

Workshop



Workshop on Oral, Gastrointestinal and Pulmonary GvHD

November 17 – 18, 2017

**University Hospital Regensburg
Regensburg, Germany**



Abstracts

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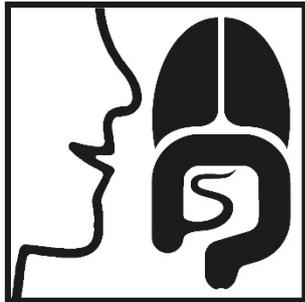
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Abstracts of Invited Lectures

Falk Workshop

WORKSHOP ON ORAL, GASTROINTESTINAL AND PULMONARY GVHD



Regensburg, Germany
November 17 – 18, 2017

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Session I

Pathophysiology of acute and chronic GvHD I

Role of APC's in GvHD

Geoffrey R. Hill

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Graft-versus-host disease (GvHD) results from the interaction of naïve donor T cells with antigen presenting cells (APC) that are presenting host-derived peptides within MHC class I or class II. These APC may be either host (direct antigen presentation) or donor (indirect antigen presentation) in origin. Subsequently, donor CD8 or CD4 T cells are activated and differentiate along various T cell paradigms, either pathogenic (Th1/Th17) or regulatory (Tr1/Treg), depending on concurrent cytokine-dependent cues. We, and others, have demonstrated that recipient APC are the most potent in driving pathogenic GvHD, and depending on whether the dominant response is MHC class I or class II restricted, the important recipient APC are either hematopoietic or non-hematopoietic, respectively. Despite long-standing dogma, it is now clear that recipient dendritic cells (DC) are not required to induce either MHC class I or class II restricted GvHD and in fact attenuate disease. We will now present new data demonstrating the importance of recipient DC subsets in invoking transplant tolerance, at the expense of graft-versus-leukemia. Furthermore, this effect can be augmented by new strategies that prevent GvHD. We have now also isolated the important non-hematopoietic APC that invoke lethal GvHD. In contrast, donor DC act as critical rheostats of GvHD severity and colon-derived CD103+ DC are critical at amplifying the inflammatory cytokine storm that results in lethal acute GvHD of the GI tract. Importantly, a number of therapeutic interventions that interrupt this process are now testable in the clinic.

Effector T cell programs in GvHD

R. Chakraverty

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Acute graft-versus-host disease (GvHD) occurs as a result of a tissue-tropic, pathogenic immune response orchestrated by donor T cells following allogeneic hematopoietic stem cell transplantation. Tissue inflammation frequently emerges despite the concurrent use of immune suppressive agents targeting systemic T cells; early treatment resistance is common and associated with a high risk of mortality. Although pro-inflammatory immune signatures from blood can predict patients likely to develop breakthrough or treatment-resistant acute GvHD, it is currently unclear whether earlier interventions can change the disease course. There is therefore an unmet need to identify targetable pathways that are critical to the initiation and propagation of tissue injury. Following experimental bone marrow transplantation (BMT), allogeneic T cells undergo an initial 3–4 day phase of activation and proliferation in recipient secondary lymphoid organs (SLO), before exit into the blood and subsequent trafficking to peripheral tissues where they are first detectable at day 6–7. Fate mapping of allogeneic T cells in GvHD suggests that early differentiation programs of effector T cells (T_E) are highly plastic leading to a high level of heterogeneity at a population level. Such diversity could potentially arise through either stochastic or instructional mechanisms, the latter reflecting responsiveness to environmental cues. Although most studies have focussed upon how such instructions could impact upon early effector programs in SLO, T_E will also be subject to a distinct repertoire of signals following their recruitment to non-lymphoid tissues. Indeed, recent studies in healthy volunteers have revealed unexpected diversity in the phenotypic and functional properties of T cells isolated from peripheral tissues compared to blood or lymph node, suggesting that effector programs initiated in lymphoid organs can be over-written when T cells are recruited to other sites. Although dynamic interactions in tissues regulate effector responses to commensal flora or are required for specialized memory differentiation, the extent to which peripheral tissues directly re-program T cells for pathogenicity has not been explored in GvHD. To investigate the role of GvHD target organs in shaping pathogenic T cell function, we have used a network biological approach to construct an unbiased, high-resolution spatial map of effector $CD8^+$ T_E differentiation at multiple locations during the evolution of GVHD. We have identified wide variation in effector programs in mice and humans according to location, with effector programs in target organs being highly divergent from those primed in lymph nodes. Furthermore, we have found that evidence of T_E re-programming through mechanisms that are tissue-autonomous and required for pathogenicity. Our data suggest the need for precision targeting of immune pathological processes that are specific to individual target organs.

