic signature following allo-HSCT.

Disclosure of conflict of interest

No disclosures
Lymphangiogenesis as therapeutic target during acute GVHD

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Abstract

Introduction Lymph vessels play a crucial role for immune reactions in health and disease. The inhibition of lymphangiogenesis has been used to reduce tumor metastasis and to prevent graft rejections after solid organ transplantation. The role of lymphangiogenesis during allo-HSCT is unknown. Material and Methods We performed HSCTs in different well characterized murine acute GVHD (aGVHD) models using chemotherapy (Bu/Cy) or radiation conditioning. Target organs were immunohistologically stained and analysed for lymph vessel density and T-cell infiltration. Human duodenal biopsies (n=31) and colon biopsies (n=21) without GVHD vs. aGVHD grade III-IV were stained against podoplanin and lymph vessels were counted. To inhibit lymphangiogenesis, allo-HSCT recipients received i.p. injections of anti-VEGFR-3 antibody or control antibody every second day from day 0 until day +16 or till organ harvesting. Target organs were analysed by immunostaining and FACS measurement. For tumor experiments, allo-HSCT recipients were injected with 5x10⁵ tumor cells along with the bone marrow transplant in different models. Quantification was performed with Image J analysis of microscopic image data. The severity of aGVHD was quantified by histology, clinical scoring and mortality. Tumor growth was monitored by bioluminescence imaging and mortality. Results Our results demonstrate that in experimental mouse models aGVHD is associated to increased lymphangiogenesis in colon (Fig. 1A), the mesentery and lymph nodes. Next, we checked human colon and duodenum biopsies by histological analyses. Fig. 1B shows representative pictures of duodenum biopsies without GVHD and aGVHD grade III. Lymph vessel density was significantly increased in biopsies with aGVHD grade III-IV compared to biopsies without GVHD (Fig. 1C). We used the anti-VEGFR-3 antibody mF4-31c1 to inhibit lymphangiogenesis and found that antibody treatment was successful in reducing lymph vessel density in colon (Fig. 1D), the mesentery and peripheral lymph nodes. Further, allo-HSCT recipients treated with mF4-31c1 had significantly lower organ damage, clinical scores and mortality during aGVHD (Fig. 1E). Another effect of anti-VEGFR3 antibody treatment was improved immune reconstitution after allo-HSCT, which is most likely due to reduced bone marrow aGVHD. Finally, we checked the impact of anti-VEGFR-3 treatment on the GVT effect. We found no significant differences in tumor growth and tumor-related mortality after anti-VEGFR3 treatment vs. control antibody treatment indicating preserved GVT activity. Conclusion In summary, we present novel evidence that aGVHD is associated to lymphangiogenesis in intestinal lesions and in lymph nodes. Our data show that anti-VEGFR-3 treatment ameliorates lethal GVHD and identifies the lymphatic vasculature as novel therapeutic target in the setting of allo-HSCT.
Disclosure of conflict of interest

None
Regulatory B cells promote graft-versus-host disease prevention and maintain graft-versus-leukemia activity following allogeneic bone marrow transplantation

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Abstract

INTRODUCTION Prophylaxis and treatment of graft-versus-host disease (GVHD) have been restricted to either functional inactivation of donor T cells using immunosuppressive drugs, or depletion of donor T cells. These strategies might lead to significant toxicities of the immunosuppressants, delayed immune reconstitution, a high rate of opportunistic infections, and increased risk of hematological malignant relapse. Regulatory B cells (Bregs) are involved in the pathogenesis of GVHD. However, whether Bregs can alleviate acute GVHD without compromising graft-versus-leukemia (GVL) effects remains unclear. MATERIAL AND METHODS Here, we evaluated the role of Bregs in acute GVHD and GVL activity in both a mouse model and a clinical cohort study including 74 patients who underwent an allogeneic stem cell transplantation. RESULTS In the acute GVHD mouse model, cotransplantation of Bregs prevents onset through inhibiting Th1 and Th17 differentiation and expanding regulatory T cells. In the GVL mouse model, Bregs contributed to the suppression of acute GVHD but had no adverse effect on GVL activity. In the clinical cohort study, a higher dose of Bregs in allografts was associated with a lower cumulative incidence of acute GVHD but not with increased risk of relapse. CONCLUSION Our data demonstrate that Bregs can prevent acute GVHD and maintain GVL effects and suggest that Bregs have potential as a novel strategy for acute GVHD alleviation.

Figure 1. Injection of Breg ameliorates GVHD

Lethally irradiated BALB/c recipients (8 Gy) were transplanted with 5×10^6 TCD-BM derived from B6 mice (n=11) or with TCD-BM plus spleen T cells (n=14). Breg (3×10^6) was injected i.p. into T cell recipients at the time of transplantation (n=15). (A) The survival of BMT recipients was monitored over time. (B) Recipient mice were assessed every 2 d for clinical severity of GVHD; clinical scores are shown. (C) Histopathology of skin, liver, intestine and colon of BMT recipients 14 d after transplantation (original magnification ×200). Upper panel is TCD-BM + T cells + Breg group, middle panel is TCD-BM + T cells group, and lower panel is TCD-BM group. (D) Pathologic damage in the intestine and colon was assessed using a semiquantitative scoring system, as described in Materials and Methods. Results are representative of three independent experiments. Data are mean±SEM. *p<0.05, **p<0.01.
Disclosure of conflict of interest

The authors declare no conflict of interest