

IDENTIFICATION OF ORAL RISK FACTORS FOR CHRONIC GRAFT VERSUS HOST DISEASE IN HAEMATOLOGICAL PATIENTS WHO UNDERWENT ALLOGENEIC HAEMATOPOIETIC STEM CELL TRANSPLANTATION

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SUMMARY

Objective. The aim of this prospective observational study was to identify local risk factors for the development of clinical manifestations of oral chronic Graft versus Host Disease (cGvHD) in a cohort of patients affected by haematological malignant diseases who underwent allogeneic haematopoietic stem cell transplantation (HSCT).

Materials and methods. In the context of an active collaboration between the Rome Transplant Network of the Hematology and the Oral Pathology Division at "Policlinico Tor Vergata", in Rome, 47 haematological patients were included in this trial based on a systematic dental screening and follow-up protocol. The dental checks were planned 1 month before the transplant procedure while the subsequent follow ups were scheduled on day +100, +180, +365 and + 730 after the transplant. The tool used for the dental checks was a detailed report including all the potential oral features responsible of mechanical, chemical or infective injuries, except for the drugs.

Results. Overall, 64% of patients (N=30) did not perform dental hygiene during the screening pre-transplant and 53% (25/47) developed cGvHD with oral involvement. The most part of patients (84%) who experienced oral manifestations of cGvHD during the follow-up period after HSCT did not perform dental hygiene before the transplant procedure. Moreover, the comparison between the "presence" or "absence" of dental hygiene before the allogeneic HSCT showed a statistical significant increasing during the follow-up period in the occurrence of oral lesions due to the cGvHD for patients who lack pre-transplant dental care (p=0.029).

On the contrary, the frequency of the other factors such as malocclusions, fractured teeth, incongruous prosthesis, food, smoke, alcohol and bad habits, resulted similar between the group with or without typical oral lesions of cGvHD.

Conclusions. The prevention of oral infectious complications provided by primary and secondary dental cares can result in a great benefit for haematological patients who underwent allogeneic HSCT. The combined hematological and dental management represents a clinical need before and after allogeneic HSCT for the removal of inconvenient issues with impact on the short and long-term outcome. Poor dental hygiene seems to be a local risk factor for the development of oral lesions due to cGvHD. However, a larger cohort of patients is necessary to confirm these preliminary data and to evaluate the best preventive and therapeutic oral hygiene protocol in this specific setting.

Key words: allogeneic HSCT, dental hygiene, oral lesions, cGvHD.

Introduction

Allogeneic HSCT from an HLA-identical siblings, unrelated donors or mismatched relatives may improve overall survival (OS) and disease free survival (DFS) in the hematological malignant diseases, regardless of the donor's type (1-6). However, the occurrence of the foremost allograft's complication, known as graft versus host disease (GvHD), is affected by several factors including quality of the graft, prophylaxis and donor/recipient pair features mainly associated to the HLA direction mismatching, maybe except that for the single cord blood transplant (7-11).

Historically, graft-versus-host disease can be classified as either acute or chronic form, according to the timing of onset: an early form called acute GvHD (aGvHD) that occurs within 100 days after the transplant and a late form called chronic GvHD (cGvHD).

Acute GvHD is mediated by donor lymphocytes infused into the recipient where they encounter profoundly damaged tissues from the effects of the underlying disease, prior infections, and the transplant conditioning regimen. The allogeneic donor cells meet a foreign environment that has been altered to promote the activation and proliferation of inflammatory cells. Thus, aGvHD reflects an exaggerated response of the normal inflammatory mechanisms that involves donor T cells as well as multiple innate and adaptive cells and mediators. Three sequential phases illustrate the complex cellular interactions and inflammatory cascades that evolve to aGvHD: 1) activation of antigen presenting cells; 2) donor T cell activation, proliferation, differentiation and migration; and 3) target tissue destruction (12).