Innate lymphoid cells in graft-versus-host disease

M.-C. Brueggen

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Only a few years ago, innate lymphoid cells (ILCs) have entered the stage of immune defense. Belonging to the innate immune system, ILCs are an extremely small population; they lack a recombinant antigen recognition receptor but share striking similarities with Th lymphocytes regarding their transcription factor- and cytokine-profiles. Based on these features, ILCs are currently subdivided into three groups. ILCs respond, mostly by cytokine production to different, often epithelial cell-derived mediators (e.g. IL1 β , TSLP). This function contrasts with the mounting of an antigen-specific (adaptive) immune response by T cells. If, and whether yes, which type(s) of innate antigen recognition receptors ILCs express/use, remains to be clarified. Recent evidence has pointed towards an involvement of ILCs in the pathogenesis of graft-versus-host disease but a lot remains to be elucidated.

CD4⁺CD25⁺ regulatory T cells in allogeneic stem cell transplantation

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Graft-versus-host disease (GvHD) is a major complication after allogeneic stem cell transplantation (SCT) and induced by donor T cells recognizing major or minor histocompatibility antigens of the recipient. After their activation and expansion, such allo-reactive effector T cells attack typical target organs, such as skin, liver and gut. A main goal of current research in SCT is the separation of beneficial donor T cell effects, such as the graft-versus-leukemia/lymphoma response of donor T cells, from harmful effects, such as severe GvHD. In murine disease models, we and others previously showed that the adoptive transfer of donor CD4⁺CD25⁺ regulatory T cells (Treg) does not induce GvHD after allogeneic SCT, but protects from GvHD otherwise induced by co-transplanted conventional donor T cells. Importantly, donor Treg cells do not completely paralyse donor T cell functions, as their graft-versus leukaemia/lymphoma activity can be maintained in the presence of Treg cells. Thus, the adoptive transfer of CD4⁺CD25⁺ Treg cells seems an attractive strategy for the prevention of GvHD after allogeneic SCT and has been tested successfully in first clinical trials. We now examined the therapeutic efficacy of *in vitro* expanded donor Treg for the treatment of ongoing acute GvHD in murine models. Donor Treg ameliorated aGvHD after haploidentical BMT, improved survival of GvHD mice, fostered immune reconstitution as well as tissue repair, particularly within the gastrointestinal tract. Strategies and preliminary findings from the efforts to translate these findings into clinical trials will be presented.

Session II

Pathophysiology of acute and chronic GvHD II

The role of B cells in chronic GvHD

Thomas Winkler

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Chronic GvHD (cGvHD) remains the leading cause of nonrelapse morbidity and mortality in survivors of allogeneic hematopoietic stem cell transplantation (allo-HSCT). A substantial dysregulation of the B cell compartment has been described over the last 10 years. The anti-CD20 antibody rituximab was tested in a series of clinical studies for efficacy in treating cGvHD, with clinical response rates between 50 and 70% in patients with steroid-refractory cGvHD. These results provide evidence for the involvement of B cells in the etiopathogenesis and/or the perpetuation of cGvHD, but the mechanisms how B cells contribute are entirely unclear. In addition, the incomplete response in a large fraction of patients remains unexplained.

One obvious pathogenic role of B cells might be mediated by antibody-mediated effector functions. The presence of antibodies against Y chromosome-encoded histocompatibility antigens (H-Y antigens) in sex-mismatched allogeneic transplantation and the correlation with cGvHD would support this notion. However, these allo-antibodies that could also be viewed as auto-antibodies are found infrequently and the role in pathogenesis beyond some diagnostic value is unclear. Other potential functions of B cells in the etiopathogenesis of cGvHD include antigen-presentation, regulation of the cellular immune response and cytokine production. Dysregulations in these functions will be discussed.

