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Workshop on Oral cGVHD & Clinical Practice in cGVHD
November 22 – 23, 2013
University Hospital Regensburg
Regensburg, Germany

Abstracts
Abstracts of Invited Lectures

Falk Workshop

WORKSHOP ON ORAL cGVHD & CLINICAL PRACTICE IN cGVHD

Regensburg (Germany)
November 22 – 23, 2013

Scientific Organization:
Regensburg (Germany)
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WORKSHOP ON ORAL cGVHD

Introduction
Pathophysiology of oral cGVHD

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Background: Chronic GVHD (cGVHD) is known as a serious complication for nearly half of allogeneic hematopoietic SCT (HSCT)-recipients. An oral involvement occurs in about 80% of cases with erythema, lichen planus, hyperkeratotic plaques, pseudo-membranes and ulcers. These partially quality of life-reducing symptoms are mimicking autoimmune collagen vascular diseases and the characteristic histologic findings are subepithelial lymphocytic infiltration with epithelial changes in the oral mucosa and diffuse lymphocytic infiltration in the salivary glands. However, the molecular mechanism of the lymphocytic infiltration in cGVHD is still poorly understood.

Methods: The expression of different cytokines, chemokines and chemokine receptors in the oral mucosa of 49 HSCT-recipients with and without oral cGVHD clinically were examined. Furthermore the soluble IgA was measured in these patients and correlated to the clinical findings considering the current immunosuppressive therapy.

Results: We found differences between both patient-groups as well in expression of cytokines and -receptors as in the measured IgA-values.

Conclusions: A more accurate understanding of the molecular mechanism of oral cGVHD should lead to earlier detection of high risk HSCT-recipient. Mainly these patients need the therapeutic interruption of the cytokine network in cGVHD-progression to reduce morbidity on the one hand and to minimize the risk for the development of secondary malignancies on the other.
Salivary proteomics in oral chronic GVHD

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Saliva is a protein-rich oral fluid that provides information about systemic and oral-specific disease and diagnosis. Proteomic technologies are emerging to improve detection of protein components of human saliva for use not only in biomarker discovery, but also for the illumination of pathways involved in oral disease. These include the optimization of liquid chromatography coupled tandem mass spectrometry (LC-MS/MS) and multiplex ELISA analysis of saliva in health and disease. The mucosal alloimmune process of oral chronic graft-versus-host disease (cGVHD) is not clearly understood, and characterization of local immune mediators present at the site of disease, the oral cavity, will increase knowledge of local and systemic immune processes. Initial analysis of saliva from cGVHD patients and healthy controls using LC-MS/MS with isobaric tagging suggests impaired innate immune defenses in the oral cavity, as immune mediators, including cathelicidins, are decreased in oral cGVHD saliva. Other altered immune proteins were found in oral cGVHD saliva including increased S100 family members. Evidence for active tissue remodeling processes was detected in oral cGVHD patient saliva. This presentation will discuss use of salivary proteomics for the illumination of disease processes, and will examine some of the complex clinical and diagnostic issues related to proteomics and biomarker research in cGVHD.
Histopathology of oral cGVHD

M. Imanguli
University of Texas, Southwestern Medical Center, Dallas, TX, USA

Oral mucosa and salivary glands are among the most commonly affected areas in chronic graft-versus-host disease (cGVHD). Microscopic criteria for diagnosis of oral mucosal GVHD include keratinocyte apoptosis, disorganization of the basal layer, exocytosis and predominantly lymphocytic “lichenoid” subepithelial infiltrate. In minor salivary glands ductal and acinar cell apoptosis, periductal lymphocytic infiltration, and small duct destruction leading later to acinar fibrosis and atrophy are characteristic. Recently several advances have been made in elucidation of the composition of the infiltrating immune cell populations in cGVHD. We and others have shown that CD8 cells expressing markers of cytotoxicity (Tia-1 and Granzyme B) predominate in the infiltrate particularly in early and more severe disease. Infiltrating effector-memory type T cells display signs of type I cytokine (Th1) polarization including nuclear transcription factor T-bet, a master regulator of type I program. They express CXCR3 a Th1 chemokine receptor and are likely recruited to affected tissues in response to locally produced interferon inducible chemokines. In addition to affected keratinocytes, infiltrating cells of macrophage/dendritic cell lineage have been shown to produce interferon inducible factors. Finally, recently we performed a detailed analysis of FoxP3+ regulatory T cells in cGVHD and have shown for the first time that: 1. Foxp3+ CD4 T cells in the cGVHD affected tissue is a unique population expressing markers district from effector T cells and 2. FoxP3+ T cells develop or differentiate along the line of Th1 program, a pattern that has been shown essential for effective control of autoimmune inflammation in murine models.
Clinical manifestations and diagnosis of oral cGVHD

