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Par Thomas MUNY

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# Etude de l'impact des facteurs bucco-dentaires dans la forme endobuccale chronique de la maladie du greffon contre l'hôte (cGVHD)

# Impact of oral factors in the oral chronic graft versus host disease (cGVHD)

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***A mes proches ...***

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# Index des abréviations

**APCs**: antigen-presenting cells

**BMT**: bone marrow transplantation

**CBCT**: cone beam computed tomography

**CIs:** confidence intervals

**CML**: chronic myelogenous leukemia

**CMV**: cytomegalovirus

**DMFT**: decay missing filled teeth

**cGVHD**: chronic graft versus host disease

**aGVHD**: acute graft versus host disease

**GIC**: glass ionomere cement

**GVL**: graft versus leukemia

**HLA**: human leukocyte antigens

**HRQL**: health related quality of life

**HSCT**: hematopoietic stem cell transplantation

**MTX**: methotrexate

**NIH**: national institute of health

**ORs**: odds ratio

**PBSCT**: peripheral blood steem cell transplantation

**SCC**: squamous cell carcinoma

**SD**: standard deviation

**UCB**: umbilical cord blood

# 1. Introduction

The hematopoietic stem cells transplantation (HSCT) is the reference treatment for malignant hemopathies and non-malignant diseases of the bone marrow or the immune system. A preventive treatment for the host is required, to partially eliminate his immune system, to prevent the rejection of the transplant, and also to eliminate a varying degree malignant clones. The malignant clone's elimination, is achieved by conditioning (chemotherapy +/- radiotherapy), which varies according to its intensity.

The Graft versus Host Disease (GVHD) is the most common complication of the HSCT, with 33% to 75% for patients with aGVHD and 45% to 83% for those cGVHD (1–4). HSCT is accompanied by morbidity and mortality secondary to the toxicity of the conditioning, the graft response versus the host and the postgraft immune deficiency (5).

GVHD is an inflammatory disease, mediated by the transplant's mature lymphoid T cells, resulting from the interaction between the recipient's allogenic antigens, presented by its antigen-presenting cells (APCs), and the transplant's T cells.
The GVHD requires 3 developping elements (6):

- The host must be incapable of rejecting the graft,
- The graft must contain immunocompetent cells, there must be incompatibilities in transplantation antigens between donor and host,
- Effector cells must migrate to target tissues.

T-cells that are present in the graft can recognize and destroy the residual tumor cells of the recipient, this is a desired effect called « graft versus leukemia » (GVL).

However, the transplant's T-cells can also cause deleterious reactions to the healthy organs of the recipient, this is the GVHD reaction (5,7).

Clinical GVHD has an acute form and a chronic form. Acute GVHD (aGVHD) has relatively uniform clinical picture, generally occurs early post-transplant (4). Chronic graft versus host disease (cGVHD) is defined as a multisystem, alloimmune and autoimmune, characterized by immune dysregulation, immune deficiency, impaired organ function, and decreased survival (8). The presence of cGVHD is associated with fewer relapses but more treatment related mortality (9).

Patients with cGVHD may suffer from severe morbidity, usually affecting mostly the skin or the mouth, but also other organs as eyes, gastro-intestinal tract, liver, lungs, joints, and genitourinary tract (10,11). The presence of cGVHD is resulting in pain, impaired functional ability, and poor quality of life (8). Clinical signs are generally seen first in the buccal mucosa (12).

The oral manifestations (figure 1) most strongly associated with cGVHD are lichenoid lesions, and erythema of the oral mucosa, but other erosives or ulceratives manifestations or superficial mucoceles could be observed (13,14).

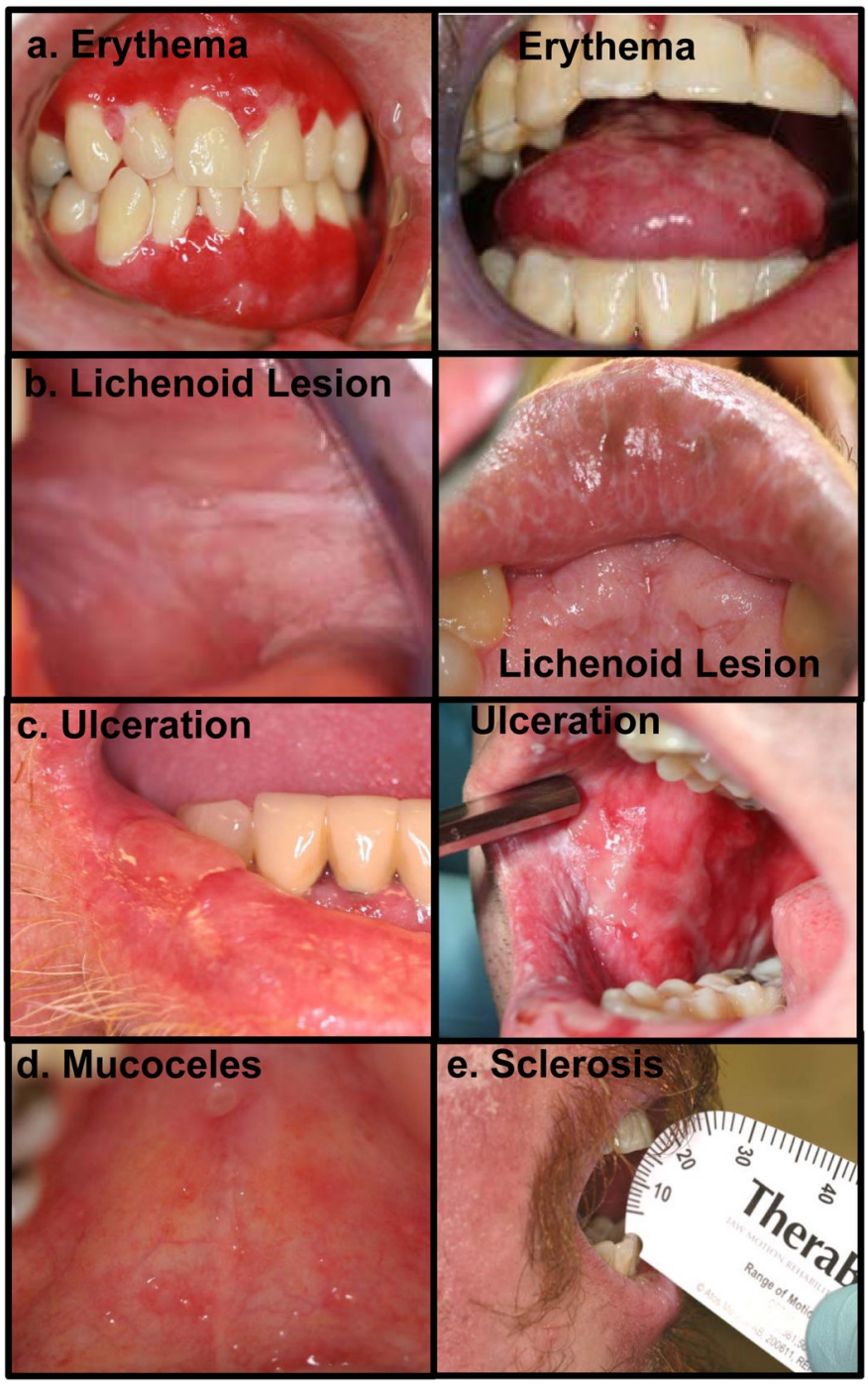



*Figure 1 : Classic oral manifestations of oral cGVHD (13,14): Erythematous lesions of the buccal mucosa in oral cGVHD (a,b). Ulcerative lesions of the buccal mucosa in oral cGVHD (c). Mucoceles lesions of the buccal mucosa in oral cGVHD (d). Sclerosis in oral cGVHD (e).*

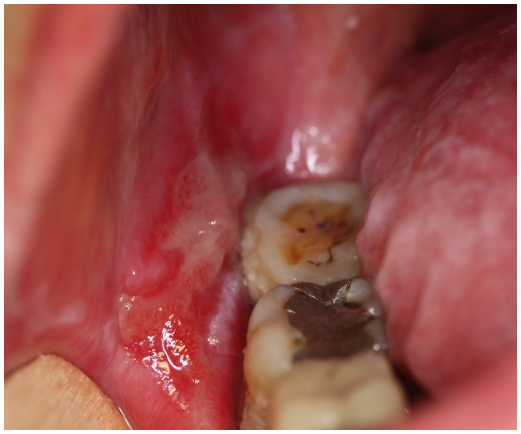
The prevalence of oral cGVHD varies according to authors, from 33% to 75% for patients with aGVHD and from 45% to 83% for those cGVHD (1–3).

Scleroderma is one of cGVHD's manifestations, including a limitate oral opening ; it is often associated with functional consequences as a poor oral hygiene, a poor diet, and contribute to infections and malnutrition (8).
The onset of cGVHD and the Health-Related Quality of Life (HRQL) decrease are closely linked (15). In addition, on 93 patients with cGVHD, 43% were malnourished as evidenced by a BMI less than 21.9 and 14% were severely malnourished by a BMI less than 18.5 (16,17).

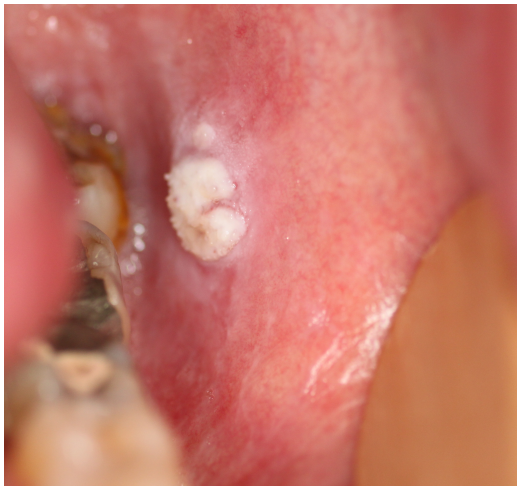
In addition, the oral manifestations of cGVHD are associated with salivary dysfunction that can be characterized by similar Sjögren syndrome manifestations: hyposalivation, xerostomia and xerophtalmia (18–21). Correlations between cGVHD severity and xerostomia or parotid gland dysfunction have been reported (22,23).

The development of oral cGVHD increases the prevalence of dental decay (24). Patients treated by adjuvant radiotherapy as conditioning regimen prior to HSCT seems to present highest Decay, Missing, and Filled Teeth (DMFT) (25). Evidence of dental plaque, gingivitis, mucitis and ulcerations could be developed unfavourably after hematopoietic stem cell transplantation (26,27).

Finally, oral cGVHD is a significant risk factor for the development of oral squamous cell carcinoma (SCC), after HSCT (figure 2) (28,29).



(a)



(b) (Courtoisie du Dr Magro)

*<u>Figure 2 : Squal celle carcinoma with oral cGVHD:</u> Squal cell carcinoma of the jugual mucosa in patients with oral cGVHD (a). Verrucous carcinoma of the jugual mucosa in patients with oral cGVHD (b).*

The main objective of our study is to improve the understanding of the cGVHD occurrence to limit its occurrence. Both general (table 1) and oral factors have been evaluated to determine their influence on cGVHD occuring.

Table 1 : General factors influence GVHD occurrence (30–37)

| **General factors** | **Influence on GVHD occurrence** |
|---|---|
| Receiver's age | High receiver age is associated with an increasing incidence of GVHD (38,39). |
| Sexe-mismatching | Match of donor and female recipient sex is associated with a reduced risk of GVHD (39). |
| Human Leukocyte Antigens (HLA) matching | The degree of HLA histocompatiblity positively influences the survival and severity of GVHD in transplant patients (40–44). |
| Allo-immunization | Previous allo-immunization of the donor increase the GVHD incidence (38). |
| Source of the transplant | cGVHD after Peripheral blood steem cell transplantation (PBSCT) may protracte and be less responsive to treatment than cGVHD after bone marrow transplantation (BMT) (45). As a source of HSCT, umbilical cord blood (UCB) present low incidence of severe GVHD (46). |
| Preventive treatments | A significant reduction of incidence of GVHD is observed in patients who received both methotrexate and cyclosporine compared to those who received cyclosporin alone (47). Methotrexate, antithymocyte globulin and prednisolone reduce the incidence of GVHD compared to methotrexate alone (48). |
| Cytomegalovirus (CMV) statu | An increased risk of aGVHD is associated with CMV seropositivity (39). |
| Haemopathy | An increased risk of aGVHD is associated with chronic myeloid leukemia (CML) (39). |
| Conditioning treatments | Reduced or non myeloablative conditioning lower the incidence of GVHD (49–51). |

None studies have been done on the influence of dental factors in the incidence of cGVHD. Yet, aGVHD seems to be associated with periapically infected teeth, and periodontal diseases (52,53).

Dental decay, periodontal and endodontic diseases cause dysbiosis and focal infections, involving immunological and inflammatory phenomena, related to the host response, which may have an impact on the incidence and severity of oral cGVHD.

Our hypothesis is that the pre existing dental oral factors with allograft are associated with the incidence of oral cGVHD. The present study aim to focuse on the oral cGVHD onset during the first post graft year and to evaluate the impact of the general and oral features on the oral cGVHD onset.

# 2. Material and methods

## *2.1 Design study*

This is an observational, retrospective, monocentric study, studying the influence of dental oral factors in the development of oral cGVHD.

## *2.2 Study population*

All the patients included were referred by the haematology department of CHU of Lille, for a pre and post-graft dental check-up.

The patients have been received at least one month before allogenic HSCT procedure and they have been followed up at 3 months, 6 months and then annually after the HSCT, in the Odontology Department of CHU of Lille.