On the other hand, the pathophysiology of cGvHD is not as advanced as that of aGvHD. Chronic GvHD is a complex, multisystem disorder with myriad manifestations that involves many different organs. It is characterized by immune dysregulation, immunodeficiency, impaired organ function and decreased survival. Alloreactive T cells have been implicated in the pathogenesis; however, the precise role of spe-

cific T cell subsets, autoantigens, alloantigens, and B cells, as well as interactions of chemokines and cytokines has not been fully elucidated (13). The clinical manifestations of chronic GvHD are often similar to an autoimmune process, suggesting similar pathophysiology. Acute GvHD typically can affect skin, liver, stomach, and/or gut (14). Chronic GvHD typically causes symptoms similar to those of autoimmune disorders such as lupus and scleroderma. Almost any organ can be affected by chronic GvHD (15). Nearly 80% of patients with cGvHD presents oral involvement, making the oral cavity one of the most frequently affected target organs and a significant cause of patient morbidity (16). Oral mucosal disease is characterized by lichenoid inflammation presenting with hyperkeratotic white striations and plaques, erythema and ulcerations, with symptoms including oral pain, food intolerance and sensitivity, and a long-term increased risk of oral squamous cell carcinoma (17). Management of oral involvement is directed to minimizing symptoms, improving functions and often requires intensive localized ancillary therapy beyond simultaneous administration of systemic immunomodulatory agents. The prevention of GvHD represents a crucial part of the allogeneic HSCT and is generally based on the use of a combination of long-term immunosuppressive drugs (18-20).

In a multidisciplinary context, this study aims to evaluate local risk factors for the development of clinical manifestations of oral chronic GvHD.

Materials and methods

From January 2010 to date, there is an active collaboration between the Rome Transplant Network of Hematology and the Oral Pathology Division at "Policlinico Tor Vergata", in Rome. The Rome Transplant Network is a JACIE (*Joint Accreditation Committee of ISCT and EBMT*) accredited Metropolitan Transplant Program that performs about 70 allogeneic HSCT for year, ac-

According to an established policy for the donor identification and standard transplant procedures (21, 22). In this cooperative context, a dental screening and follow-up protocol has been defined for all candidates to allogeneic HSCT. Pediatric age, logistical situations or lack of willingness of the patients to be enrolled in this observational study were considered as exclusion criteria. The protocol consisted of 5 dental checks: before the allogeneic HSCT, on day +100, + 6 months, + 1 and + 2 year after the transplant procedure. The aim of the first check up was to point out the characteristics of the patient's oral cavity through a specific form, as

shown in Figure 1. In this haematological setting, the primary dental prevention consisted of periodical odontostomatological visits, food education and home fluorine prophylaxis. The secondary dental prevention was the removal of possible causes that could compromise the transplant outcome, such as caries, billed-teeth, incongruous prosthesis and bad habits before the transplant procedure, whereas the follow-up after HSCT was performed for monitoring the potential development of oral cGvHD and to treat possible urgent dental diseases. Overall, 47 patients have been enrolled (22 males and 25 females) with a median age of 58 years (46-77

RISK FACTORS FOR ORAL ULCERS

Surname..... Name..... Date of birth.....

Traumatism

- Bites Occlusal traumatism.....
- Fractured dental elements.....
- Non-congruent prosthesis.....
- Tooth-brushing.....

Poor oral hygiene.....

Oral habits.....

Food rich in spicy and elaborate foods
(Spicy foods, animal fats, nuts, mustard, cheese and chocolate)

Smoke.....

Alcol.....