Our own preliminary data obtained from detailed immunophenotyping of lymphocyte subpopulations after allo-HSCT revealed clearly elevated frequencies of antibody-secreting plasmablasts in patients with moderate and severe cGvHD. This expansion of plasmablasts is often accompanied by the expansion of another B cell subpopulation with low CD21 expression distinct from immature B cells and plasmablasts. Although the origin and function of these CD21^{low} B cells is not entirely clear, some evidence suggests a chronic activation by antigen and TLR ligands. In a first attempt to understand the origin of the elevated frequencies of plasmablasts CD38^{hi}CD27^{hi} plasmablasts from a series of patients with cGvHD were sorted to perform repertoire analysis by next generation sequencing (NGS). Preliminary results reveal a striking oligoclonality and somatic mutations suggest an antigen-driven origin presumably in germinal centers.

Our findings will be discussed in the context of currently discussed models about the role of B cells in cGvHD.

Innate immunity

Robert Zeiser

Section for Tumor Immunology, Department of Hematology, Oncology and Stem Cell Transplantation, University of Freiburg, Germany

Despite major advances in recent years, graft-versus-host disease (GvHD) remains a major life-threatening complication of allogeneic hematopoietic cell transplantation (allo-HCT). To improve our therapeutic armory against GvHD preclinical evidence is most frequently generated in mouse and large animal models of GvHD. However as every model has shortcomings it is important to understand how predictive the different models are and why certain findings in these models could not be translated into the clinic. Weaknesses of the animal GvHD models include the irradiation only-based conditioning regimen, the homogenous donor/recipient genetics in mice, canine or non-human primates (NHP), anatomic site of T cells used for transfer in mice, the homogenous microbial environment in mice housed under SPF conditions and the lack of pharmacological GvHD prevention in control groups. Despite these major differences towards clinical allo-HCT, findings generated in animal models of GvHD have led to the current gold standards for GvHD prophylaxis and therapy. The homogenous nature of the pre-clinical models allows for reproducibility, key for the characterization of the role of a new cytokine, chemokine, transcription factor, microRNA, kinase or immune cell population in the context of GvHD. Therefore when carefully balancing reasons to apply small and large animal models it becomes evident that they are valuable tools to generate pre-clinical hypotheses which then have to be rigorously evaluated in the clinical setting.

Role of antimicrobial peptides and Paneth cells

James L.M. Ferrara

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Regenerating islet-derived 3 (Reg3 γ), a Paneth cell antimicrobial peptide, is an important biomarker of gastrointestinal (GI) graft-versus-host disease (GvHD) but its mechanistic role in GvHD is not known. Paneth cells decrease during severe GvHD in both clinical and experimental BMT, and therefore we evaluated whether the loss of Reg3 γ would amplify GvHD severity. We have performed extensive experiments correlating Reg3 production in human and experimental BMT samples. In several mouse models IL-22, the principle inducer of Reg3 γ , decreased prior to loss of Reg3 γ during GvHD and injections of IL-22 reversed ongoing GvHD. We next compared GvHD in wild type and Reg3 γ deficient recipients and observed that treatment of mice with IL-22 prevented GvHD mortality in wildtype but not in Reg3 γ deficient mice, where GvHD mortality was more rapid. Analysis of the GI tract showed that IL-22 treatment dramatically decreased infiltration of both IFN γ + and IL-17A+ effector CD4+ and CD8+ T cells in wildtype mice but not in Reg3 γ deficient mice. We evaluated the mechanisms of Reg3 γ protection of GI crypt using mice whose Lgr5+ intestinal stem cells (ISCs), known targets of GvHD, produce green fluorescent protein and thus allowed their quantification by FACS. IL-22 decreased the dramatic loss of ISCs caused by GvHD in wildtype mice but did not change the even greater loss of ISCs in Reg3 γ deficient mice. We next measured proliferation and apoptosis of ISCs by EdU marking and Annexin V staining, respectively. GvHD dramatically increased the proliferation of ISCs all mice, independently of the production of Reg3 γ . IL-22 treatment prevented apoptosis, however, only in wildtype mice. As a result, the number of ISCs correlated directly with Reg3 γ production after BMT, confirming its role as an ISC survival factor. In conclusion, we have discovered a novel and unexpected function for Reg3 γ , an important biomarker of GI GvHD. In addition to its well-defined antimicrobial properties, Reg3 γ is therefore a key survival protein for ISCs and implications for novel strategies to GvHD prevention and treatment will be discussed.