The data collected during the dental examinations were transcribed in writing on a pre-filled form (Appendix 1), completed by the paper and computer files of each patient. All the data was recorded in a protected and anonymised EXCEL document.

## *2.3 Consent*

All patients gave their informed consent according to institutional guidelines and in accordance with the Declaration of Helsinki (Appendix 2).

## *2.4 Inclusion criteria*

### 2.4.1 Inclusion criteria

Inclusion criteria were:

- Patients followed up in the dentistry department of the Lille CHRU (University Hospital);
- Over 18 years old;
- Informed consent obtained;
- Candidate for an allogeneic HSCT for haematological malignancies.

### 2.4.2 Non inclusion criteria

Non inclusion criteria were:

- Non consenting patients;
- Patient who has already been transplanted;
- Patients whose oral cavity has not been previously examinated.

### 2.4.3 Exclusion criteria

Exclusion criteria were :

- Transplant cancelled or postponed;
- Patients who died before 3 months;
- Patients with less than 3 follow-up appointments.

## *2.5 Data collection*

Data were collected over 2 years from 22 February 2018 to 22 March 2020, patients seen in their first dental consultation until 22 January 2019 were inclued.

Follow-up was carried out before the transplant, at 3 months, at 6 months and at 12 months after the transplant.

During the pre-graft dental index, following data was collected (Appendix 1):

- age, gender
- birth date
- Investigator code
- patient anonymous code
- medical history
- haemopathy
- preventive graft treatment
- origin of allograft: (BMT, PBSCT)
- conditioning graft
- donor
- histocompatibility
- smoker patient
- alcohol consumption
- xerostomy
- salivary pH
- dental metal filing
- dental prosthesis
- dental resins filing
- dental decay
- apical infectious foci
- periodontal disease

During post-graft dental index, following data was collected (Appendix 3):

- investigator code
- patient anonymous code
- date of transplant
- medical history
- smoker patient
- alcohol consumption
- chimerism
- xerostomy
- salivary pH

- oral cGVHD
- location of cGVHD
- manifestation of cGVHD
- impact of cGVHD
- dental contact of cGVHD

The evaluation was carried out by two different investigators, dentist clinicians in the CHU of Lille. Pre and post-graft dental index have been realised following the NIH cGVHD Activity Scale scores (54). Oral cGVHD differents scales are illustrated in appendix 4.

Also pre and post-graft dental index were created among pre-filled diagnosis of functional impact (appendix 5) and pre-filled diagnosis for description of oral cGVHD (appendix 6) used in CHU of Lille.

Medical history and transplant data were collected with the medical questionnaire, medical letters and patient medical records.

All patients were instructed to refrain from eating, drinking, smoking, and oral hygiene procedures for a minimum of 120 min before the saliva procedure.

Xerostomia was evaluated by sucre under the tongue, measuring the time to be completely dissolved, when the time reaches or exceeds 3 minutes, it‘s noticed as a salivary dysfonction (55). After, pH was measured by salivary bands which detected after few minutes, the pH, with differents colors (appendix 7).

Dental data were evaluated during the clinical exam and confirmed with orthopantogram. In case of doubts with radiology interpretation, others examinations were realised as retro-alveolar radiography or Cone Beam Computed Tomography (CBCT).

Dental metal filling inclued amalgam, crown cast and metal ceramic crown; dental resines filling inclued Glass Ionomere Cement (GIC) or composite; dental prosthesis inclued stellite or removable resin prosthesis.

## *2.6 Assessment criteria*

Main assessment criteria is the emergence of oral cGVHD during the first year post transplant.

## *2.7 Statistical Analysis*

Categorical variables are expressed as numbers (percentage). Continuous variables are expressed as means (standard deviation, SD) in the case of normal distribution or medians [range] otherwise. Normality of distribution is assessed using histograms and the Shapiro-Wilk test.

The factors that have an impact on cGVHD population or no cGVHD population and dead patients are analyzed by performing logistic regression models. Odds ratio (ORs) are represented as effect size measures, with their 95% confidence intervals (CIs).

These results are adjusted on the clinically knew risk factors (periodontal disease, origin of allograft, histocompatibility) using the logistic regression model.

Also, to compare association between histocompatibility and origin of allograft, we used Fisher exact test.

Statistical testing is done at the two-tailed α level of 0.05. Data are analyzed using SAS software package, release 9.4 (SAS Institute, Cary, NC, USA).

# 3. Results

## *3.1 Flow chart*

109 patients were seen in pre-graft dental check-up. Among them, 38 were excluded because they presented one of the 3 exclusions criterias:

- 17 patients died before 3 months
- 10 patients had their graft cancelled or postponed

**FLOW CHART**

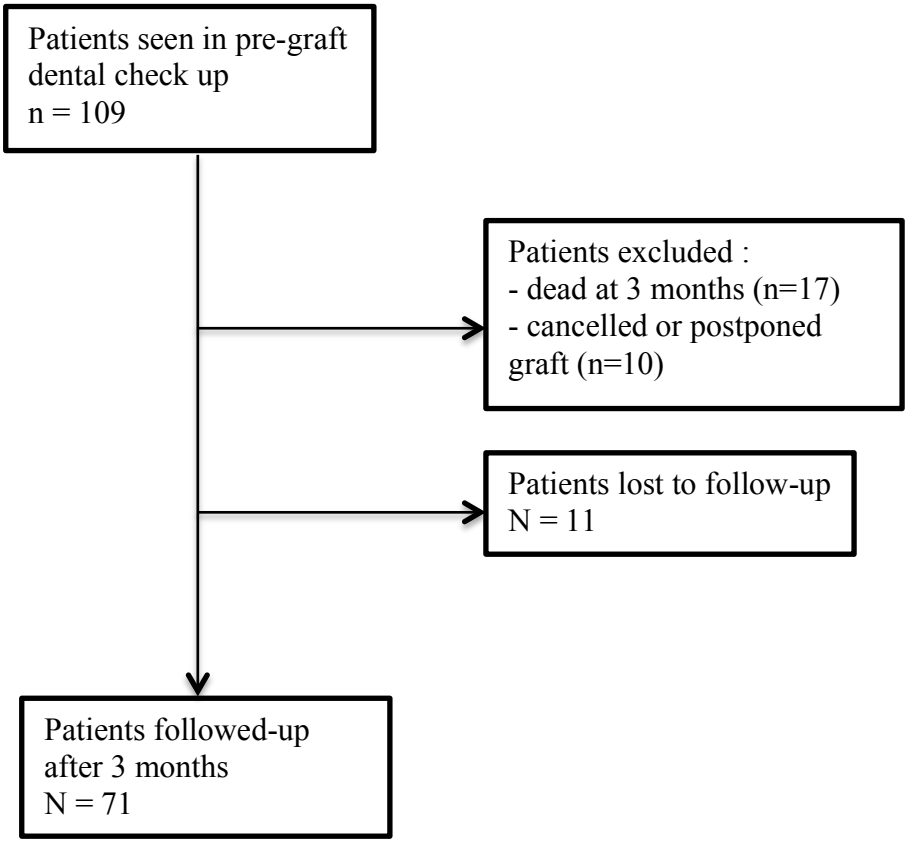



*Figure 3: Flow Chart.*

### *3.2 Descriptive results*

The initial population's features are presented on table 2.

Table 2 : The initial population's features : expressed in number (n) and percentage (%).

| **Features of initial population n = 71** | | |
|---|---|---|
| **Gender** | men | **39 (54.03)** |
| | women | **32 (45.07)** |
| **Mean age** | mean (SD) | **55 (11.7)** |
| **Haemopathy** | Lymphoma/ chronic lymphatic leukaemia | **9 (12.68)** |
| | Acute myeloblastic or lymphoblastic leukaemia/ myelodisplastic syndrome | **56 (78.87)** |
| | Myeloproliferative syndrome / myelofibrosis, chronic myeloid leukaemia | **4 (5.63)** |
| | Myeloma | **2 (2.81)** |
| **Preventive graft treatment** | Ciclosporin + methotrexate | **50 (70.43)** |
| | Ciclosporin + cellcept | **4 (5.63)** |
| | Endoxan, ciclosporin, cellcept | **7 (9.86)** |
| | Others | **10 (14.08)** |
| **Origin of allograft** | Pluripotent steem cells | **48 (67.61)** |
| | Bone marrow | **23 (32.39)** |
| **Conditioning graft** | Myeloablative | **41 (57.75)** |
| | Reduced | **30 (42.25)** |
| **Donor** | related | **27 (38.03)** |
| | non related | **44 (61.97)** |
| **Histocompatibility** | 10/10 | **50 (70.42)** |
| | 9/10 | **12 (16.90)** |
| | Haploid | **9 (12.68)** |
| **Smoker patient** | yes | **29 (40.85)** |
| | no | **42 (59.15)** |

| | | |
|---|---|---|
| **Alcohol consumption** | yes<br>no | **6 (8.45)**<br>**65 (91.55)** |
| **Dental metal filling** | between 0 and 4<br>between 5 and 10<br>> a 10 | **28 (39.44)**<br>**26 (36.62)**<br>**17 (23.94)** |
| **Dental prosthesis** | yes<br>no | **7 (9.86)**<br>**64 (90.14)** |
| **Dental resins filling** | between 0 and 4<br>between 5 and 10<br>> a 10 | **57 (80.28)**<br>**13 (18.30)**<br>**1(1.40)** |
| **Dental decay** | 0<br>1 or 2<br>> 2 | **39 (54.93)**<br>**20 (28.17)**<br>**12 (16.90)** |
| **Apical infectious foci** | yes<br>no | **14 (19.72)**<br>**57 (80.28)** |
| **Periodontal disease** | periodontal disease<br>periodontal health | **39 (54,93)**<br>**32 (45,07)** |

The mean age of initial population was 55 (31-73).

56 patients presented an acute hematopoïetic diseases as myeloblastic, lymphoblastic leukaemia or myelodisplastic syndrome.

Ciclosporine and methotrexate was taken as a preventive graft treatment by 50 patients (70.43). Origin of allograft was pluripotent steem cells for 48 patients (67.61) and bone marrow for 23 (32.39).

Conditioning graft was myeloablative for 41 patients (57.75) and reduced for 30 patients (42.25). Donnor was related for 27 patients (38.03) and non related for 44 patients (61.97).

Histocompatibility was 10/10 for 50 patients (70.42).

42 patients (59.15) were non smoker, and 29 (40.85) were smokers, 65 patients (91.55) didn’t consume alcohol.

Considering restaurative dental care :

- 28 (39.44) had beetween 0 et 4 dental metal filling, 26 (36.62) had between 5 et 10 and 17 (23.94) had more than 10.
- 57 patients (80.28) had between 0 et 4 dental resins filling, 13 (18,30) had between 5 and 10 and 1(1,40) had more than 10.

64 patients (90.14) didn’t have dental prosthesis.

Considering infected sites:

- 39 patients (54.93) didn’t have any dental decay, 20 (28.17) had 1 or 2 dental decay and 12 (16.90) had more than 2.
- 57 patients (80.28) didn’t have apical infectious foci, 39 patients (54.93) had a periodontal disease and 32 (45.07) didn’t have one.

Among 71 patients, 26 had cGVHD including 22 oral cGVHD, 6 died between 3 and 12 months, none of the patients with oral cGVHD died (figure 4). In this study we were interested in oral cGVHD but we noticed that 26 patients had cGVHD (cutaneous, digestive, ocular or vaginal).

Of the 6 patients who died, 2 patients died at 6 months and 4 patients died at 12 months. In this study, the 2 groups considered were oral cGVHD and no oral cGVHD. Dead patients were included in the no oral cGVHD group. The majority of oral cGVHD were diagnosed during the 6th and 12th month (Figure 5).

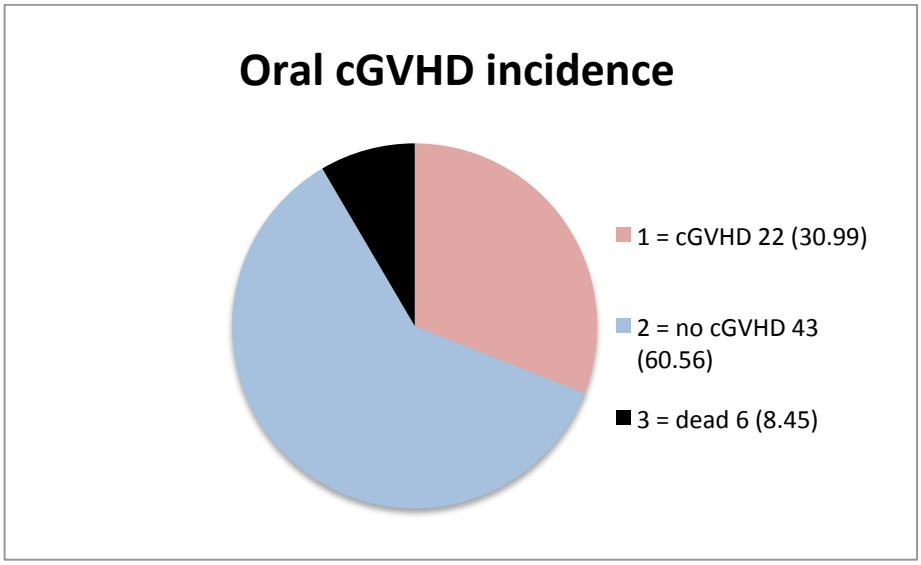



*Figure 4: Repartition of oral cGVHD incidence in the population.*

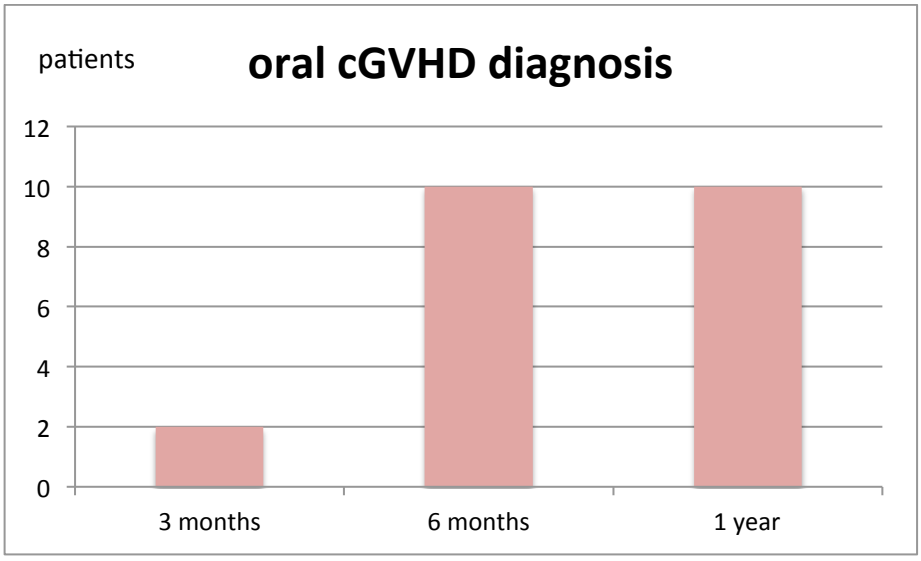



*Figure 5: Time of oral cGVHD diagnosis.*

cGVHD features are presented in table 3 and table 4.