Prof. Dr. Sharon Elad
University of Rochester Medical Center, Eastman Institute for Oral Health, Division of Oral Medicine, Rochester, NY, USA

Chronic graft-versus-host disease (cGVHD) affects numerous oral tissues, such as the oral mucosa, the salivary glands and the musculoskeletal tissues. It may be associated with severe symptoms and variable clinical presentation. Oral cGVHD may debilitate the basic oral functions and impact advertently on the quality of life. Secondary oral complications related to the oral cGVHD pose additional risks for the patients. The 2005 National Institutes of Health developed a consensus paper delineating criteria for clinical trials for the diagnosis and activity assessment of oral cGVHD. The clinical presentation of oral cGVHD as well as the practical applications of the NIH criteria will be reviewed.
Immunosuppressive treatment of oral cGVHD
Topical steroids in the treatment of oral cGVHD

Prof. Dr. Sharon Elad
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Topical steroids are a well-recognized treatment in numerous immunologic diseases affecting the oral mucosa, including chronic graft-versus-host disease (cGVHD). The topical steroidal preparations share the same mechanism of action; however, they differ in their anti-inflammatory potential and in their pharmacological properties. This presentation will review various topical steroids used for the management of oral cGVHD and their side effects.
Topical calcineurin inhibitors in oral cGVHD

M.H. Albert
Department of Pediatric Hematology/Oncology, Dr. von Haunersches Kinderspital, Ludwig-Maximilians-University, Munich, Germany

Oral chronic graft-versus-host disease (GVHD) frequently presents in patients with sclerotic features of skin GVHD and is often associated with considerable limitations of oral food intake and decreased quality of life. Systemic tacrolimus is efficacious for prophylaxis and treatment of acute and chronic GVHD and topical tacrolimus has shown activity in chronic GVHD skin lesions.

We therefore initiated a pilot study to investigate the safety and efficacy of topical tacrolimus ointment in children with oral GVHD. Six patients suffering from oral GVHD (five chronic and one acute) were included in the study. Tacrolimus ointment 0.1% was applied twice daily using sterile gauze. The only side-effects observed were a slight burning discomfort after the first application in one patient and after food intake in another patient. Tacrolimus was absorbed systemically in four of six patients. Of six patients, we observed a complete response in two, a very good partial response (VGPR) in two, and a PR in two patients, respectively.

We conclude that topical application of tacrolimus ointment holds promise as a safe and efficacious treatment for oral cGVHD. Experience with the use of other calcineurin inhibitors will also be reviewed.
Ultraviolet phototherapy for management of oral cGVHD

Nathaniel S. Treister
Division of Oral Medicine & Dentistry, Brigham and Women's Hospital, Boston, MA, USA

Oral chronic graft-versus-host disease (cGVHD) is a frequent and potentially disabling complication of allogeneic hematopoietic cell transplantation. While management with topical immunosuppressive agents (e.g. corticosteroids) is generally effective, some patients do not experience adequate response. One novel approach to managing oral cGVHD is the intraoral application of ultraviolet light-based phototherapy. Treatment protocols have been reported using both methoxy-psoralen-activated ultraviolet A (PUVA, n = 4) and broad spectrum ultraviolet B (n = 1), using both commercially available and custom-engineered phototherapy devices. Treatments were provided 2–4 times per week, according to various regimens with and without dose escalations, for up to 3–4 months. Responses were variable but generally favorable, suggestive of clinical response. Mucosal erythema and mild burns were reported in roughly half of the patients in three studies. Limitations include the overall small number of subjects (1–7, 14 total), inconsistent (and often insufficiently described) response criteria, and incomplete clinical data describing concurrent systemic immunosuppression. In order to determine the true safety and efficacy of this potentially beneficial therapy, a well-designed, multi-center study must be conducted, with adequate long-term follow-up to assess for late complications (e.g. secondary malignancies). At present, intraoral phototherapy for management of oral cGVHD should be considered experimental and only provided therapeutically within the context of a clinical trial.
Systemic treatment of oral cGVHD