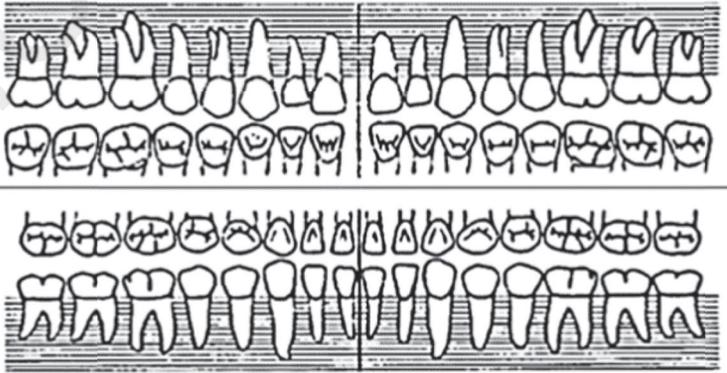


Figure 1
Data report of risk factors for oral ulcers.

years) affected by acute leukemia, myeloproliferative and lymphoproliferative malignant disorders in 33, 2 and 12 cases, respectively. As stem cell source, 31 patients received PBSC, 14 BM and 2 CB, from unrelated, HLA identical sibling or mismatched relative donor in 22, 20 and 5 cases, respectively. Acute and chronic GvHD were graded according to Glucksberg, Schulman and NIH criteria (14, 15).

Statistical analysis

Patient characteristics and data are summarized using descriptive techniques, including absolute and relative frequencies for categorical variables, while continuous variables are expressed as median and range. The interdependence between groups is evaluated using both the Wilcoxon and the Chi-square tests. A p-value of <0.05 was considered as statistically significant. All the analysis are conducted using software SAS 9.3.1.

Results

The analysis of this cooperative prospective clinical trial has shown a lack of dental hygiene during the pre-transplant screening in 30 out of 47 patients, corresponding to 64% of them (Figure 2). During the follow-up period, 25 out of 47 experienced cGvHD with oral involvement that was associated with poor hygiene in 21/25 cases (84%). The comparison between the “presence” or “absence” of dental hygiene before allogeneic HSCT, showed a statistical significant increasing in the occurrence of oral lesions due to the cGvHD for patients who lack pre-transplant hygienic dental care ($p=0.029$). Moreover, the oral manifestations of cGvHD were observed in a significant minority of patients belonging to the group who underwent dental hygiene before-allogeneic HSCT ($p=0.003$) (Figure 3).

On the contrary, the frequency of other oral pre-transplant factors such as malocclusions (21%), fractured teeth (9%), incongruous prosthesis (11%), food (17%), smoke (12%), alcool (13%)