54.54 percent of patients had 1 area of location, 31.82 percent had 2 areas and 13.64 percent had generalised achievement.

Table 3 : Precise location of oral cGVHD

| location / Oral cGVHD | Lingual | Jugual | palatine | Maxillary gums | Mandibulary gums |
|---|---|---|---|---|---|
| 1 | X | X | | X | |
| 2 | | X | | | |
| 3 | X | | | | |
| 4 | | X | | X | |
| 5 | X | X | | X | X |
| 6 | X | | | | |
| 7 | | X | X | | |
| 8 | X | X | | | |
| 9 | | X | | X | |
| 10 | | X | X | | |
| 11 | X | X | | X | |
| 12 | X | X | | | |
| 13 | X | | | | |
| 14 | | X | | | |
| 15 | X | X | X | | |
| 16 | X | X | X | X | X |
| 17 | | | | | X |
| 18 | X | X | X | X | X |
| 19 | | X | | | |
| 20 | X | X | | | |
| 21 | | X | | | |
| 22 | X | X | | | |

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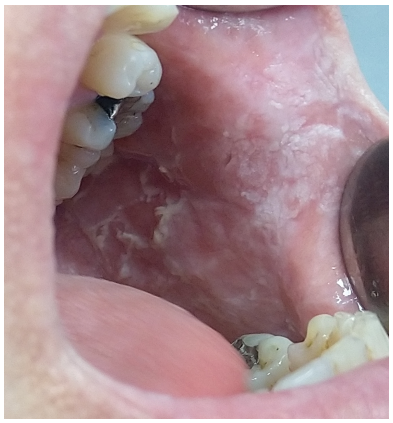
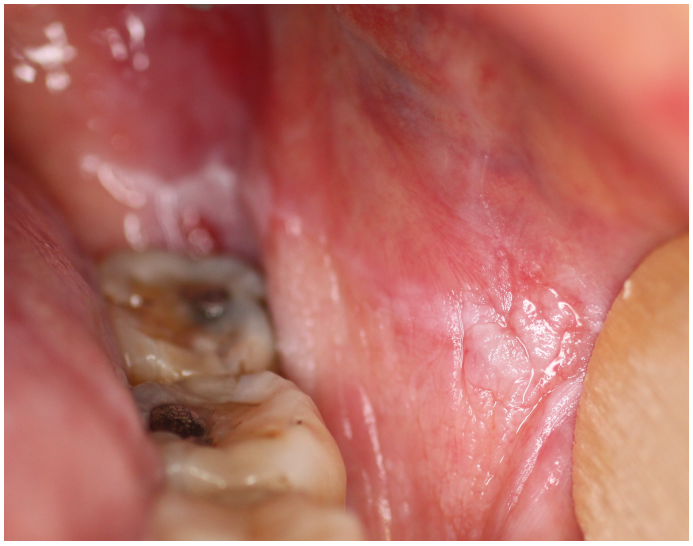
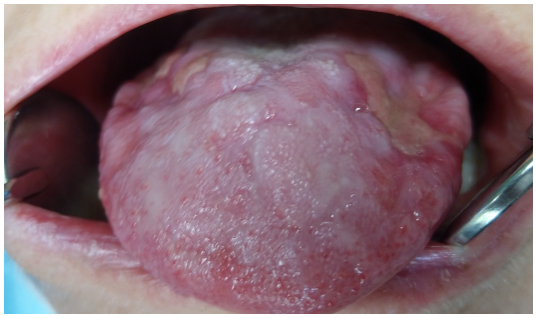
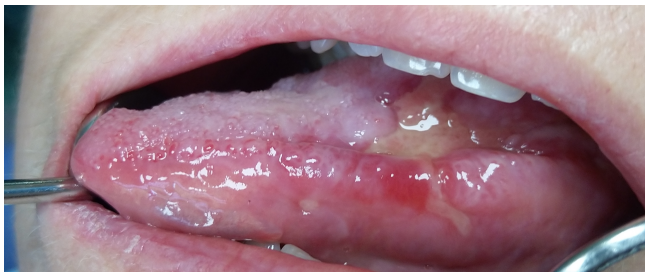
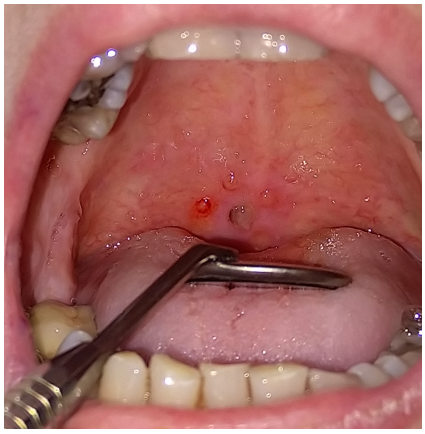
 (a)

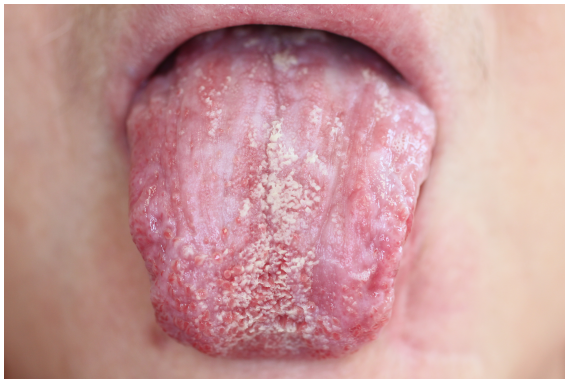
 (b)

 (c)

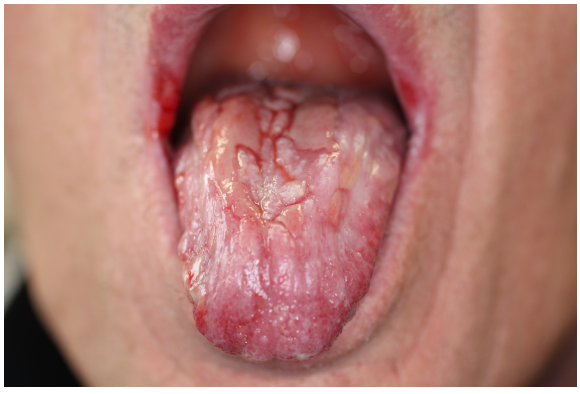
 (d)



(e)



(f)



(g)

*Figure 5 : Changes of buccal mucosa in cGVHD: Lichenoide lesion of jugual mucosa (a,b). Lingual ulcerative lesion (c). Lingual erythema and ulcerative lesion (d). Palatine mucoceles lesion (e). Lingual leucoplasie lesion, depapillation (f). Lingual leucoplasie, ulcerative lesion (g).*

Table 4: Oral cGVHD specificities

| Oral cGVHD population n = 22 | |
|---|---|
| **Location** | |
| - 1 area | **12 (54.54)** |
| - 2 area | **7 (31.82)** |
| - generalised achievement | **3 (13.64)** |
| **Manifestation** | |
| - erythema, petechiae | **8 (36.36)** |
| - lichenoid | **14 (63.64)** |
| **Impact** | |
| - no | **14 (63.64)** |
| - moderate impact, not restrict feeding | **5 (22.73)** |
| - severe impact, restrict feeding | **3 (13.63)** |
| **Dental contact** | |
| - no | **17 (77.27)** |
| - yes | **5 (22.73)** |

36.36 percent of patients had erythema and petechiae (Figure 5: d,e), 63.64 percent had lichenoid lesions (Figure 5: a,b).

63.64 percent of patients didn't have any functional impact with their oral cGVH, 22.73 percent had moderate impact, not restrict feeding, and 13.63 percent had severe impact, restrict feeding.

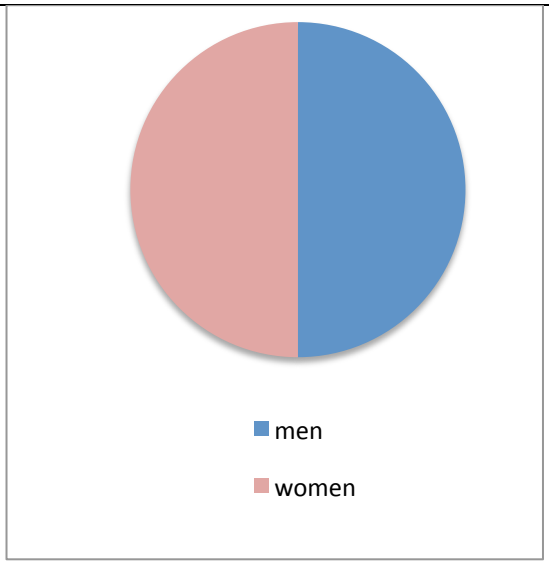
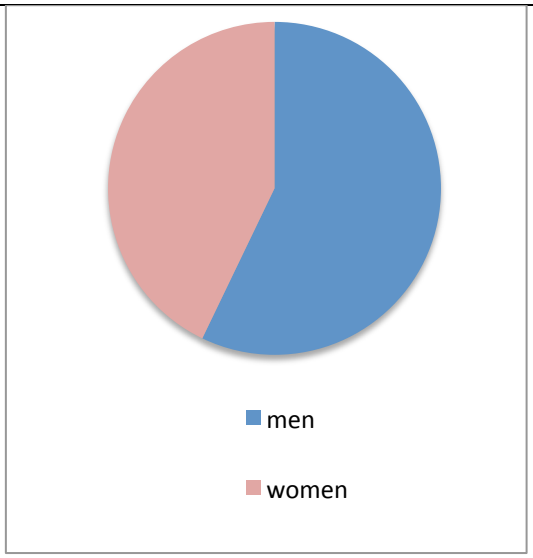
77.27 percent of patients didn't have dental contact with their oral cGVH, 22.73 percent had dental contact with their oral cGVH.

