180-Day screening study for predicting the risk factors for developing acute oral Graft-versus-Host disease in paediatric patients subjected to allogenic haematopoietic stem cells transplantation

**ABSTRACT**

**Aim** In this study, 58 paediatric patients were prospectively evaluated with a number of screening studies performed between 0 and 180 days after allogenic hematopoietic stem cells transplantation (HSTC) to detect any risk factors for developing oral manifestations of acute Graft-versus-Host Disease (a-GvHD).

**Materials and methods** A total of 58 paediatric allogenic HSTC patients (37 males aged 1 to 15, and 21 females aged 4 to 18), entered the study and were observed by a trained dental team for a period of 6 months following transplantation while assuming cyclosporine, an immunosuppressive agent with a-GvHD prophylactic activity. Mean age at transplantation was 7.2 years old. Screening studies included physical examination, complete blood counts and liver function tests. Complete extraoral and intraoral clinical examinations were performed for all patients to detect oral lesions. Furthermore, some variables (sex, number of HSTC performed in the same patient, degree of HLA disparity and the positive/negative result of cytomegalovirus antigenemia test during the three months after engraftment) were investigated in the attempt to evaluate their predictive and/or diagnostic value in paediatric HSTC recipients.

**Results** Twenty-two percent of the patients developed oral a-GvHD. The oral changes included mucositis, erosions and/or ulcerations; xerostomia, pain and bleeding were also referred. The variables investigated for predictive and/or diagnostic value in paediatric HSTC recipients included: sex (relative risk 4.94, 95% confidence interval 0.119-2.052, P= 0.1242); number of HSTC performed in the same patient (relative risk 5.4, 95% confidence interval 0759-3.843; P= 0.0714); degree of HLA disparity (relative risk 0.24, 95% confidence interval 0.058-0987, P= 0.0428); and the result to cytomegalovirus (CMV) antigenemia test during the three months after engraftment (relative risk 0.86, 95% confidence interval 0.273-2.712, P= 1).

**Conclusion** Patients presenting two or more risk factors should be closely monitored for development of clinical oral a-GvHD, as oral complications are a significant cause of morbidity and potential mortality for children undergoing HSTC and can interfere significantly with transplant recovery.

**Key words:** a-GvHD; Oral complications; Paediatric dentistry.

**Introduction**

Haematopoietic Stem Cells Transplantation (HSTC) is frequently performed to restore haematologic and immunologic competence after chemotherapy and radiation therapy for a range of childhood malignancies, as well as to treat various congenital conditions in which haematologic and immunologic functions are depressed or absent. Potentially devastating complications may occur during the pre-engraftment period after HSTC, when marrow aplasia may occur for several weeks until engraftment occurs, as well as during the post-engraftment period (the three months after engraftment) and in the subsequent months and years.

A major late complication of allogenic HSTC is the development of Graft versus Host Disease (GvHD). GvHD is a syndrome with various clinical, pathological and immunological manifestations, observed in recipients of allogenic HSTC, which is attributed to the transplantation of immunologically activated T lymphocytes from a genetically disparate donor into the immunocompromised host [Ferrara et al., 1991]. It may be either acute or chronic [Forkner, 1938]. Acute GvHD (a-GvHD) results from the attack of cytotoxic donor T lymphocytes on host tissues, seen most dramatically on epithelial cells [Armitage, 1994]. The involvement of the oral mucosa as manifestation of GVHD in humans had already been recognized by Sale et al. [1981] in the early 1980s [Manusè and Carrasi, 2005]. Oral a-GvHD lesions closely resemble those seen in a variety of autoimmune connective tissue diseases [Rodu and Gockerman, 1983] [Manusè and Carrasi, 2005], including lupus erythematosus and Sjögren syndrome; oral pain may be the first presenting symptom, but mucosal dryness and erythema can also be observed. Mucosal atrophy, mucoceles, pseudomembranes, ulcerations and a reduced range of movements of the mouth can often be observed [Schubert et al., 1984; Rugarli, 2000]. These problems frequently result in a decreased food intake with a consequent worsening in weight loss and anorexia: in general, impact on life quality of patients is very negative. The actual goals of our study are to define the risk factors for developing oral a-GvHD in children subjected to HSTC, and to describe the oral manifestations of a-GvHD.
Materials and methods

Fifty-eight patients (37 males aged 1 to 15 years, and 21 females aged 4 to 18 years) receiving allogenic HSTC from October 2005 to September 2007 entered the study. Mean age at transplantation was 7.2 years. The preparatory regimen before the infusion consisted in a chemotherapeutic treatment, which included thiotepa (THOT), ciclophoshamide (CTX) busulfane (BUS), fludarabine (FLUD), melphalan (MELPH), cyclosporine-A (CSA), metotrexate (MTX) antitimocite globuline (ATG), VP16, followed sometimes by total body irradiation (TBI) (Table 1). The screening for oral a-GvHD lesions was performed during the six months following transplantation (from the day of the transplantation – day 0 – until the interruption of the asministratio of cyclosporine – day 180). Screening included physical examination, complete blood count, and liver function tests. Complete extraoral and intraoral clinical examinations were performed for all patients. Parental and Ethic Committee consent were obtained. In addition, parents were allowed to assist for encouraging and/or helping the child to remember and refer symptoms; parental assessments were used as surrogates for children who were pre-verbal. All lesions in the oral cavity were recorded and photographed. A standardised evaluation form especially designed for these patients was completed at every patient visit. Furthermore, other variables were investigated in the attempt to evaluate their predictive and/or diagnostic value in paediatric HSTC recipients. They included the following: sex, number of HSTC performed in the same patient, degree of HLA disparity and the result of the cytomegalovirus (CMV) antigenemia test during the three months after engraftment. The resulting data were analysed with the Fisher’s exact test.