Hildegard T. Greinix
Department of Internal Medicine I, Medical University of Vienna, Austria

Once diagnosis of chronic graft-versus-host disease (cGVHD) is established according to NIH consensus guidelines, patients’ organ manifestations should be assessed and the severity of functional impairment and patients’ complaints should be evaluated. The oral cavity is one of the most frequent sites of cGVHD involvement. Mild manifestations of cGVHD may be treated with topical immunosuppressive agents and therapy should be continued as long as symptoms are present. In the presence of remission of symptoms topical treatment can be withdrawn. Patients with moderate and severe cGVHD require systemic immunosuppressive therapy. Additional topical treatment can be administered to speed up the response or to improve local response rates but it does not replace the need for systemic immunosuppression. Internationally established standard first-line treatment of cGVHD are corticosteroids at 1 mg/kg/day as has been recommended by the German/Austrian/Swiss consensus conference on clinical practice in cGVHD. Currently, we do not have published data from retrospective or prospective studies available that would allow replacement of first-line corticosteroids by other treatment options. The potential benefit of calcineurin inhibitors (CNIs) in combination with corticosteroids in first-line treatment of cGVHD is less clear since the evidence for its use is scarce. In standard-risk patients defined as de novo or quiescent onset of cGVHD and platelet counts above 100 G/L, the use of CNIs in addition to corticosteroids may be considered for those patients who are at high risk for corticosteroid-related complications. Clinical evidence suggests that both CNIs may be equally effective in this scenario although a direct comparison of cyclosporine A and tacrolimus in the treatment of cGVHD is lacking. Approximately half of the patients with cGVHD respond to first-line treatment and patients with corticosteroid-refractory cGVHD have significant morbidity and a poor prognosis. Second-line treatment of cGVHD is almost solely based on phase II studies or retrospective analyses. Based on the German/Austrian/Swiss consensus conference on clinical practice in cGVHD CNIs as well as immunomodulating strategies including extracorporeal photopheresis (ECP) and inhibitors of the mammalian target of rapamycin (mTOR-I) and cytostatic agents such as mycophenolate mofetil (MMF) are to be used for second-line therapy of cGVHD. ECP has an excellent safety profile and has a well documented steroid-sparing effect. For patients with mucocutaneous manifestations of cGVHD administration of methotrexate, hydroxychloroquine, or clofazime resulted reportedly in improvements. Since viral and fungal infections of the oral mucosa are frequently present in patients with cGVHD, sufficient diagnostic procedures and prophylactic oral hygiene should be performed. In view of the sparse evidence for most immunosuppressive treatment strategies in cGVHD, prospective clinical trials are urgently needed for evaluation of treatment options in cGVHD.
Supportive care of oral cGVHD
Supportive care

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

Good basic oral care is important to minimize local factors that could aggravate or trigger oral symptoms.

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 the alterations in the salivary composition and antimicrobial protective characteristic. Mouth-drying agents such as tricyclic antidepressants, SSRI, anti-histamins should be avoided. Salivary stimulant 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 mucoceles 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 Cucurmin are reported to be beneficial in some patients.
Laser treatment in oral GVHD

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Background: Painful oral mucositis, widespread premalignant lesions and reduced intraoral wound healing are critical challenges in HSCT-patients aftercare. Recent data could show a benefit of low level laser therapy (LLLT) and light-emitting diode (LED)-therapy in HSCT–recipients reducing the incidence and painfulness of oral mucositis. In addition both modalities could improve wound healing in oral mucositis after chemotherapy. Furthermore the evaporation of widespread premalignant lesions with the CO₂-laser is known as a useful tool in non-cGVHD patients.

Methods: A LLLT-device was used during 15 treatment sessions in 3 HSCT-recipients with painful oral mucositis. In addition a CO₂-laser device was applied in 4 HSCT-recipients suffering from widespread oral leukoplakia to evaporate these premalignant lesions after punch-biopsy (3 mm) for exclusion of malignancy.

Results: In all HSCT-recipients (n = 3) with painful oral mucositis the LLLT could improve patients discomfort. Furthermore the evaporation of widespread oral leukoplakia by a CO₂-laser leaded to no evidence of disease in all HSCT-recipients (n = 4) without critical wound healing.