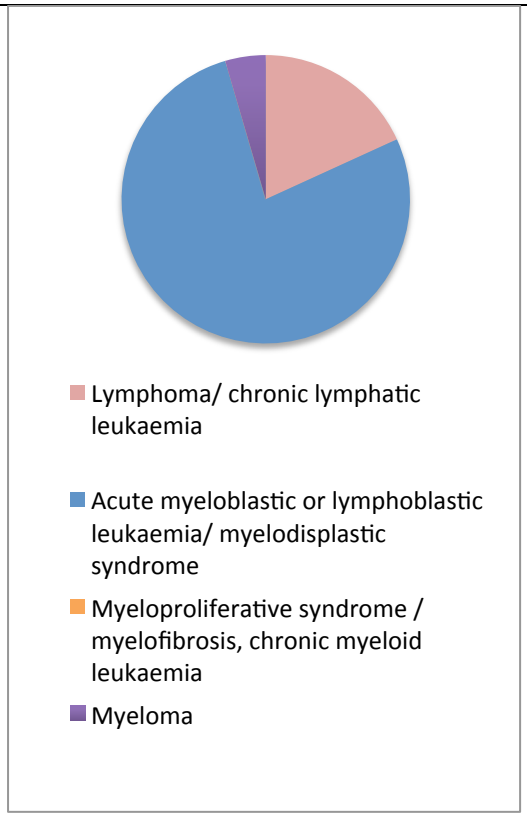
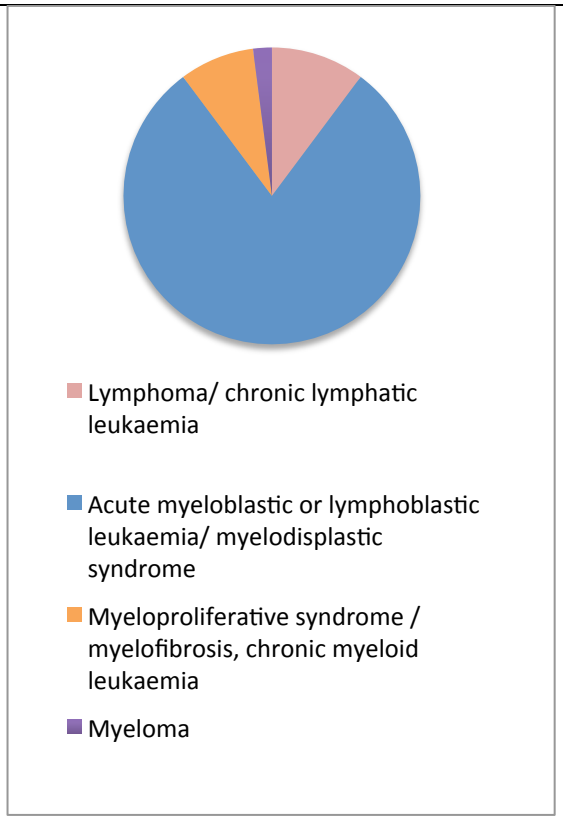
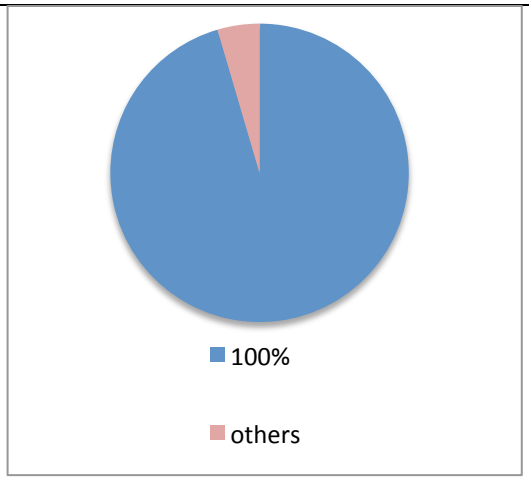
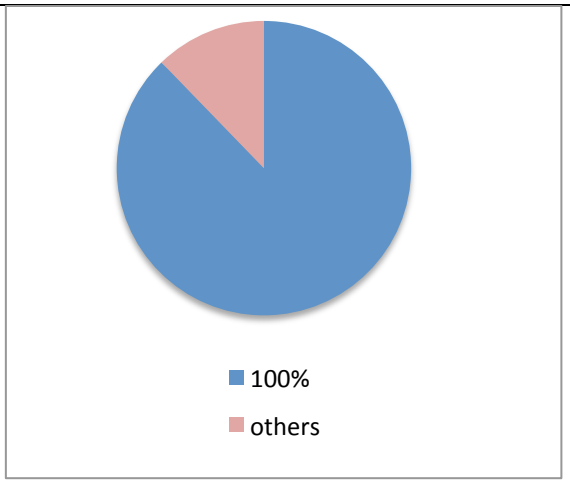
Data on pH and xerostomia were collected throughout the follow-up and are presented in appendix 8 and 9.

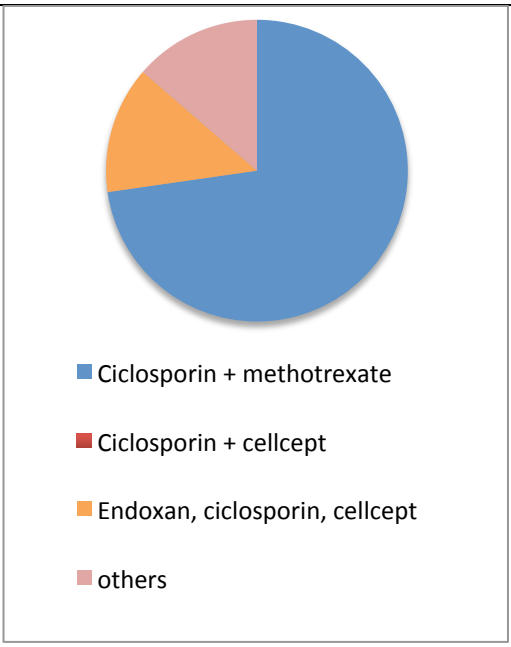
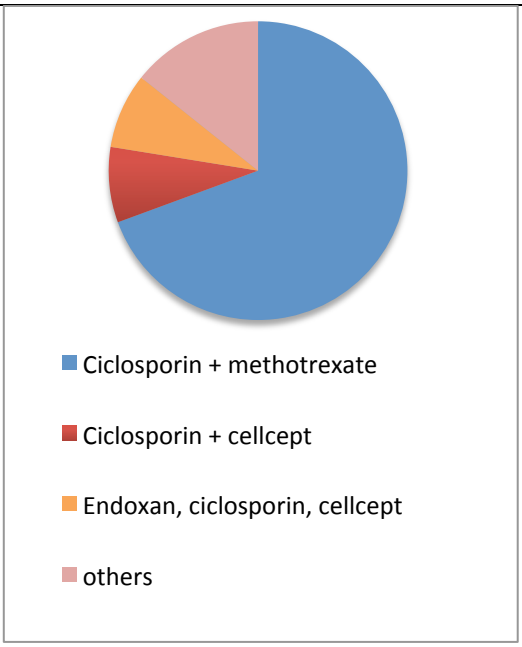
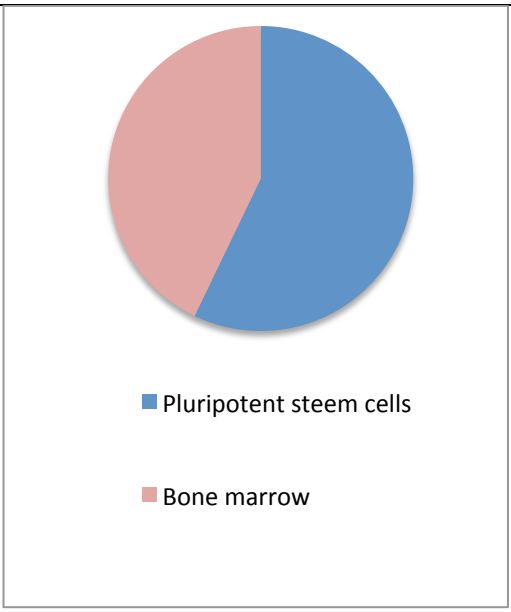
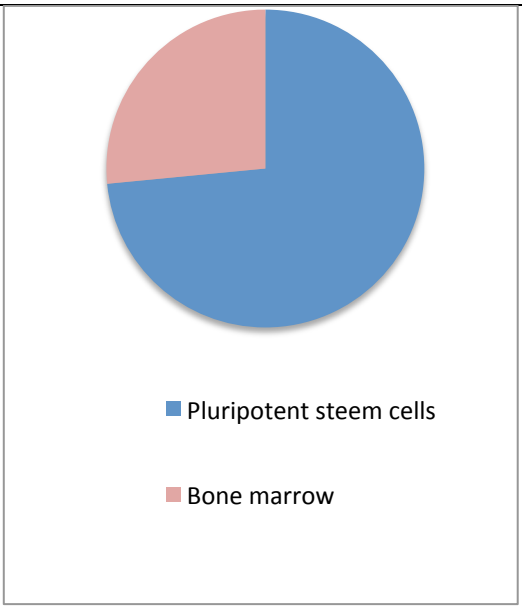
### *3.3 Influence of general factors on the development of oral cGVHD.*

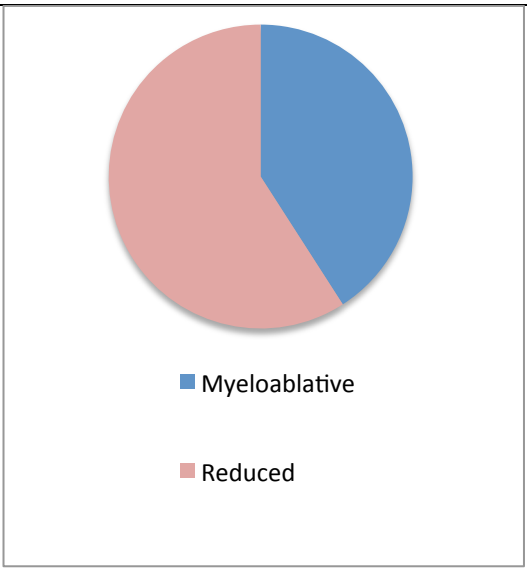
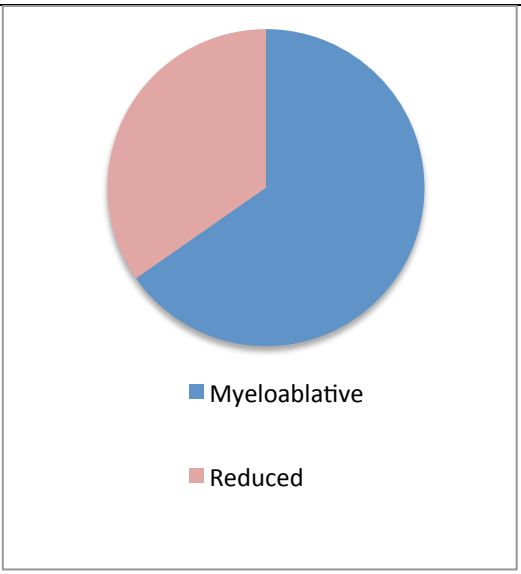
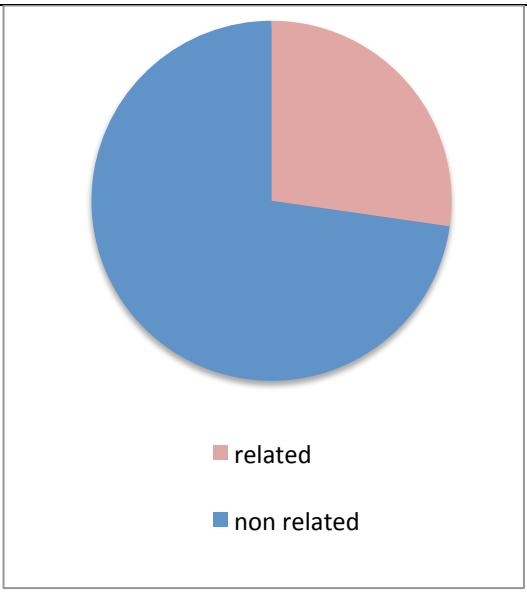
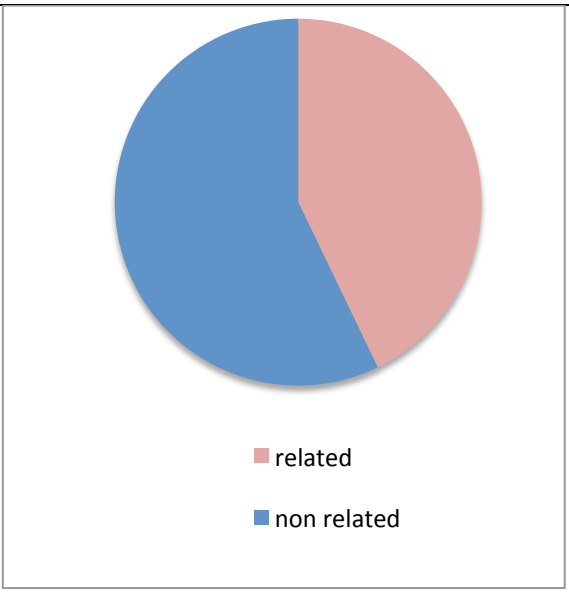
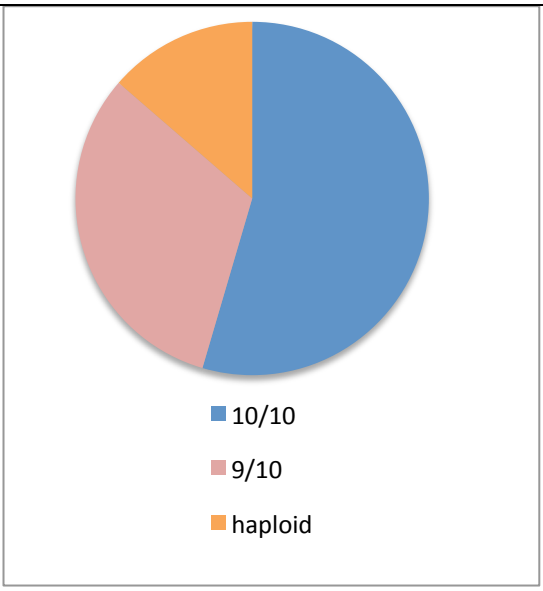
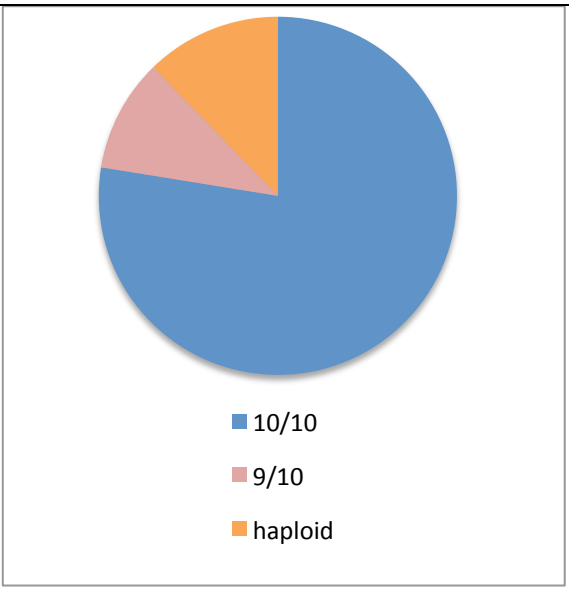
The descriptive features of following general factors were assessed below:

- Gender (figure 7);
- Haemopathy (figure 8);
- Chimerism (figure 9);
- Preventive graft treatment (figure 10);
- Origin of allograft (figure 11);
- Conditioning graft (figure 12);
- Donor (figure 13);
- Histocompatibility (figure 14).

| | **Oral cGVHD** | **No oral cGVHD + dead** |
|---|---|---|
| *Figure 7: Gender in oral and no oral cCVHD and dead patients.* |  |  |

| | | |
|---|---|---|
| *Figure 8: Haemopathies in oral and no oral cCVHD and dead patients.* |  |  |
| *Figure 9: Chimerism in oral and no oral cCVHD and dead patients.* |  |  |

| | | |
|---|---|---|
| *Figure 10: Preventive graft treatment in oral and no oral cCVHD and dead patients.* |  |  |
| *Figure 11: Origin of allograft in oral and no oral cCVHD and dead patients.* |  |  |

| | | |
|---|---|---|
| *Figure 12: Conditioning graft in oral and no oral cCVHD and dead patients.* |  |  |
| *Figure 13: Donors in oral and no oral cCVHD and dead patients.* |  |  |
| *Figure 14: Histocompatibility in oral and no oral cCVHD and dead patients.* |  |  |

The influence of general factors on oral cGVHD occurrence in the two differents populations is presented in table 5.