Results

Out of a 58 HSTC subjects included in the study, 13 (22%) showed oral manifestations of a-GvHD, 25 (34%) developed a-GvHD with no oral involvement, and 20 (34%) did not develop the disease at all. In addition, all the 13 cases showing oral manifestations developed a-GvHD; but while 8 of them recovered from the acute form (62%), 5 developed chronic GvHD (38%).

Oral mucosal a-GVHD was observed in 13 (22%) of 58 HSTC. The prevalent clinical aspect was a diffuse mucositis. Among oral lesions, ulcerations (53%) (Fig. 1) and erosions (46%) (Fig. 2, 3) were the prevalent types, as reported in the literature [Darmstadt et al., 1992; Treister et al., 2005], often in combination with hyperkeratosis (38%), atrophic (30%) and hyperplasic (23%) areas, vescicles (23%), papules (15%), and mucoceles (7%). Xerostomia, pain and bleeding were also often referred (Table 2).

Tongue (76%), hard palate (69%) and the mucosa of the cheeks (61%) were the areas most frequently affected by oral lesions. The sites less frequently involved were: soft palate (38%), alveolar mucosa (30%), lips (15%) (Fig. 4), mouth floor (15%), and keratinized gingiva (15%) (Table 3).
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The variables investigated for their predictive and/or diagnostic value in paediatric HSTC recipients included sex, number of HSTC performed in the same patient, degree of HLA disparity, and the result of the cytomegalovirus (CMV) antigenemia test during the three months after engraftment (Table 4).

Results of the statistical analysis performed using Fisher's exact test are summarised in Table 5.

Discussion

GVHD is classified as either acute or chronic: a-GvHD occurs within the first 100 days after allogenic HSTC and c-GVHD occurs thereafter. The clinical manifestations of a-GvHD are similar to those of a wide range of autoimmune diseases. Tissue damage seems to be mediated largely by activated donor T cells that recognise host antigens as foreign and attack target organs such as the skin, the liver and the gastrointestinal tract.

In patients undergoing HSTC from matched unrelated donor (MUD) the risk to develop a-GvHD has been reported with a probability rate 4 times higher than that found in patients undergoing transplantation from a matched related donors, as not fully compatible HLA cells transplantation can favour the development of the disease. Other risk factors for a-GvHD in the paediatric population are sex, number of HSTC performed in the same patient, degree of HLA disparity, and the result of the cytomegalovirus (CMV) antigenemia test during the three months after engraftment (Table 4).
population include sex, number of HSTC performed in the same patient and the positive/negative result to cytomegalovirus (CMV) antigenemia test during the three months after engraftment. The incidence of oral a-GvHD seems to be surprisingly prevalent (probability rate 2 times higher) in males. Furthermore Sale et al. [1981] in a study conducted on 129 adult patients who developed oral and ophthalmic a-GvHD, found no statistically significant differences between the two sexes. Therefore, the existing correlation between oral a-GvHD and male sex in growing patients evidenced by our study could be worthy of further examination.

As far as the number of HSTC performed in the same patient is concerned, patients who underwent just one HSTC showed an increased risk of developing oral a-GvHD (probability rate 5.4 higher) than patients who underwent a double HSTC.

The correlation with a positive cytomegalovirus antigenemia test and a-GvHD, reported by Annoek et al. [2000] has been examined but with no statistically significant results. Their research was based on a sample of adult patients, while our study deals with growing patients, which could represent a confounding factor.

Conclusion

Patients presenting two or more risk factors should be closely monitored for development of clinical oral a-GvHD as post-transplant immunosuppression is tapered so that effective therapy can be started early. Oral complications are a significant cause of morbidity and potential mortality for children undergoing HSTC; they can occur at all stages of HSTC and can interfere significantly with transplant recovery.

Development of validated age-appropriate evaluation strategies is critical. In addition, studies suggest that active participation of the dental team in the follow-up of these patients is likely to significantly affect not only the proper management of oral lesions, but also the establishment of other diagnosis and treatment strategies. The dental health care team should play a key role in supporting these patients: untreated dental caries and periodontal disease may result in severe infections of the mouth and/or life-threatening systemic spread of the microbial pathogens. In very serious forms, feeding could become a problem. Furthermore, the observation of impaired dental growth and development that seem to be due to the HSTC-conditioning regimens may have major significance for ongoing management of oral health, including restorative and orthodontic treatments [Majoran et al., 2000]. Prevention and/or diagnosis and management of oral complications in a-GvHD can improve the success of a transplant by reducing morbidity, improving the quality of life and decreasing the cost of care. The identification of treatment strategies for this condition will be an invaluable advance in the effective management of these patients.

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