Conclusions: Our and the literature findings suggest that LLLT and LED-therapy can reduce discomfort and the incidence in HSCT-recipients with oral mucositis. Furthermore CO₂-laser evaporation can help oral clinicians to deal with widespread premalignant lesions. The data of improved wound healing by using LLLT or LED in non-cGVHD with oral mucositis could change aftercare strategies in oral cGVHD-patients, too.
Pediatric aspects of oral cGVHD

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Oral chronic graft-versus-host disease (cGVHD) is frequent and has a major impact on the burden of the disease and quality of life of children, adolescents and their families. Both cGVHD and therapy may have direct effects on the oral mucosa and salivary glands and indirect effects on dental function and craniofacial development. Compared to adults, considerably fewer studies have been performed in children due to the lower number of patients and because reported data is very heterogeneous. Hence, disease management still relies mainly on clinical experience and data from non-transplanted patients.

Here, we provide information on specific pediatric issues regarding clinical presentation, diagnosis and disease management. We also want to focus on infections and supportive therapy for cGVHD patients of quite different age and developmental stage. The knowledge of long-term effects and their risk factors are of importance when dealing with a growing child. Further information about the long-term follow-up together with oral care providers may lead to individualized management of pediatric cGVHD patients.
Sclerotic oral chronic graft-versus-host disease

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Sclerosis affecting the oral cavity is a rare but potentially severe and physically debilitating complication of chronic graft-versus-host disease (cGVHD). Limited mouth opening interferes with eating, speaking, and oral hygiene, and can be associated with chronic pain. The oral cavity can be affected by sclerosis of the perioral skin (from the outside) or the mucosa (from the inside). Sclerosis of the skin affecting the neck and face is typically diffuse (within the context of more widespread involvement) and results in progressively limited oral opening and pain. Oral mucosal sclerosis tends to be more defined and focal, often affecting the posterior buccal mucosa in areas of long-standing oral cGVHD changes. Other mucosal features include loss of the buccal vestibules, tightening and shortening of muscle frena, and localized periodontal defects. Due to difficulty with maintaining oral hygiene, which is often exacerbated by accompanying salivary gland hypofunction, patients with sclerotic oral cGVHD are at high risk for dental caries. Physical therapy stretching exercises may be effective in achieving improved mouth opening and function. Oral hygiene reinforcement, dietary counseling, caries prevention measures, and routine dental visits are critical for maintaining dental health. Early identification and intervention of oral sclerotic disease is important for reducing progression and minimizing complications and associated morbidity.
Dental issues in oral GVHD

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Oral graft-versus-host disease (GVHD) is associated with a number of dental complications. Typical dental issues include the decay of tooth tissues due to rampant caries, which is most frequently a result of the impaired remineralization due to a decrease in saliva secretion (hyposalivation). Moreover, there is a frequently observed loss of periodontal attachment due to bad oral hygiene; this phenomenon may be attributed to the pain caused by mucosal GVHD and, as a result, limited compliance of the patients to conventional oral hygiene procedures. Dental treatment in patients with oral GVHD should focus on prophylaxis and hygiene to prevent tooth and periodontal tissues from decay, and should start prior to transplantation and continue after the diagnosis of oral GVHD. Dentists should provide saliva substitutes with favorably neutral pH to counterbalance a decline in saliva secretion; moreover, special dental care products with remineralizing capacities can be applied and recommended. Regular topical application of fluoride is mandatory to prevent the development of caries lesions; carious lesions should be restored accordingly. Regular careful and thorough oral hygiene procedures (manual removal of plaque and debris) should be applied to keep periodontal tissues in a healthy condition; in addition, mild antimicrobial mouth rinses can be used. Moreover, the patient should be advised to reduce the intake of low-molecular carbohydrates for minimizing his individual caries risk.
Secondary malignancies in oral GVHD

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Background: Long lasting chronic graft-versus-host disease (cGVHD) and its therapy (CyA, Tacrolimus, Thalidomide and Irradiation) increase the risk for solid cancers, particularly squamous cell carcinomas (SCCs) of the oral cavity and skin in recipients of hematopoietic stem-cell transplants to a 10-fold compared to the general population. Up to 80% of long-term survivors after HSCT present oral manifestations of cGVHD comprising atrophy, erythema, lichenoid lesions, xerostomia and oral pain. Strategies to prevent cGVHD should be linked to the development of more effective and less carcinogenic treatments for patients with symptomatic cGVHD.