Pathophysiology of intestinal tolerance

Pavan R. Reddy

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Allogeneic hematopoietic stem cell transplantation is potentially curative therapy for many malignant diseases whose applicability has been impeded by the development of its most serious complication, graft-versus-host disease (GvHD). GvHD results from the damage caused to the host epithelial cell targets by the many immune cells and inflammatory cytokines. The primary mortality from GvHD results from its impact on the gastrointestinal (GI) tissues. While significant progress is being made in understanding the complex role of various immune cells in causing GvHD, little is known about the role played by the target tissues themselves in regulating the severity of disease. Specifically, induction of host intestinal epithelial cell (IEC) apoptosis by the alloreactive donor T cells and inflammatory cytokines causes GI GvHD; but the IEC intrinsic resilience mechanisms against allo-immune T-cell mediated damage, the epigenetic mechanisms that are critical for these mechanisms, and their regulation by the tissue resident microflora generated metabolites remains poorly understood. IEC homeostasis and resistance depends on complex interactions between the metabolic energy substrates (such as short chain fatty acids and amino acid metabolites) and the regulation of transcription and epigenetic chromatin modifications such as histone acetylation. The significant alterations in substrates that are derived from microbial metabolites, specifically the essential short chain fatty acids (SCFA) such as butyrate and its impact on the resilience of GI tract against allo-T cell mediated damage will be presented. The mechanisms of butyrate mediate GI effects in GvHD, specifically the role of surface GPCR receptors will be addressed. Lastly, clinical strategies that could be developed from this experimental data will be presented.

Session III

Lung GvHD

Pathophysiology of lung GvHD

G.C. Hildebrandt

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Allogeneic hematopoietic cell transplantation (allo-HCT) is a potentially curative treatment option for a variety of hematological malignancies. One of the major toxicities occurring later after allo-HCT is the development BOS/BO and restrictive lung injury, the former generally accepted and the latter possibly considered as manifestations of chronic graft versus host disease. The pathophysiology of lung GvHD is not entirely understood, although substantial progress has been made over the last few years. We will review data on the role of anti-inflammatory approaches on BOS/BO development and on novel strategies to target fibrosis. T cell subpopulations involved in lung GvHD development have been recently reported and the role of the epithelium in protecting from BO/BOS becomes more evident.

As alloreactive T cells have been reported to undergo metabolic reprogramming during GvHD development, and similar to gut microbiota and its local immune system, the lung microbiota can exert inflammatory or anti-inflammatory influences on immune cells and we will discuss preliminary data on differences observed between syngeneic and allogeneic recipients using a murine BMT model.

Diagnosis of lung GvHD

J. Halter

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A wide variety of pulmonary and extra-pulmonary causes may lead to impaired lung function and dyspnea after allogeneic HCT. Currently the only diagnostic or distinctive lung chronic GvHD is bronchiolitis obliterans syndrome (BOS) or - if biopsy-proven – bronchiolitis obliterans (BO). Mainstays for diagnosis of BOS are pulmonary function test (PFT), lung imaging (especially CT scan) and microbiologic methods to exclude infection, preferentially including sampling by broncho-alveolar lavage.

New NIH consensus diagnostic criteria of BOS by lung function test include for adults a) FEV1/FVC or SVC < 0.7 (whichever is greater), b) FEV1 < 75% of predicted and irreversible with $\geq 10\%$ decline in < 2y as well as c) absence of infection and d) either a preexisting diagnosis of cGvHD or one of 2 supporting features of BOS, that are evidence of air trapping by expiratory CT, small airway thickening or bronchiectasis or evidence of air trapping in PFT by RV > 120% or RV/TLC > 90% confidence interval. By comparison with histology from open lung biopsy a number of patients fulfilling the BOS criteria by lung function can be identified that show other histologic changes than classic BO. Furthermore some patients with histology-proven BO do not fulfill the lung function test criteria. Simultaneously presence of interstitial fibrosis and infection are two reasons.