Table 5: Influence of general factors on oral cGVHD occurrence.

| **Oral cGVHD population (n=22) versus no oral cGVHD population + dead (n=49) p Value / Odds Ratio (ORs) and confidence intervals (CIs).** | |
|---|---|
| **Gender** | p = 0.5764 / 1.333 (0.486-3.658) |
| **Haemopathy** | p = 0.8131 / NS |
| **Chimerism** | p = 0.9993 / NS |
| **Preventive graft treatment** | p = 0.9869 / NS |
| **Origin of allograft** | p = 0.1192 / 2.308 (0.806-6.607) |
| **Conditioning graft** | p = 0.0579 / 2.719 (0.967-7.643) |
| **Conor** | p = 0.2150 / 2.000 (0.669-5.982) |
| **Histocompatibility** | p = 0.0855 / NS |
| **Age** | p = 0.4359 / 0.983 (0.942-1.026) |

No significant difference between the oral cGVHD group and the no oral cGVHD group have been observed among general factors (table 5).

The chimerism in the two differents populations is presented in table 6.

Table 6: Chimerism percentage among oral cGVHD occurrence.

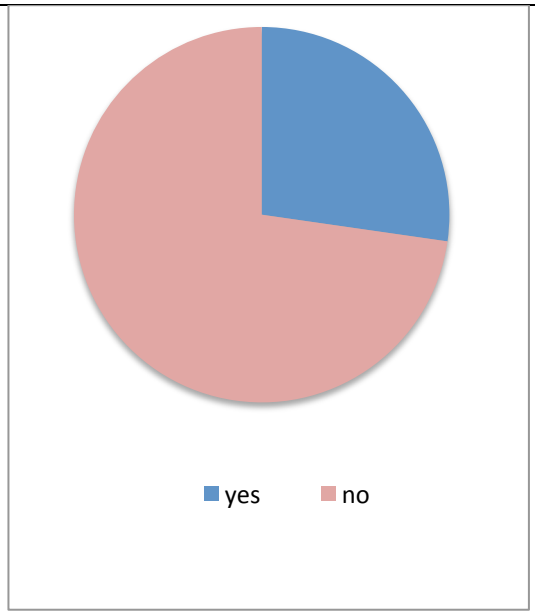
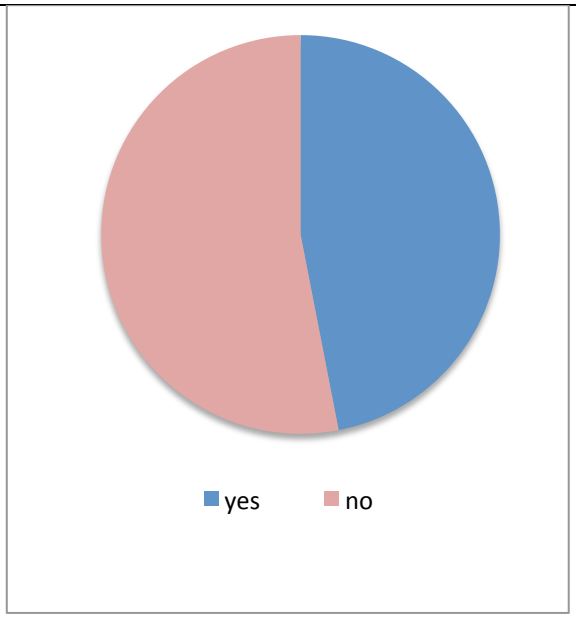
| **Initial population n = 71** | **Oral cGVHD n = 22** | **No oral cGVHD + dead n = 49** |
|---|---|---|
| **Chimerism** | | |
| - 100% | **21 (95.5)** | **43 (87.8)** |
| - others | **1 (4.5)** | **6 (12.2)** |

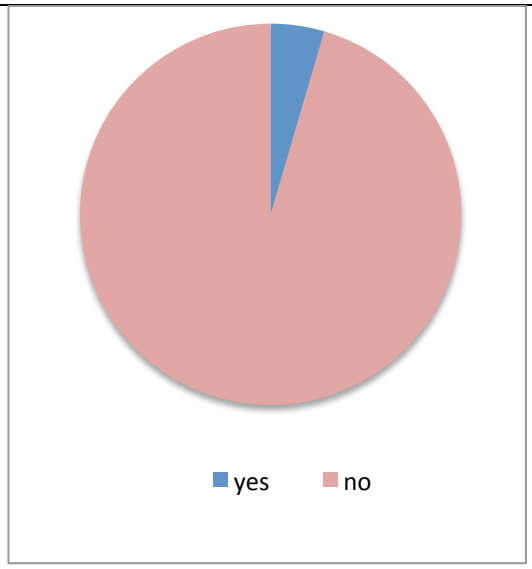
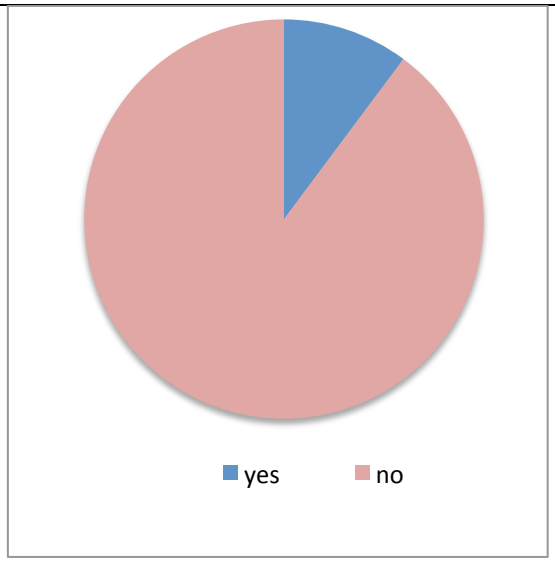
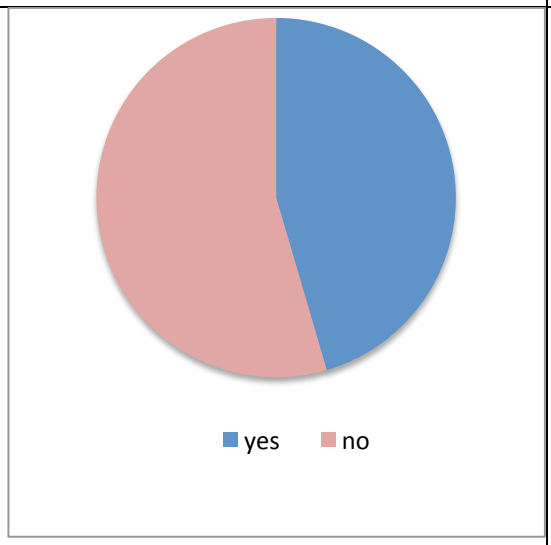
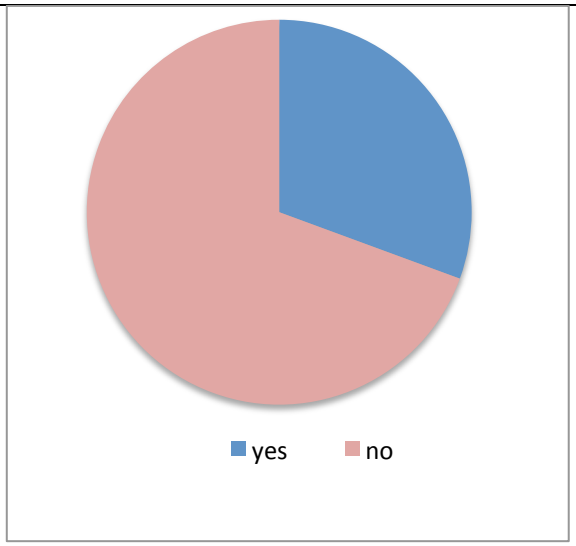
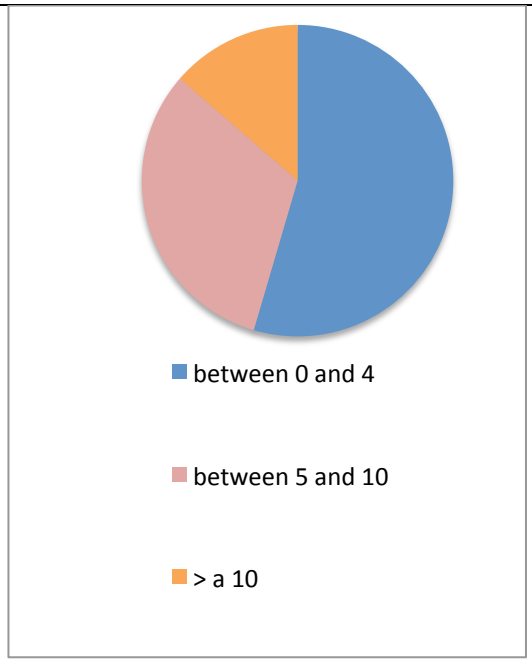
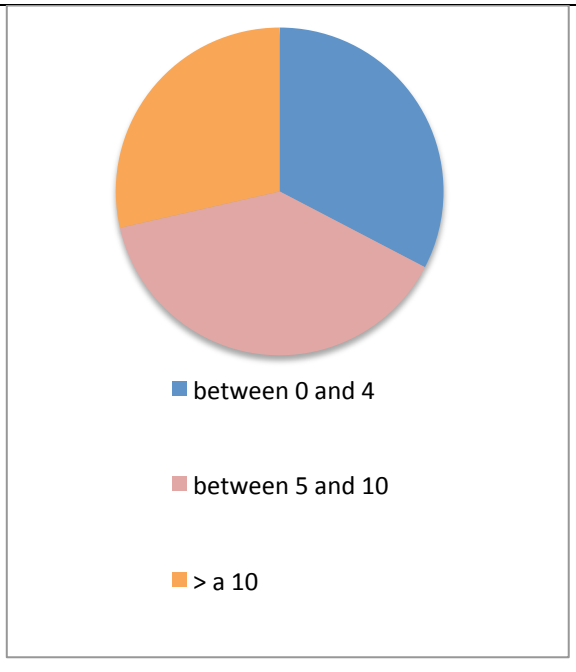
Among 22 patients with oral cGVHD, 95.5 had a 100% chimerism at 3 months, in the population with no oral cGVHD and dead patients, 87.8 percent of patients had a 100% chimerism at 3 months (table 6).