Methods: The medical history of HSCT-recipients since 2004 in our clinic who developed an oral (OSCC) or facial skin squamous cell carcinoma (FSCC) was reviewed and compared with the latest literature.

Results: 32 patients with OSCC (n = 11) and FSCC (n = 21) were identified at a median time of 10 years after HSCT. All of them suffered from cGVHD of the facial skin and/or the oral mucosa. Multifocal incidence was found in 48% in the FSCC- and 27% in the OSCC-group. A tumor relapse was observed in 76% (FSCC) and 36% (OSCC) of cases. Because of a short period interdisciplinary recall the surgical treatment could be performed in low tumor stages with a five-year overall survival of 82% in the OSCC- and 100% in the FSCC-group.

Conclusions: Our and the literature findings suggest that oral cGVHD may be considered as a potential early predictor for the development of general cGVHD on the one hand. Otherwise cGVHD of the facial skin and oral mucosa can be estimated as an important risk factor for the development of OSCC and FSCC in HSCT-recipients. These cancers may be more aggressive compared with the non-HSCT population because of frequently multifocal scattering and local relapse. Both SCC were multifocal scattered and relapsed locally frequently. Accurate follow-up and collaboration between hematologists and oral health specialists are crucial for early diagnosis and treatment of oral and dermal (pre-)malignant lesions for best patients outcome.
Current concepts in clinical care of cGVHD
Pathophysiology of chronic GVHD

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Older patient’s age, increasing use of peripheral blood stem cells, introduction of toxicity reduced conditioning regimens with reduction of early complications and failure of current immunosuppressive strategies to induce tolerance contribute to an increasing incidence of clinical chronic GVHD. In contrast, pathophysiological concepts still show lack of coherence and fail to explain the different clinical entities and polymorphic clinical manifestations. Thymic epithelial damage by acute GVHD explains the association of acute and cGVHD by dysfunctional selection of donor-derived T-cells and is well known for many years; it becomes now more and more clear that B cell niches in the bone marrow and splenic niches are as important targets of acute GVHD and thus induce substantial B-cell and splenic dysfunction in chronic GVHD. As a consequence, reactive BAFF-levels are increased early in the course of stem cell transplantation, and auto- as well as alloreactive B-cells are induced which are not only indicators but also directly contribute to pathogenesis of cGVHD. Fibrosis is another hallmark of cGVHD representing dysregulated resolution of inflammation; fibrosis can partially be explained by a shift from type 1 cytokine producing cells to type 2 cytokines, especially TGFβ, in cGVHD. Finally, the balance of immunoregulation is disturbed as shown by the positive results of low dose IL2-treatment on regulatory T-cells in cGVHD. Further clarification of pathophysiological concepts is needed to allow development of more specific therapeutic approaches.
Diagnosis and grading of cGVHD

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In 2005 the National Institutes of Health (NIH) consensus development project proposed criteria for diagnosis and staging of both overall severity as well as organ severity of chronic graft-versus-host disease (cGVHD) based on expert opinion and retrospective data analyses. First, acute GVHD has to be distinguished from cGVHD based on clinical manifestations and not time of onset of symptoms. Within the category of cGVHD, classic cGVHD with manifestations of only cGVHD and overlap syndrome of cGVHD with both acute and cGVHD features were distinguished. Diagnosis of cGVHD requires the presence of at least one diagnostic clinical sign of cGVHD or the presence of at least one distinctive manifestation confirmed by pertinent biopsy or other relevant tests such as Schirmer test in case of ocular involvement. Furthermore, other possible diagnoses including infections and organ toxicities have to be excluded. Eight organs including skin, mouth, eyes, genitalia, gastrointestinal tract, liver, lung and muscle, fascia and joints were defined to be assessed for presence or absence of cGVHD manifestations. Extent and severity of cGVHD for each organ or site taking functional impact into account should be scored from 0 (no involvement) until 3 (severe). Based on the number of organs or sites involved and the degree of involvement in affected organs global assessment of cGVHD severity including mild, moderate or severe form of cGVHD should be performed.