Nevertheless, these consensus criteria clearly represent an important step forward for standardized diagnosis of lung GvHD. But since BOS is a small airway disease none of these tests is very sensitive for early detection nor specific. Because the beginning of lung cGvHD is stealthy repeated testing is necessary to follow the individual's FEV1 slope or trajectory. Handheld spirometry may provide an alternative to classic plethysmography but optimal frequency and time points for monitoring need to be defined. New promising methods include Nitrogen (N₂) washout by single or multiple breaths for early diagnosis of small airway disease and follow up of patients with established BOS. Parametric response mapping (PRM) based on computed tomography may improve diagnosis and especially monitoring for progression of established BOS. Both methods are resource-intensive and need to be further validated.

Elevated levels of CD19⁺CD21^{low} B cells, matrix metalloproteinase 3 (MMP3) and plasma osteopontin are examples of candidates for BOS biomarkers that have been identified in patients after allogeneic HCT. Further testing of their predictive and discriminatory value together with a number of other markers identified in the blood or bronchial fluid of lung transplant patients may change the diagnostic approach for BOS in the future fundamentally.

Treatment of lung GvHD

Steven Z. Pavletic

National Cancer Institute, NIH, Bethesda, Maryland, USA

Bronchiolitis obliterans syndrome (BOS), a manifestation of chronic graft-versus-host disease, remains a serious and an increasing problem after allogeneic HSCT. The exact pathogenesis still remains unclear what prevents more effective interventions. BOS is also frequently under diagnosed or too late recognized in the clinical setting. Once respiratory symptoms appear, most allo-HSCT recipients show already severe airflow obstruction. The prognosis of BOS is poor though more recent survival data seem to be improving from historical 15% at 5 years. For diagnosis of BOS 2016 NIH criteria are a contemporary standard. Computerized tomography (CT) scans and pulmonary function testing also play a vital role as well as timely access to sub specialist care. Future advances in the therapy of BOS may need to include development of better early intervention strategies based on identification of reliable early clinical and biological markers of the disease. It would be also important to improve understanding of the biological heterogeneity of this devastating complication after allogeneic HSCT. Very few prospective studies of therapeutic or supportive care interventions have been conducted so far and no phase III randomized controlled trial specifically for BOS has been conducted. Though some improvement has occurred in the past decade in the therapeutic paradigm of BOS, the overall mortality and morbidity remain very high. The ideal treatment would lie in early and accurate early detection or prevention.

Session IV

Oral GvHD

Microbiome in oral chronic GvHD

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School of Dental Medicine University of Zagreb, Croatia

The microbiome is defined as a sum of microorganisms (microbiota) residing in the certain habitat (oral cavity, gut, skin etc.), their genetic information and environment in which they interact. Prerequisite for the maintenance of immunologic homeostasis in epithelial tissue is diverse microbiome. In normal state microbiome remains relatively stable but in disease this stability dramatically changes. Studies of the intestinal microbiome in graft-versus-host disease (GvHD), which have applied advanced genomic technologies, revealed changes in microbiome diversity and kinetics, taxonomic variation and temporal variability. Loss of microbiome diversity, shift toward specific species, depletion of commensal microbiota during the course of allogeneic hematopoietic stem cell transplantation (HSCT) are associated with the development of acute GvHD, infections and higher mortality.

Oral cavity houses the second most diverse and complex microbial community after the gut, harbouring over 700 species of bacteria distributed in diverse oral niches. Studies have shown that oral microbiome is key source for many oral and systemic diseases. However, the role of oral and salivary microbiome in chronic GvHD is still insufficiently researched.

Chronic GvHD is major late complication of allogeneic HSCT which affects oral cavity in up to 80% of patients. Diagnosis of oral cGvHD is established when diagnostic signs of oral lichen planus-like lesions are present. Among distinctive signs of oral GvHD the most prominent are oral ulcers. These lesions are susceptible to increased colonization of oral microbes which may initiate ecological (dysbiotic) shift and cause pathological changes. In the state of host-related perturbations the balance of the species and composition of local microbiota changes. Since some gut bacteria could be found in the oral cavity as well, further studies should disclose interrelationship of the oral and gut microbiom in patient with cGvHD taking into account diversity of the oral niches and modifiable factors driving oral dysbiosis.

This lecture will summarize the current knowledge of the complex roles of the microbiome on. GvHD and present our own results of studies on oral microbiome in patients with chronic GvHD.