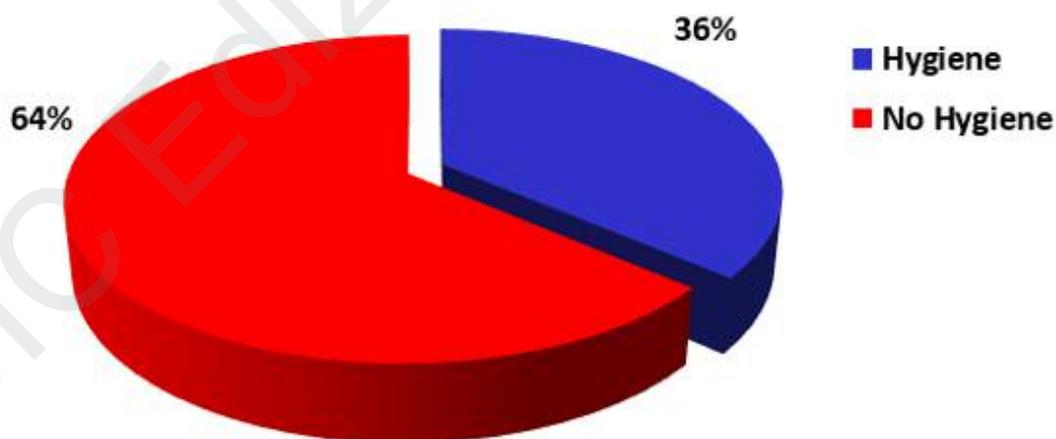
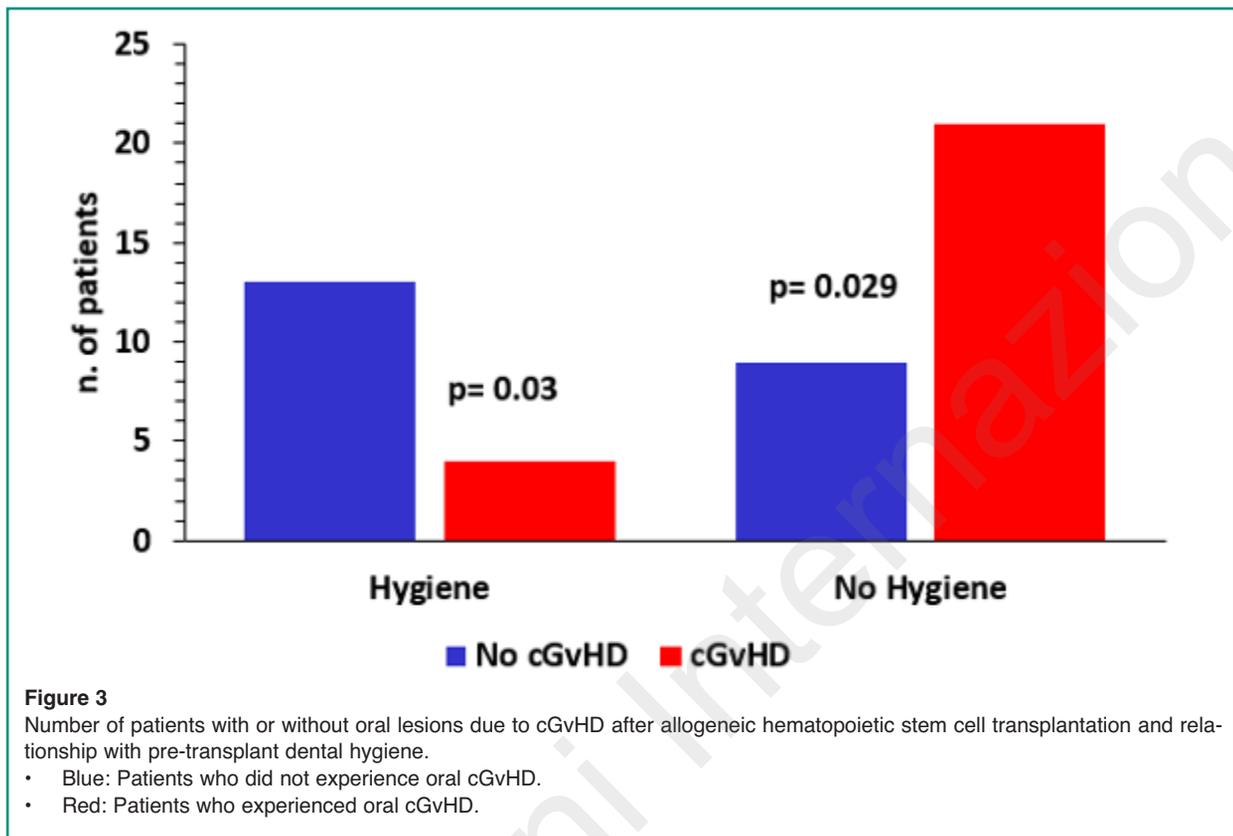


Figure 2

Frequency of patients who performed or did not perform dental hygiene before the allogeneic hematopoietic stem cell transplantation.

- Blue: Group of patients who carry out hygiene.
- Red: Group of patients who did not carry out hygiene.



and bad habits (17%), resulted similar between the group with or without typical oral lesions of cGvHD.