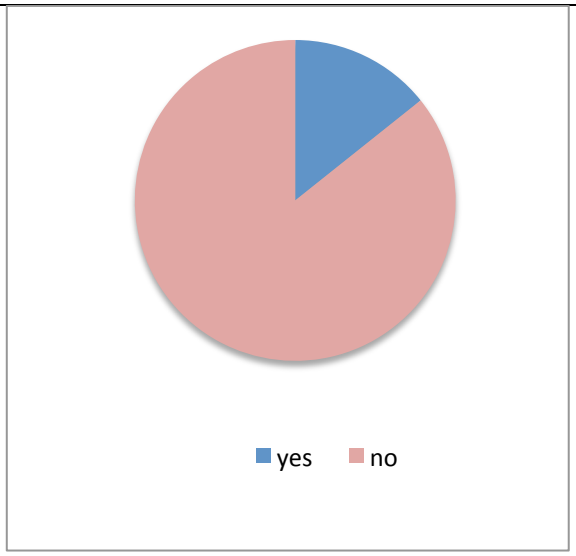
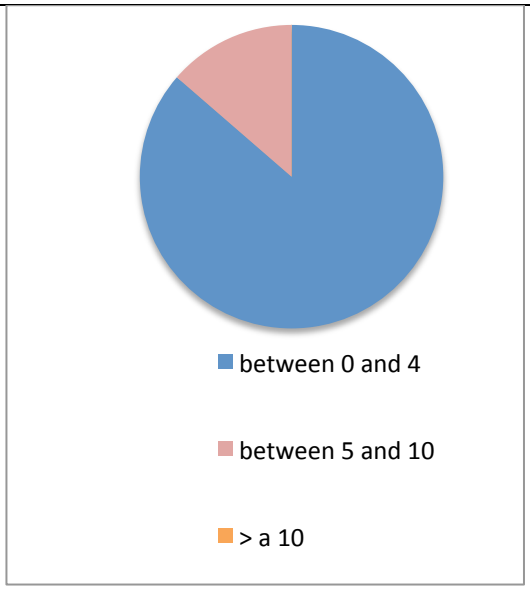
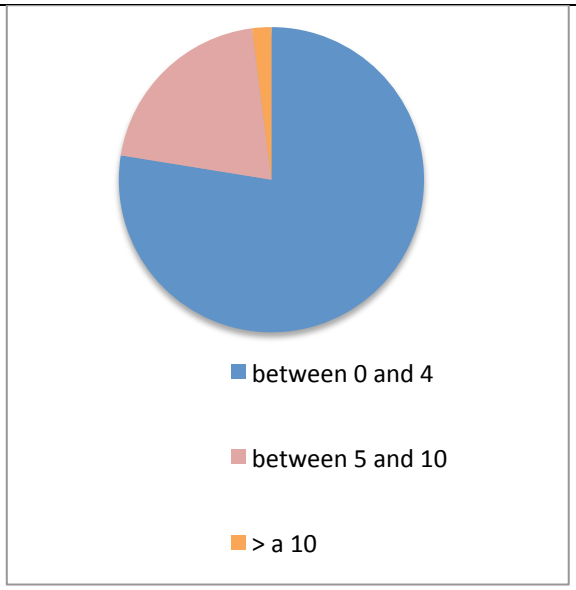
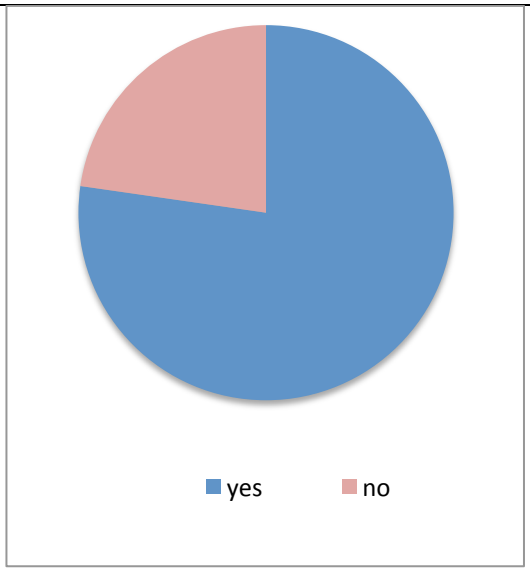
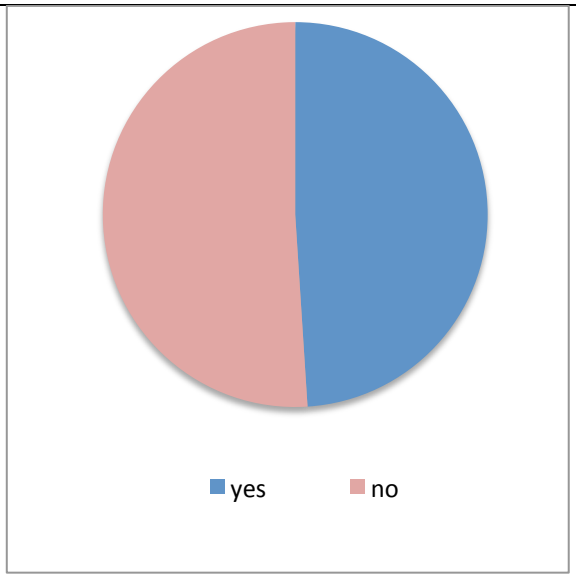
### 3.4 *Influence of oral factors on the development of oral cGVHD.*

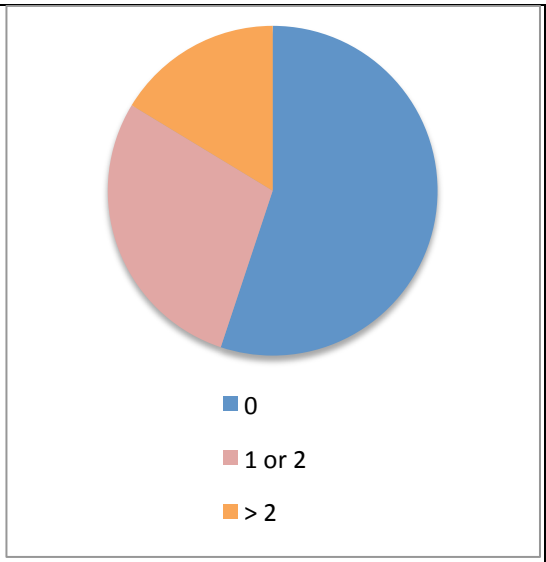
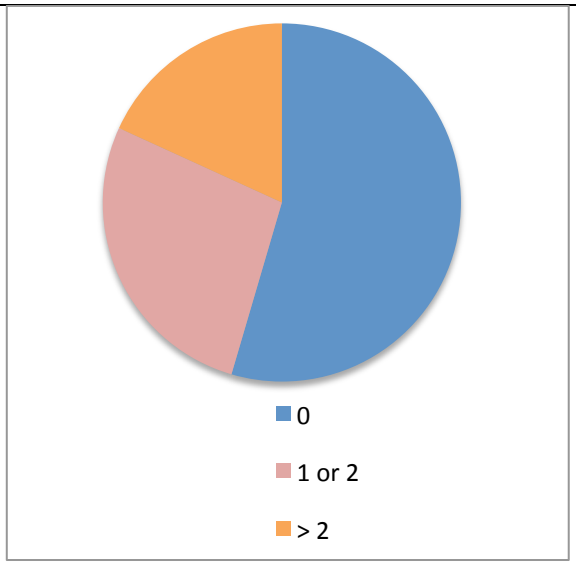
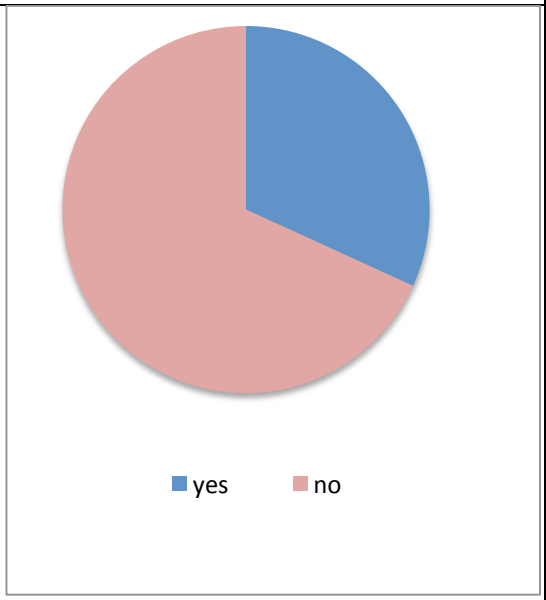
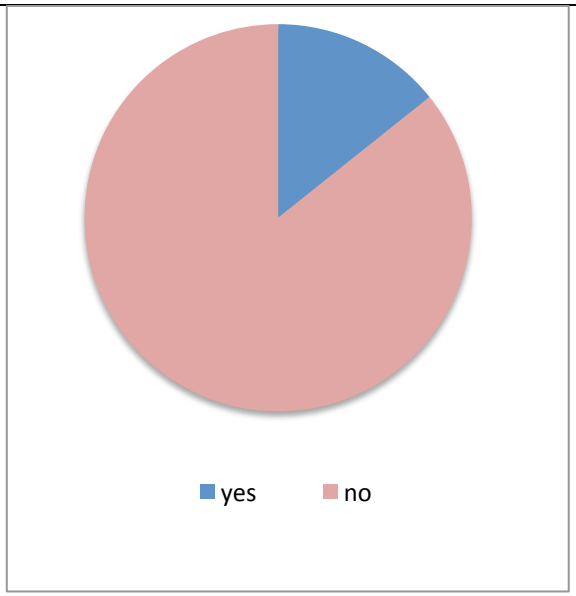
The descriptive features of following oral factors were assessed below:

- Smoker patient (figure 15);
- Alcohol consumption (figure 16);
- Xerostomy (figure 17);
- Dental metal filings (figure 18);
- Dental prosthesis (figure 19);
- Dental resins filings (figure 20);
- Periodontal disease (figure 21);
- Dental decay (figure 22);
- Apical infectious foci (figure 23).

| | **Oral cGVHD** | **No oral cGVHD + dead** |
|---|---|---|
| *Figure 15: Smoker patients in oral and no oral cCVHD and dead patients.* |  |  |

| | | |
|---|---|---|
| *Figure 16: Alcohol consumption in oral and no oral cCVHD and dead patients.* |  |  |
| *Figure 17: Xerostomy in oral and no oral cCVHD and dead patients.* |  |  |
| *Figure 18: Dental metals filings in oral and no oral cCVHD and dead patients.* |  |  |

| | | |
|---|---|---|
| *Figure 19: Dental prosthesis in oral and no oral cCVHD and dead patients.* |  |  |
| *Figure 20: Dental resins filings in oral and no oral cCVHD and dead patients.* |  |  |
| *Figure 21: Periodontal disease in oral and no oral cCVHD and dead patients.* |  |  |

| | | |
|---|---|---|
| *Figure 22: Dental decay in oral and no oral cCVHD and dead patients.* |  |  |
| *Figure 23: Apical infectious foci in oral and no oral cCVHD and dead patients.* |  |  |

The influence of oral factors on oral cGVHD occurrence in the two differents populations is presented in table 7.

Table 7: Influence of oral factors on oral cGVHD occurrence.

| **Oral cGVHD population (n=22) versus no oral cGVHD population + dead (n=49) p Value / Odds Ratio (ORs) and confidence intervals (CIs)** | |
|---|---|
| **Smoker patient** | p = 0.1239 / 0.424 (0.142-1.265) |
| **Alcohol consumption** | p = 0.4403 / 0.419 (0.046-3.816) |
| **Xerostomy** | p = 0.1679 / 2.083 (0.734-5.914) |
| **Dental metal filings** | p = 0.3611 / NS |
| **Dental prosthesis** | p = 0.9670 / NS |
| **Dental resins filings** | p = 0.4106 / NS |
| **Periodontal disease** | p = 0.0145 / 4.173 (1.328-13.113) |
| **pH** | p = 0.5451 / 1.500 (0.403-5.579) |
| **Oral Bacterial foci** | p = 0.3048 / NS |
| **Dental decay** | p = 0.7672 / NS |
| **Apical infectious foci** | p = 0.0933 / 2.800 (0.841-9.315) |

Periodontal disease criteria had been significantly different between the oral cGVHD group and the no oral cGVHD group (p=0.0145) (table 7).

Periodontal disease criteria increased 4.173 times the risk of oral cGVHD occurrence (IC = 1.328- 13.113).

No significant difference between the oral cGVHD group and the no oral cGVHD group were been observed among others oral factors (table 7).

The analysis of oral factors adjusted in oral cGVHD in the two differents populations is presented in table 8.

Table 8: Analysis of oral factors adjusted in oral cGVHD occurrence.

| **Adjusted analysis**<br>**Oral cGVHD population (n=22) versus no oral cGVHD population + dead (n=49)**<br>**p Value / Odds Ratio (ORs) and confidence intervals (CIs)** | |
|---|---|
| **Periodontal disease**<br>**Origin of allograft**<br>**Histocompatibilty**<br>**Age** | p = 0.0389 / 3.644 (1.068-12.431)<br>p = 0.0938 / 2.811 (0.839-9.419)<br>p = 0,0666 / 5,769 (1.300-25.602)<br>p = 0,8603 / 0,996 (0.949-1.045) |
| **Histocompatibility**<br>**Origin of allograft** | p = 0.0414 / 6.196 (1.502-25.564)<br>p = 0.0459 / 3.246 (1.022-10.313) |

Adjusted with origin of allograft, histocompatibility and age, periodontal criteria was significantly different between the oral cGVHD group and the no oral cGVHD group (p=0.0389) (table 8).

Adjusted with origin of allograft, histocompatibility and age, periodontal criteria increased 3.644 times the risk of oral cGVHD occurrence (IC = 1.068-12.431).

The association of the histocompatibity and origin of allograft is reported to significantly differ between the cGVHD group and the no cGVHD group (respectively p=0,0414, p=0,0459).

Histocompatibility and origin of allograft were independant parameters when their correlation has been tested by the Fischer's test (p=0.52, higher than the probability table P = 0.0378).

The analysis of xerostomy in the two differents populations is presented in table 9.

Table 9: Analysis of xerostomy and pH in oral cGVHD and no oral cGVHD and dead patients.

| **Initial population n = 71** | **Oral cGVHD n = 22** | **No oral cGVHD + dead n = 49** |
|---|---|---|
| **Xerostomy** | | |
| - no | **12 (54.5)** | **34 (30.6)** |
| - yes | **10 (45.5)** | **15 (69.4)** |
| **pH** | | |
| mean (SD) | **6,5 (0.45)** | **6,4 (0.37)** |

Among 22 patients with oral cGVHD, 54.5 percent didn't have xerostomy and 45.5 percent had xerostomy (table 9).

Mean pH in oral cGVHD population was 6.5. Mean pH in no oral cGVHD population and dead patients was 6.4 (table 9).

In the population with no oral cGVHD and dead patients, 30.6 percent of patients didn't have xerostomy, 69.4 percent of patients had xerostomy.

# 4. Discussion

The cGVHD prevalence varies in the litterature, from 17% to 25% in pediatric population, and from 28% to 67% in adults population (56–61). In our study, 37% of patients presented cGVHD and 31% of patients presented oral cGVHD. The large range of cGVHD occuring observed between the different studies could be linked to the distinct features of the initial populations, concerning HLA matching or origin of stem cell source, mean age, haemopathies and difficults to class the GVH precisely as aGVH delayed, aGVH persistent, aGVH recurrent, cGVHD, cGVHD overlap.

Oral impairment varies between 33% and 75% for patients with aGVHD and more than 80% for those with cGVHD, as in our study where 85 percent of patients with cGVHD had oral impairment (1).