Immunosuppressive treatment of oral chronic GvHD

Sharon Elad, D.M.D., M.Sc.

Division of Oral Medicine, Eastman Institute for Oral Health, Rochester, NY, USA

Graft-versus-host disease (cGvHD) may affect several oral tissues, among the most common oral tissue is the mucosa. Since oral cGvHD may cause intense pain, impair eating, disturb speech and reflect on quality of life treatment for the oral manifestations of cGvHD are essential. The goals of oral cGvHD therapy include reduction of symptoms, resolution of painful lesions, prevention of secondary complications and screening for oral cancer.

Immunosuppressive treatment has a fundamental role in the management of oral mucosal cGvHD. While the treatment for oral cGvHD is primarily systemic, topical treatment is beneficial when the oral tissues are the only site of involvement or when the oral cGvHD is resistant for systemic immunosuppressive treatment. The topical immunosuppressive agents for oral cGvHD may be classified into steroids and non-steroids groups. In the recent years a few randomized controlled trials were conducted to assess topical steroids for oral cGvHD. Among the most studied steroids in oral mucosal cGvHD are dexamethasone (as an active control), budesonide, and clobetasol. Reports about the potential of photobiomodulation for oral cGvHD open new horizons, although more research is warranted.

The presentation will review general treatment concepts for oral mucosal cGvHD with topical immunosuppressive agents, current literature about the efficacy of topical immunosuppressive agents for oral mucosal cGvHD, potential adverse effects of topical immunosuppressive, and considerations in customizing the topical preparation for the patient's needs. Likewise, the presentation will address economic aspects of the US health system and how it may influence on the selection of the topical treatment for oral cGvHD.

The scientific evidence and the practical considerations will be combined into a matrix that may be used as a tool for the selection of the best topical immunosuppressive agents for each patient.

Supportive care

E.M. Wagner-Drouet

Department of Medicine III, Johannes Gutenberg-University Mainz, Germany

Oral chronic GvHD is an important long-term complication of allogeneic HSCT. Unfortunately responses to immunomodulation are often partial and patients experience recurrence of the symptoms significantly impairing their quality of life. Individually designed treatment of symptoms is important in addition to the treatment of GvHD. Thus education, primary and secondary prevention of GvHD and infection as well as management of symptoms especially pain, become a major issue.

Good basic oral care is important to minimize inflammation and infections that could trigger oral symptoms. Close cooperation with a dentist or dental surgeon is recommended to improve mucosal irritation or pressure marks caused by dental prosthesis. Mucosal infections mainly caused by candida spec, or herpes viruses should be diagnosed, consequent treatment with local or systemic drugs is indicated.

Hygiene measures including different mouth rinses (alcohol free) may be helpful, but have no proven evidence. Mint flavored toothpaste and whitening products often cause discomfort, toothpaste marked for children or sensitive teeth is better tolerated. Oral care protocols could be helpful.

Artificial saliva and cholinergic agonists (Cevimeline, Pilocarpine) may be beneficial for patients with salivary gland involvement and dry mouth. Pilocarpine treatment may normalize alterations in the composition of saliva and could improve antimicrobial activity. Mouth-drying agents such as tricyclic antidepressants, SSRI, antihistamins should be avoided. Salivary stimulants like sugar free candies or gums could also be beneficial. Two studies also reported better salivary flow rate 12–24 weeks after acupuncture.

Patients should be informed about increased sensitivity to hot, cold, spicy and acidic food or carbonated beverages. Sodium bicarbonate mouthwash may improve taste disturbance.

Painful mucocelles can be treated with Pyralvex.

Growth-factors (Palifermin, Repifermin), radical scavenger (Amifostine), anti-inflammatory rinses (Kamillosan, Prostaglandin E1), L-Glutamin and zinc supplementation, as well as natural agents such as milk proteins (PV701), Aloe vera rinses and Curcumin are reported to be beneficial in some patients.