During the last years a U.S. consortium performed a large prospective study on the natural history of cGVHD including the prognosis of the newly defined subcategories of cGVHD. In Europe, the German/Austrian/Swiss consensus group on clinical practice in cGVHD conducted a survey of current practices of diagnosis, staging and overall grading of cGVHD in daily clinical routine and discussed the acceptance of the NIH recommendations in several meetings. Thereby, a consensus was achieved among members of numerous hematopoietic stem cell transplant (HCT) groups representing 88% of all HCT activities in Germany, Austria and Switzerland. Overall, the NIH criteria for diagnosis and staging of cGVHD were considered to be very feasible for use in daily clinical practice. For both definitions of cGVHD as well as overall and organ specific severity staging high rates of acceptance were obtained among the vast majority of HCT centers in Germany, Austria and Switzerland. In addition, medical consultants from gastroenterology, pulmonary diseases, ophthalmology, gynecology and others agreed on the proposed diagnostic procedures for establishing the diagnosis of cGVHD and the severity scoring of affected organs in HCT clinical practice.
Histopathology of cGVHD

Dr. Elisabeth Huber
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The histopathological examination in chronic graft-versus-host disease (cGVHD) is not mandatory for the diagnosis of cGVHD. Referred to the guidelines of NIH Consensus conference the diagnosis bases upon the diagnostic signs and symptoms which establish the diagnosis of cGVHD without further investigations. If only distinctive clinical signs which are not associated with acute GVHD are present or other differential diagnoses are possible, biopsies or other laboratory findings are necessary to confirm the diagnosis of active cGVHD and exclude other conditions, i.e. infections or drug toxicity. Biopsies cannot only prevent incorrect treatment, but can also contribute to a basis for further investigations for the characterization of the pathophysiology of cGVHD.

Principally, biopsies are taken from skin, liver, gastrointestinal tract, oral mucosa and conjunctiva, rarely from the lung, muscle and fascia. Besides minimal criteria for active GVHD, specific histological criteria for cGVHD are described for most organs according to the guidelines of NIH Consensus conference. However, GVHD diagnosis is a multimodal approach to which clinical presentation (including treatment history and laboratory findings), macroscopy and histopathology contribute in equal parts. Therefore, the interpretation of histological changes doesn’t always yield a definitive diagnosis, particularly in early biopsies. Moreover, e.g. in gut or liver, clear histological changes are not known that differentiate acute and chronic GVHD. As GVHD is a dynamic process the histopathological findings depends on the timepoint of biopsy in relation to the onset of symptoms. By now many additional stainings have been investigated to characterize different inflammatory cell populations or identify apoptoses. Even if these additional analyses are not necessary for histopathological diagnosis of GVHD, they provide the opportunity for further important pathogenetic studies.
Response evaluation of chronic GVHD

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Chronic graft-versus-host disease (cGVHD) research activity has increased in the past decade. The 2005 National Institutes of Health consensus conference recommended new tools for diagnosis, severity scoring and response criteria to be used in clinical trials. A number of studies have now evaluated these tools in practice, and results are mixed. The severity scoring tools seem to work well and correlate with patient-reported quality of life, symptoms and survival. However, the response tools classified a high percentage of patients with progressive disease that was not deemed clinically significant by patients or clinicians. The calculated categories of complete response, partial response, stable disease and progressive disease did not correlate with patient- or clinician-reported response rates or survival, although there were some correlations with changes in patient-reported quality of life and symptoms. The U.S. Chronic GVHD Consortium has launched a new observational study enrolling 368 patients who are just starting new treatments for cGVHD. Clinician and patient-reported data, chart review, laboratory results and biologic samples are collected serially with the goal of devising and validating a better tool to assess response based on analysis of empirical data.
Treatment of chronic graft-versus-host disease