11 patients were lost to follow, due to a relapse, an hospitalisation or an alteration on their state of health preventing them from going to a dental consultation.

The cGVHD is typically presented as occurring after the first 100 days after the transplant, howewer it is not the time of onset but the clinical presentation that characterizes the cGVHD. Our diagnostic of cGVHD was only based on the clinical criteria of the NIH consensus (30,62).

Clinical aspects frequently found were lichenoid lesions with 64 percent of our patients, associated with diagnosis of cGVHD (63,64).

There are three differents sources for allogeneic HSCT: BMT, PBSCT, and Umbilical Cord Blood (UCB). In our study, we only considered the BMT or PBSCT sources and we did not find a significative difference between the origin of transplant and the incidence of oral cGVHD, altought results suggested that cGVHD after PBSCT may be more protracted and less responsive to treatment than cGVHD after BMT (46).

As a source of HSCT, UCB has advantages of rapid availability, tolerance, and low incidence of severe cGVHD, however none of our patients had received this source of transplant. For 10 years haploidentic transplants increased a lot, so there are many possibilities to find a compatible donnor and it provokes less relapses; also neutrophil recovery is slower in UCB (46,65,66).

Numerous studies have shown that general factors such as the age, the gender, the reduce or non myeloablative conditioning, the HLA matching, the CML or the association of methotrexte and ciclosporine as preventive treatment could reduce the others location of cGVHD onset (38–44,47,49,50). Howewer, our study didn't notice a significant impact of these generals factors on the oral cGVHD. A larger patients cohort study could be strengthen the workforce and confirm the potential impact of these general factors on the oral forms of the cGVHD.

Viral manifestations could contribute to the manifestation of cGVHD, we have received the HSV status of the patients in our study, but only 1 case was positive and then no statistical analysis was possible (67).

The prevalence of cGVHD may also vary depending on the pre-transplant oral dental conditions (decay/pre-transplant infectious foci). We know that many dental treatments are needed before HSCT as scaling, plastic fillings and extractions (68).
Oral hygiene protocols, have been created by Association of Supportive Care in cancer and International Society of Oral Oncology, to prevent infection, control pain, maintain oral function, manage complications of treatment or medication and improve quality of life (69).

A relationship between rampant caries and the oral mucosal manifestations of cGVHD has been previously suggested (70). Patients whose decay are not treated before graft are likely to develop infections (71). Also, bacterial status throught dental treatments and oral hygiene have an impact in the development of the cGVHD, the incidence of oral complications decrease for patients who completed their dental care prior to chemotherapy (72).

Digestive decontamination has a beneficial impact on the incidence of severe digestive aGVHD, similarly we could consider that bacterial decontamination by periodontal treatment could reduce oral cGVHD (73).

No association was found between the pre-graft periodontal disease and the risk factor of sepsis in patients receiving an hematopoietic stem cell transplant (74). Howewer, other studies suggested that periodontal disease and GVHD might be associated, less sites with bleeding and less oral mucitis were noticed for patients who received pre-transplant periodontal treatment (53).

In the present study, presence of periodontal disease is significantly more important in the oral cGVHD group compared to the controle group (p=0.0145). Periodontal disease criteria increased 4.173 times the risk of oral cGVHD occurrence (IC = 1.328- 13.113). Progression of GVHD is summarised in three sequential steps or phases: activation of antigen prensenting cells; donor T-cell activation, proliferation, differentiation, and migration; and target tissue destruction (12,75). An hypothesis to explain the relation between periodontal disease and oral cGVHD might be that periodontal disease changes inflammatory status with an augmentation of pro inflammatory markors, with the same mecanism and steps of GVHD, provoking the activation and the migration of T-cells with the consequence of tissular destruction and oral cGVHD.

Thus, the reduction of inflammatory pro markors like IL-1ra, CSTB or cytokines, lymphoctopenia and diminution of IgG could be associated with a diminution on the oral cGVHD's incidence (76–79).

One limitation of the present study is the heterogeneity of the population with the multiplicity of general factors. Limited approches, for example with standardized preventive treatments or with haemopathy patient cohorte, could be enhance the workforce of the evaluation of the impact of the numerous factors. Our study evaluate a very large number of oral modalities but doesn't investigate the precise dental location of reconstructions, decay, infectious foci.

These evaluations could be interestingly impact the extent of oral cGVHD. Larger sample, could permit to precise the impact and the severity of oral factors in the developement of oral cGVHD.

In addition, in the present study periodontal disease has been classified as periodontal health versus periodontal disease, it would be interesting to use the classification of Chicago, using grade and stage to specify the impact of the periodontal disease in the occurrence of cGVHD (79).

A perspective could be to look at the influence of gingival inflammatory factor or bone loss in the occurrence of oral cGVHD. Also, mecanisms studied by Page in the analysis of the pathogenesis of periodontis might be similar (80).

Finally, numerous authors have studied biomarkers to predict GVHD occurrence (81,82). Mass spectrometry, is a valuable aid in the early detection of GVHD, through the reduction of known salivary proteins, as salivary lactoperoxidase, or lactotransferrin in relation to impaired oral antimicrobial host immunity (83).

Precise diagnostic on cGVHD consists in the biopsy of the accessory salivary glands which showed atrophy and infiltration by lymphocytes (84–87). Also, this biopsy illustrated the relationship between GVHD and damages to the labial and lacrimal glands (88). An histological classification system has been developped, for cGVHD of minor salivary glands based on the degree of lymphocytic infiltration and destruction of glandular acins (89). Thus it will be interesting to use this technic to precise the diagnostic of oral cGVHD.

Salivary proteins might be interesting biomarkers in the prediction of GVHD incidence (90). Another perspective could be to analyse the salivary composition before allograft.

# 5. Conclusion

Oral cGVHD is a common manifestation of PBSCT in patients with haemopathies. These consequences can strongly affect the patient, limiting his alimentation. Therefore, it is necessary to better understand this manifestation, reaction, and to prevent more possible the known risk factors.

This study showed the role of periodontal disease in the development of oral cGVHD. Indeed oral factors are little known unlike general factors. Periodontal disease factor is a strong lead, because 50 percent of population has a periodontitis. It is the first time that pre-existing periodontal disease is reported as a local oral factor which could influence cGVHD occuring. So it is really necessary to planify a dental monitoring, before, during and after the transplant. It is very important to raise the patient’s awareness of oral hygiene, to explicate and motivate dentists consults, to realise dental care and to stabilise all peridontal diseases in the event of haemopathies or futur transplant, preventing patients to oral cGVHD occurrence.

Today, symptomatics treatments exist for GVHD, corticosteroids are the systemic treatments of choice, but no topical treatment has been identified as treatment of choice (91). More, intraoral NB-UVB may be effective for management of refractory oral cGVHD (92). Oral forms of cGVHD that are refractory to treatment and have functional repercussions on the patient's diet and quality of life make them an indesirable consequence we have to prevent.

None treatment exist to cure the GVHD so the best way is to prevent his apparition, minimizing all known risk factors.

It will be necessary to reassure, to explain to patients the issues of oral health in the prevention of oral cGVHD, and to strengthen the collaboration between haematologists and dental surgeons, in order to minimize as much as possible complications of PBSCT.

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# Appendix

## *Appendix 1: Pre-graft data index.*

**Données administratives**

Code investigateur : ……

Code anonyme patient : ……..

Date de naissance : …….

Date examen oral : ……..

**Facteurs oro-médicaux**

| | | |
|---|---|---|
| Diabète déclaré traité | OUI | NON |
| VHC + | OUI | NON |
| Tabagisme chronique | OUI | NON |
| Addiction à l'alcool | OUI | NON |

Facteurs médicamenteux présents (ulcérations/xérostomie/réactions lichénoides) OUI NON

Xérostomie (morceau de sucre n°4 sub-lingual fondu en + de 3 mn) OUI NON

pH salive totale à distance des repas (+2h00) ……

**Facteurs bucco-dentaires**

Métaux non précieux :

Métaux précieux :

Résines composites :

Foyers infectieux dentaires (caries, péricoronarite, parodontite, gingivite*)

| **Score** |
|---|
| 0 = absence |
| 1 = 1 à 4 foyers |
| 2 = 5 à 9 foyers |
| 3 = 10 et + foyers |
| *gingivite = score 1 |

## *Appendix 2: Writed consent.*

**Information pour enregistrement anonyme des données dans le registre d'évaluation de l'impact des facteurs bucco-dentaires préexistant à l'allogreffe dans la maladie du greffon contre l'hôte chronique endobuccale**

Madame, Monsieur,

Vous êtes atteint d'une maladie dont le traitement va nécessiter une allogreffe de cellules souches hématopoïétiques, c'est-à-dire une greffe de moelle issue d'un donneur compatible avec vous.

Ce traitement a été choisi après présentation de votre dossier en réunion de concertation pluridisciplinaire.

Nous vous proposons d'enregistrer les données cliniques vous concernant afin d'améliorer l'évaluation des conséquences de ces traitements

L'objectif de cette étude, que nous vous proposons, est de permettre l'amélioration de la prise en charge des patients devant bénéficier du même traitement grâce à l'analyse statistique du registre obtenu.

Les données enregistrées sont anonymes. Chaque individu est identifié par un code UPN *(unique patient number / numéro unique du patient*) et personne, en dehors de l'hôpital où vous êtes traité, ne peut vous identifier et/ou avoir accès aux données vous concernant. Ce registre vous garantit toute confidentialité de votre vie privée.

**Consentement pour l'enregistrement anonyme des données dans le registre d'évaluation de l'impact des facteurs bucco-dentaires préexistant à l'allogreffe dans la maladie du greffon contre l'hôte chronique endobuccale**

Afin que la procédure soit suivie de façon légale, nous vous demandons votre consentement pour que les données cliniques, biologiques ou radiographiques inhérentes à votre état buccal et à votre maladie soient recueillies et enregistrées dans la base de données de ce registre.

Je soussigné(e) (nom et prénom du patient)…….reconnait avoir été informé(e) des principes de ce registre et je consens à ce que ces données anonymes soient enregistrées et analysées ultérieurement avec l'ensemble des données des autres patients.
Signature du (de la) patient(e)

Je confirme (nom du praticien)……avoir clairement expliqué le principe de ce registre au (à la) patient(e).

Signature du praticien

***Appendix 3: Post-graft data index.***

## Données administratives

Code investigateur : ……

Code anonyme patient : ……..

Date de naissance : …….

Date examen oral : ……..

Date de la greffe : ……..

## Facteurs oro-médicaux

Diabète déclaré traité OUI NON

VHC + OUI NON

Tabagisme chronique OUI NON

Addiction à l'alcool OUI NON

Facteurs médicamenteux présents (ulcérations/xérostomie/réactions lichénoides) OUI NON

Xérostomie (morceau de sucre n°4 sub-lingual fondu en + de 3 mn) OUI NON

pH salive totale à distance des repas (+2h00) ……

## Evénements post-greffe

Prophylaxie GVH COR MTX mycophénole M autre : ……

Survenue d'une GVH aiguë de J0 à J90 OUI NON

Survenue d'une mucite OUI NON

# Survenue d'une GVHDc

| | | | | |
|---|---|---|---|---|
| **Grade** | **0** = absence | **1** = faible<br>thérapeutique locale éventuelle | **2** = sévère<br>polythérapie systémique | **3** = sévère réfractaire |
| **Localisation** | **1** = orale | **2** = orale + 1 autre localisation | **3** = orale + 2 ou + autres localisations | **4** = pas de localisation orale |
| **Atteinte orale** | **0** = absence | **1** = symptômes légers<br>sans gêne à l'alimentation | **2** = symptômes modérés<br>gêne partielle à l'alimentation | **3** = symptômes sévères<br>gêne importante à l'alimentation |

**Scores atteinte orale (échelle de Carpenter)**
(lèvres = 20%, face dorsale linguale = 20%, voile du palais et face ventrale linguale = 20%, autres muqueuses orales = 40%)

**TOTAL**

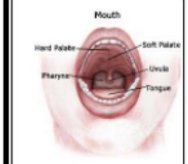
| | | | | |
|---|---|---|---|---|
| Erythème | **0** | **1** = léger / modéré (<25% $S^2$) | **2** = modéré (≥25% S²) / sévère (<25% S²) | **3** = sévère (≥25% S²) |
| Lésions lichénoïdes | **0** | **1** = <25% $S^2$ | **2** = 25-50% S² | **3** = >50% S² |
| Ulcérations | **0** | **0** | **3** = ≤20% S² | **6** = >20% S² |
| Kystes mucoïdes | **0** | **1** = 1 à 5 | **2** = 6 à 10 | **3** = + de 10 |

**Atteintes orales et contact direct avec matériaux**

| | | |
|---|---|---|
| Métaux non précieux | OUI | NON |
| Métaux précieux | OUI | NON |
| Résines composites | OUI | NON |

## *Appendix 4: Oral cGVHD differents scales.*

**a.**

| Component | Findings | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Mouth   | Mucosal change | No evidence of cGvHD | | Mild | | Moderate | | Severe | |
| | Erythema | None | 0 | Mild erythema or moderate erythema (<25%) | 1 | Moderate (≥25%) or Severe erythema (<25%) | 2 | Severe erythema (≥25%) | 3 |
| | Lichenoid | None | 0 | Hyperkeratotic changes(<25%) | 1 | Hyperkeratotic changes(25-50%) | 2 | Hyperkeratotic changes (>50%) | 3 |
| | Ulcers | None | 0 | None | 0 | Ulcers involving (≤20%) | 3 | Severe ulcerations (>20%) | 6 |
| | Mucoceles* | None | 0 | 1-5 mucoceles | 1 | 6-10 scattered mucoceles | 2 | Over 10 mucoceles | 3 |
| | | | | | | | | | |
| | | | | *Mucoceles scored for lower labial and soft palate only | | | | Total score for all mucosal changes | |