Session V

GI GvHD

Impact of microbiota in experimental GI GvHD

Marcel R.M. van den Brink

Professor of Medicine and Immunology, Division of Hematologic Oncology, Weill Cornell Medical College, New York, NY, USA

In recent years, it has become clear that the intestinal microbiome can regulate the physiology and pathophysiology of many organs and diseases. The intestinal flora can impact a variety of clinical outcomes after allogeneic hematopoiesis transplantation, especially GvHD. Over the last decade, we have systematically collected stool samples for patients undergoing allogeneic hematopoietic transplantation. Our results thus far in mouse and men have demonstrated that a loss of diversity of the microbial flora increases the risk of lethal graft vs host. In addition, we have found association between changes in the intestinal flora and GvHD relapse and bacterial infections. The major factors that can induce changes in the intestinal flora are the use of antibiotics and changes in diet in the post transplant period. Based upon our results so far, we are developing therapeutic approaches including antibiotic stewardship, probiotics and prebiotics.

Pathophysiology of microbial changes in clinical GvHD

Daniela Weber

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Graft-versus-host disease (GvHD) of the gastrointestinal (GI) tract is still a severe complication in patients undergoing allogeneic stem cell transplantation (ASCT). The development of new techniques like metagenomic sequencing provided deeper insights into the composition of the intestinal microbiome and highlighted the role of microbiota for the pathophysiology of GI GvHD. During the course of ASCT a loss of intestinal microbiome diversity and a shift towards an enteropathogenic flora has been observed. Furthermore, patients with severe disruptions of intestinal microbiota composition and a loss of protective bacteria, e.g. members of the group of Clostridiales, showed a worse outcome and a significantly increased GvHD-related mortality. Commensal bacteria produce metabolites like indole or short chain fatty acids like butyrates that exert a variety of protective and anti-inflammatory effects contributing to intestinal homeostasis and epithelial integrity. A major risk factor for the loss of commensal bacteria is the use of systemic broad spectrum antibiotics for prophylaxis and treatment of neutropenic infections. It has been shown, that both, the kind of antibiotics and also the timing of beginning of antibiotic treatment influences the outcome of patients after ASCT. Antibiotics with efficacy against anaerobic bacteria and also the use of antibiotics with beginning before transplantation resulting in microbiome disruption early after ASCT significantly worsened the outcome of patients post-transplant. But also GI GvHD itself contributes to microbiome changes. In 2013 Levine and colleagues observed a loss of Paneth cells in intestinal biopsies of patients with acute GI GvHD assuming a destruction of these cells by cytotoxic T cells and a consecutively translocation of Reg3 α into the blood. Paneth cells are important for the regulation of intestinal microbiota composition as they produce antimicrobial peptides (AMPs) like α -defensins and Reg3 α . Our results showed a loss of Paneth cells associated with a reduction of AMPs in patients with upper GI tract GvHD which are likely to contribute to further changes of the intestinal microbiome composition. However, also the use of systemic antibiotics and the associated dysbiosis seems to influence the production of AMPs, as we found significantly increased Reg3 α -levels in the serum of patients treated with broad-spectrum antibiotics. These new insights into the role of microbiota in the pathophysiology of acute GI GvHD ignite a rethinking about possible strategies to protect and/or restore intestinal microbiota, e.g. by fecal microbiota transfer, the use of Clostridial-sparing antibiotics and the administration of prebiotics. These new approaches may contribute to prevention and treatment of acute GI GvHD in patients undergoing ASCT.

Microbiota transfer as treatment of GvHD

C. Högenauer

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The intestinal microbiota is essential for maintaining human health, defending against intestinal pathogens and for a normal function of the intestinal immune system. According to recent publications alterations of the intestinal microbiota, which are termed as dysbiosis, seem to be involved in a variety of intestinal inflammatory disease. Dysbiosis is suspected to be involved also in the pathogenesis of intestinal graft-versus-host disease (GvHD) and has some prognostic implications in this disease. Fecal microbiota transplantation (FMT) is a therapeutic intervention aiming on correcting these alterations by delivering fecal microorganisms from a healthy person to the intestines of a patient. Up to now, recurrent *Clostridium difficile* infection is the only indication for FMT supported by solid scientific evidence. The use of FMT for treating *Clostridium difficile* infection in immunocompromised patients has also been shown to be effective and safe. Currently FMT is investigated for a variety of intestinal and extraintestinal diseases. So far small randomized controlled studies showed an efficacy of FMT in inflammatory bowel diseases, especially for chronic active ulcerative colitis, and showed positive results for the eradication of multi-resistant bacteria from the intestine of carriers for these organisms. The published experience for the use of FMT in therapy refractory intestinal GvHD is limited to two small case series, which however show promising results for at least a subgroup of patients. It needs to be mentioned, that FMT in intestinal GvHD is an experimental therapy and should currently be performed only in clinical trials. As there are no large systematic methodological investigations, several questions about techniques, donor screening and selection and especially short and long term safety issues remain.