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Chronic graft-versus-host disease (cGVHD) remains the leading cause for late morbidity and mortality after allogeneic hematopoietic stem cell transplantation and requires immunosuppressive treatment frequently applied for prolonged periods. Mild cGVHD defined as mild involvement of maximal 2 organs excluding lung is usually treated topical by calcineurin inhibitors (CNI) or steroids or in the presence of visceral involvement with systemic steroids alone with a dose of 0.5–1 mg/kg/day aiming to control symptoms. Moderate to severe cGVHD requires systemic immunosuppression with steroids being the backbone of treatment usually applied with an initial dose of 1 mg/kg/day prednisolone or methylprednisolone applied once daily. Additional agents applied in combination with steroids in 1st line treatment are CNIs (cyclosporine or tacrolimus), and mycophenolate mofetil (MMF), while extracorporeal photopheresis (ECP) and mTOR-inhibitors (sirolimus or everolimus) are currently explored within clinical trials in 1st line treatment. If symptoms progress within 2 weeks of treatment or fail to improve after 4–8 weeks 2nd line treatment is indicated. The same applies if symptoms of cGVHD reappear once steroids are reduced below 0.5 mg/kg/day. For 2nd line treatment steroids, CNIs, ECP, mTOR-inhibitors, and MMF may be applied. Treatment options after failure of 2nd line treatment are agents indicated but not applied before with a pulse of steroids and rituximab being additional options. Rituximab may be used earlier in specific circumstances like auto-antibody-mediated cytopenias. Advanced-line treatment options being considered are: methotrexate, hydroxychloroquine, clofazimine, pentostatin, thoraco-abdominal irradiation, imatinib, and cyclophosphamide, whereas the use of retinoids, azathioprine, and thalidomide should be restricted to specific clinical circumstances. Of note, steroids remain an important treatment component after failure of 1st line treatment. Beside systemic immunosuppressive treatment topical immunosuppressive agents may be applied in addition to speed up response, to spare systemic immunosuppression or to intervene in the presence of mixed response. Since no predictors of response are yet available neither for single immunosuppressive agents nor combination therapies, most patients receive empirical treatment based on the “trial and error” principle in daily clinical practice and changes of therapeutic components in case of lack of response are performed at the individual clinician’s discretion. Besides efficacy potential side-effects of immunosuppressive therapies including increased susceptibility for opportunistic infections and impaired graft-versus-leukemia effect should be kept in mind when treatment strategies for steroid-refractory cGVHD patients are evaluated. Further studies on immunosuppressive and supportive treatment of cGVHD are urgently needed to improve the currently limited evidence.
Supportive care

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In the last decade survival after allogeneic stem cell transplantation (HSCT) improved significantly. Although larger numbers of patients survive, late complications leading to morbidity, impaired quality of life and mortality are still of concern. The need for guidance about appropriate supportive care resulted in the publication of a diversity of consensus recommendations which can be summarized as follows.

A delayed immune reconstitution especially in patients with chronic GVHD increases the susceptibility for infectious complications. Preventive measures are the education of all patients regarding behaviour and warning symptoms of infections. Antibiotic, antiviral and antifungal prophylaxes are recommended including prophylaxis for encapsulated bacteria and PCP. In addition, immunization with inactivated vaccines should be initiated at six months after HSCT according to the published guidelines.

The three main ocular complications after HSCT are chronic GVHD with keratoconjunctivitis sicca, cataract and ischaemic retinopathy. Therefore, ophthalmologic examinations should be performed in all recipients at six months, twelve months and thereafter yearly.

Complications of bone, muscle and connective tissue are osteopenia or osteoporosis, steroid-induced myopathy, polymyositis and fasciitis or sclerosis. Screening for bone loss with dual photon densitometry, supplemental vitamin D as well as estrogen replacement in deficient women are recommended. In addition, patients at high risk for bone loss and patients with manifest osteopenia or osteoporosis should be treated with bisphosphonates. Regular physical activity as well as intensive physiotherapy is of paramount importance in order to maintain patients’ mobility and prevent contracture. Physical activity may also help to reduce fatigue. Psychosocial distress, insomnia or depressive symptoms are common after HSCT. Therefore, all patients should be screened with specific tools for symptoms of psychological distress and psychosocial support offered in order to increase quality of life.

Other noteworthy late effects are muco-cutaneous (e.g. alopecia, skin cancer), endocrine (e.g. hypothyreoidism, diabetes mellitus), cardiac (e.g. cardiovascular disease, cardiomyopathy), respiratory (e.g. bronchiolitis obliterans, idiopathic interstitial pneumonitis), liver (e.g. hepatitis, iron overload), renal (e.g. chronic kidney disease), genitourinary and neurological complications. In addition, long-term survivors of HCT are at risk for the occurrence of secondary malignancies. Since the risk increases over time, especially for radiation-related malignancies, clinical examination and screening for secondary malignancies are a necessary standard for all patients.

In summary, patients and health-care providers should be aware of late effects. Undoubtedly long-term follow up of HSCT recipients is a multidisciplinary approach and requires the collaboration of the transplant centre with subspecialists and primary care physicians.
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