**b.**

| | LIPS | | LABIAL MUCOSA | | BUCCAL MUCOSA | |
|---|---|---|---|---|---|---|
| | Lower | Upper | Lower | Upper | Right | Left |
| Atrophy | | | | | | |
| Pseudomembrane | | | | | | |
| Erythema | | | | | | |
| Hyperkeratosis | | | | | | |
| Lichenoid | | | | | | |
| Ulceration | | | | | | |
| Edema/Cellulitis | | | | | | |

| | TONGUE | | | FLOOR OF MOUTH | PALATE | | GINGIVA |
|---|---|---|---|---|---|---|---|
| | Dorsal | Lateral | Ventral | | Hard | Soft | |
| Atrophy | | | | | | | |
| Pseudomembrane | | | | | | | |
| Erythema | | | | | | | |
| Hyperkeratosis | | | | | | | |
| Lichenoid | | | | | | | |
| Ulceration | | | | | | | |
| Edema/Cellulitis | | | | | | | |

Total OMRS Score: _____ (range: 0 – 273; sum all items)

Instructions for Rating:

Atrophy, erythema, hyperkeratosis, lichenoid, and edema
Change is rated from normal.
0 = Normal/No change
1 = Mild change
2 = Moderate change
3 = Severe change

Ulceration and Pseudomembrane

0 = None
1 = > 0 but ≤ 1cm$^2$
2 = >1 cm$^2$ but ≤ 2 cm$^2$
3 = > 2cm$^2$

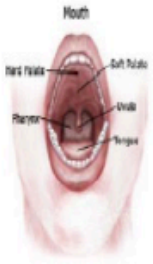
- (a) **The NIH cGVHD Activity Scale scores** the oral cavity for percent of surface area involved with erythema, lichenoid lesions and hyperkeratosis, ulceration and mucoceles (54)

- (b) **The Oral Mucositis Rating Scale** (OMRS) rates 13 locations and 7 types of lesions (93)

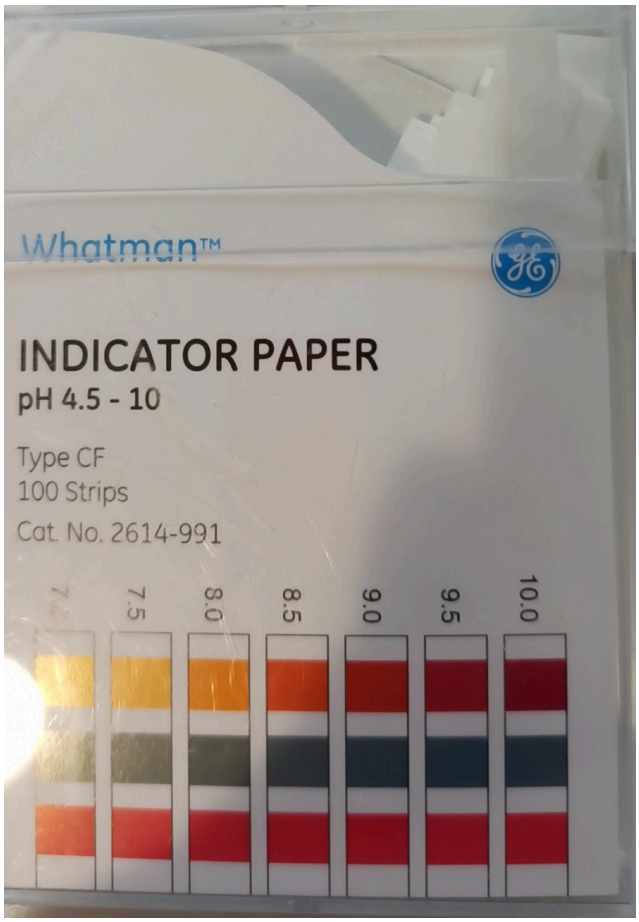
## *Appendix 5: Diagnosis filled of functional impact of oral cGVHD used in CHU of Lille.*

| | Score 0 | Score 1 | Score 2 | Score 3 |
|---|---|---|---|---|
| **Endobuccale**<br><br>Score : | ☐ Pas de lésion<br>☐<br>☐ | ☐ atteinte légère **sans retentissement** | ❑ atteinte modérée avec **limitation partielle** De l'alimentation | ❑ Atteinte sévère avec **retentissement majeur** sur l'alimentation |
| Présence d'un Lichen plan<br>☐ OUI<br>☐ NON | | | | |
| ☐ Autre lésion cutanée non liée à la GVH (spécifier) :_____ | | | | |

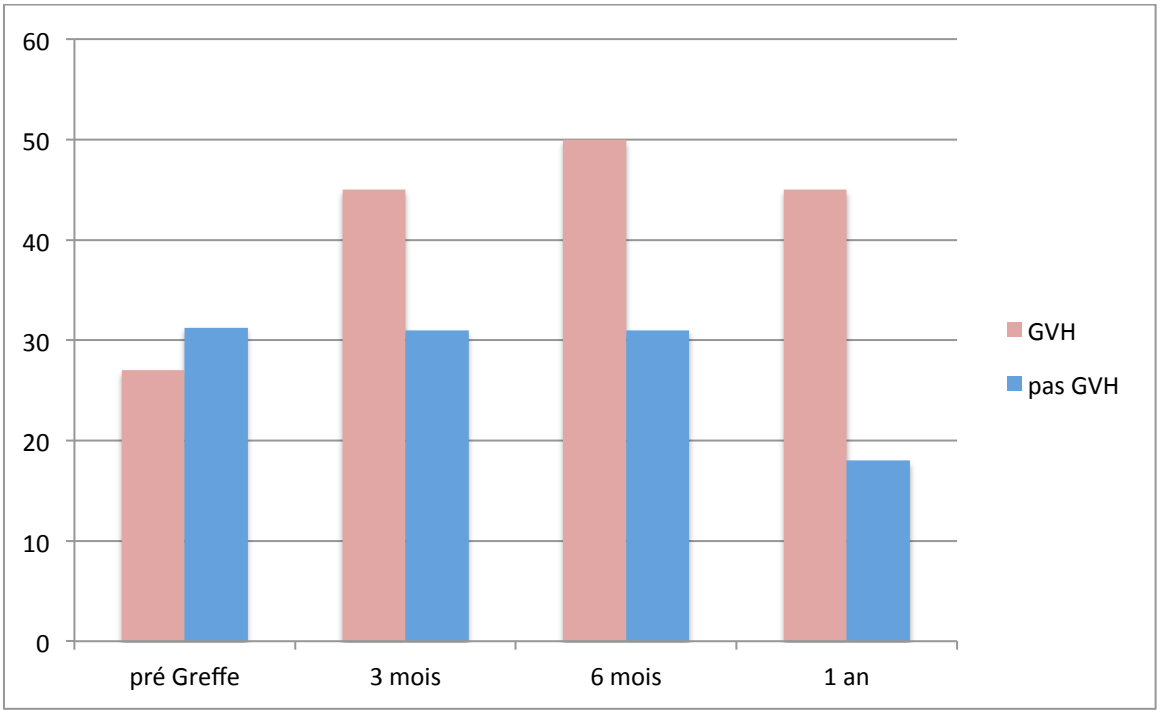
## *Appendix 6: Diagnosis filled for description of oral cGVHD used in CHU of Lille.*

| | Modification muqueuse | Aucun signe | | Léger | | Modéré | | Sévère | |
|---|---|---|---|---|---|---|---|---|---|
|  <br> | Érythème | Aucun | 0 | Érythème léger ou modéré (< 25 %) | 1 | Érythème modéré (≥ 25 %) ou sévère (< 25 %) | 2 | Érythème sévère (≥ 25 %) | 3 |
| | Lichénoïde | Aucun | 0 | Modifications hyperkératosiques (< 25 %) | 1 | Modifications hyperkératosiques (25-50 %) | 2 | Modifications hyperkératosiques (> 50%) | 3 |
| Bouche<br>Voûte palatine<br>Voile du palais<br>Pharynx<br>Luette<br>Langue | Ulcères | Aucun | 0 | Aucun | 0 | Ulcères impliquant (≤ 20 %) | 3 | Ulcérations sévères (> 20%) | 6 |
| | Mucocèles* | Aucun | 0 | 1-5 mucocèles | 1 | 6-10 mucocèles dispersés | 2 | Plus de 10 mucocèles | 3 |
| | | | | + | | + | | + | |
| | * mucocèles évalués sur la lèvre inférieure et le voile du palais uniquement | | | **Score total de toutes les modifications muqueuses** = | | | | | |

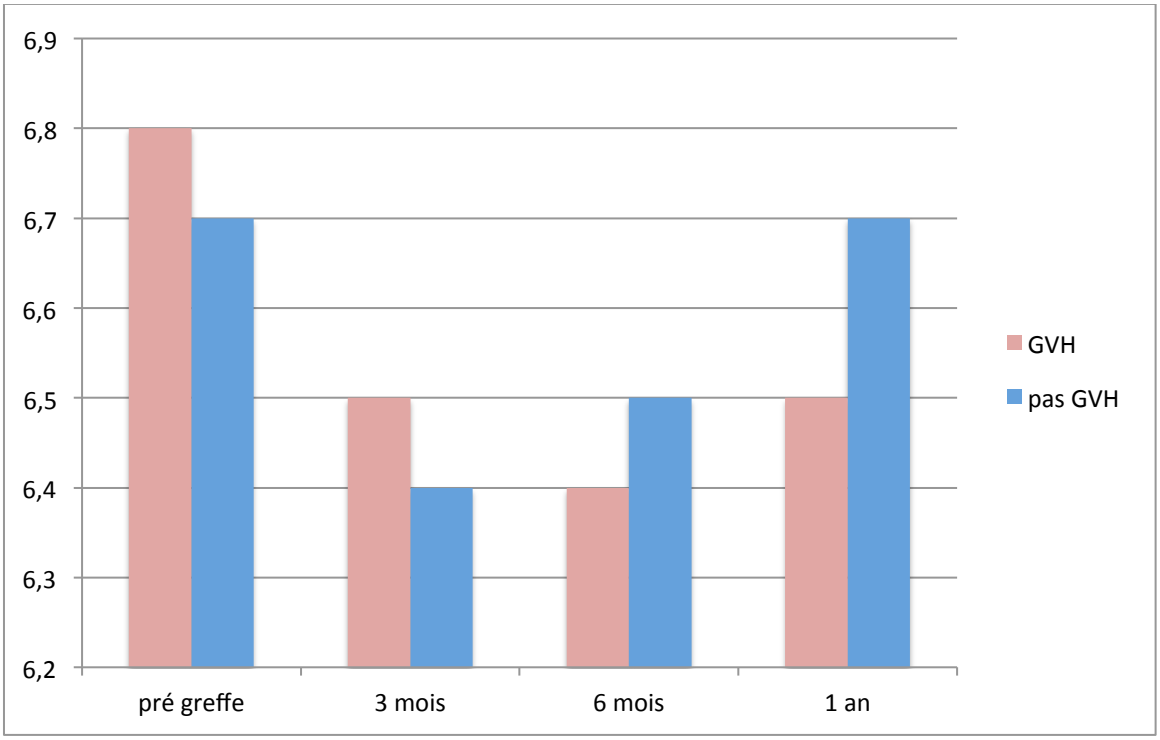
## *Appendix 7: Salivary bands to measure the pH.*



***Appendix 8 : Percentage of patients with xerostomia, according to the GVHD occurrence.***




***Appendix 9 : Measure of salivary pH, according to GVHD occurrence.***



**Thèse d'exercice : Chir. Dent. : Lille : Année [2021] – N°:**

Etude de l'impact des facteurs bucco-dentaires dans la forme endobuccale chronique de la maladie du greffon contre l'hôte (cGVHD) /
**MUNY Thomas**.- p. (*73*) : ill. (*23*) ; réf. (*93)*

**Domaines:** Hématologie – Chirurgie Orale

**Mots clés libres:** GVHD ; Facteurs bucco-dentaires ; Manifestations buccales

Oral cGVHD is a frequent complication of hematopoietic stem cells transplantation. It leads to an alteration in the patient's quality of life, which can also lead to malnutrition. The aim of this study is to evaluate the impact of oral factors on the development of oral cGVHD. This observational, retrospective, monocentric study was carried out in the Odontology Department of the CHRU of Lille from 22 February 2018 to 22 March 2020. 109 patients were included, 27 were excluded and 11 were lost to follow-up. Of the 71 patients, 22 developed oral cGVHD. The study showed that periodontal disease significantly differ between the cGVHD group and the no cGVHD group (p=0,0145), even if the periodontal disease factor was adjusted with histocompatibility, age and allograft origin (p=0.0389). The periodontal disease factor increased 4.173 times the risk of oral cGVHD occurrence. This result highlights the relationship between the state of the oral cavity and the susceptibility to develop oral cGVHD. Collaboration between the haematologist and the dental surgeon is necessary to ensure good oral hygiene and a reduction in the inflammatory state of the oral cavity, and thus prevent the development of oral cGVHD.

**JURY :**

| | |
|---|---|
| **Président :** | **Pr Thomas Colard** |
| **Assesseurs :** | **Dr Laurent Nawrocki**<br>**Dr Xavier Coutel**<br>**Dr Cecile Olejnik** |
| **Membre invité :** | **Dr Leonardo Magro** |