Diagnosis and treatment of gastrointestinal GvHD

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Early diagnosis and adequate treatment of lower gastrointestinal (GI) graft-versus-host disease (GvHD) are highly relevant as lower GI GvHD is still the most serious and life threatening manifestation of acute GvHD. Clinical symptoms associated with upper (nausea, anorexia) and lower (watery, large volume diarrhea with abdominal cramps, sometimes ileus and bleeding) suggest presence of GI GvHD. Infectious origin needs to be excluded by stool cultures, antigen and PCR assays, and GvHD should be confirmed by endoscopy and biopsy whenever possible. So far, neither radiological approaches (including MRI or contrast enhanced ultrasound) nor biomarkers in serum or stool samples (such as calprotectin) can substitute histological confirmation, although both procedures may be supplementary. While upper GI GvHD can be treated with low dose corticosteroids (1 mg/kg methyl-prednisolone [MP] equivalent) and oral budesonide, lower GI GvHD needs immediate treatment with high dose corticosteroids (2 mg/kg MP-equivalent). Classical approaches to treat steroid-refractory GvHD are TNF-blocking agents or broad monoclonal or polyclonal T cell antibodies as well as extracorporeal photopheresis, but overall the outcome is still poor. Promising new approaches need to be prospectively tested such as JAK1/JAK2 inhibitors, antibodies blocking intestinal integrins, α 1-antitrypsin or cellular therapies with regulatory T cells. However, the concept of waiting for steroid resistance needs clinical reevaluation, and risk adapted first line treatment or supplementary early microbiota modulation may turn out to be more powerful in the future. In addition, supportive treatment including prophylaxis to avoid secondary opportunistic infections in these fragile patients with epithelial barrier damage.

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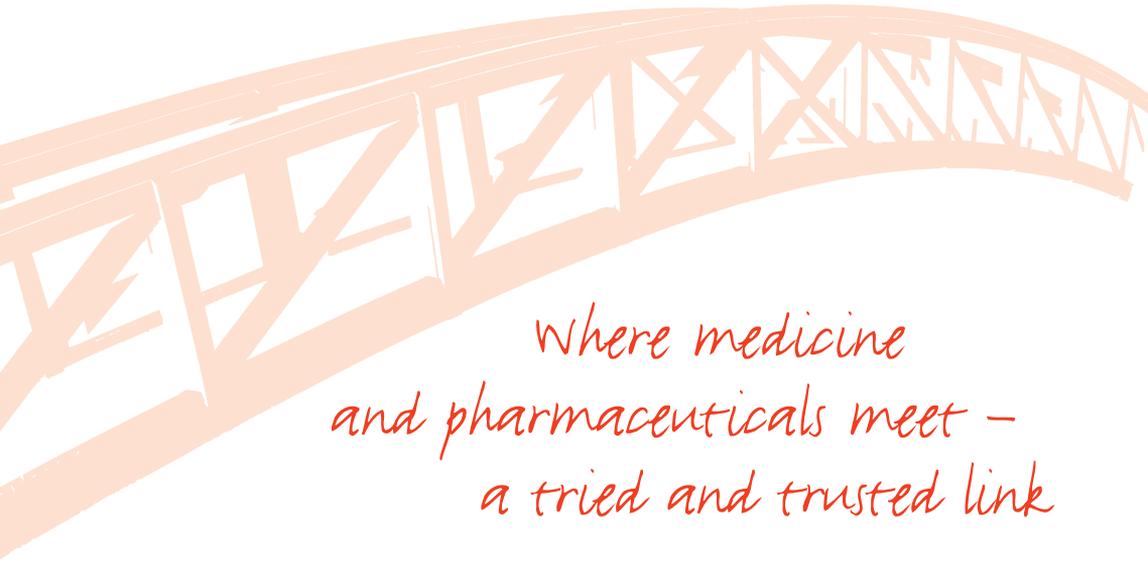
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