Discussion

Chronic graft-versus-host disease is a serious complication of allogeneic HSCT that affects approximately 25 to 80% of long-term survivors and is the leading cause of non-relapse mortality. Lichen and ulcers are common oral symptoms of cGvHD, responsible of discomfort in the diet, with consequent weight loss and serious impact on the patient's quality of life (23). Moreover, in patients who develop cGvHD, the restitution *ad integrum* of ulcerative lesions is probably hampered by the coexistence of systemic and iatrogenic factors. The local application of platelets gel for the treatment of muco-cutaneous lesions

related to GvHD has shown promising results with a quick pain resolution and, nowadays, its application meets several odontoiatric and haematological indications (24, 25).

Poor oral hygiene is not just at the origin of dental caries. Plaque is a biofilm that adheres constantly on the dental surface and if it is not removed daily through specific devices, such as brushing and dental floss, it can accumulate and risk infecting and inflaming not only the gums, but also the supporting tissues of the tooth. The result consists of gingivitis characterized by swelling, edema and bleeding. These manifestations can kick off, in frail patients such as those transplanted, to much more serious injuries that depend on the immunological status. Care of the gums through proper home and professional oral hygiene thus preserves the general good state of oral health and must be considered a dental priority. Despite advances in understanding transplant immunology and clinical management, cGvHD remains a significant cause

of morbidity and mortality for allo-HCT recipients. The oral cavity is one of the sites most frequently affected by cGvHD, with mucosa, salivary gland, and sclerotic manifestations associated with pain and impaired functions of the mouth (16). Accurate diagnosis and effective management of oral cGvHD and its complications are a key component of the allogeneic HSCT (19, 20).

In a multidisciplinary context, there is no scientific evidence concerning the role of the endo-oral risk factors in the development of oral cGvHD. Identifying local causes most frequently associated with oral symptoms in the occurrence of cGvHD may be a valuable preventive approach in the clinical management of cGvHD oral lesions.

Our prospective observational clinical trial have documented a statistical significant association between poor oral hygiene and oral manifestations of cGvHD ($p=0.029$) and a significant reduced oral symptoms of cGvHD in the patients who performed dental hygiene before allogeneic transplant procedure. On the other hand, some stomatological parameters such as malocclusions, fractured teeth, incongruous prosthesis, food, smoke, alcohol and bad habits seem not contribute to oral manifestations of cGvHD. However, this observation could depend on their treatment with prompt resolution during the screening phase before the allogeneic HSCT and to the small sample of patients with these dental characteristics in our cohort. It is well known that infections, triggering an immune response, can induce or sustain GvHD itself. The prevention of oral infectious complications, through an accurate oral care, can result in a great benefit due to the decreasing of the stimulus to the underlying immune response responsible for cGvHD oral ulcers. Furtherly, a systematic multi-disciplinary approach including dentist and dental hygienist, allows the recognition of removable conditions, like caries, broken teeth or other oral injuries, carrying out a correct causal therapy and lead to odonto-stomatological healing patients before allogeneic transplant procedure.

Conclusions

In conclusion, odontostomatological cares in hematological patients represent a clinical need before and after allogeneic HSCT in order to remove inconvenient issues and to ensure a good dental hygiene that seems to reduce the occurrence of oral cGvHD symptoms. However, a larger cohort of patients is necessary to confirm these preliminary data and to evaluate the best preventive and therapeutic oral hygiene protocol in this specific setting.

Authorship

Alessandra Picardi, MD, PhD, designated the study, drafted the manuscript and performed the allogeneic HSCT.

Patrizio Bollero, DDS, PhD designated the study, drafted the manuscript and performed the dentist treatments.

Michele Miranda collected data and performed the dental screening and follow-up of the transplanted patients.

Francesca Liciani collected data and performed the dental screening and follow-up of the transplanted patients.

Gianni Paterno, MD, collected data and performed the haematological follow-up of the transplanted patients.

William Arcese, Director of Transplant Unit, revised the manuscript and performed the allogeneic HSCT.

Conflict of interest

The Authors declare that they have no conflict of interest relevant to the manuscript submitted to ORAL & Implantology.

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