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Renato Pol [1], Tiziana Ruggiero [1,*], Luisa Giaccone [2], Davide Camisassa [3], Andrea Spadafora [3], Giulia Rivetti [3], Marta Bezzi [3], Stefano Carossa [4]

1. Oral Surgery Unit, Department of Surgical Sciences, University of Turin, Dental School, Via Nizza 230, Turin, Italy; E-Mails: renato.pol@unito.it; tiziana.ruggiero@unito.it
2. Department of Molecular Biotechnology and Health Science, University of Turin, Turin, Italy; E-Mail: Luisa.giaccone@unito.it
3. Oral Surgery Unit, Department of Surgical Sciences, University of Turin, Dental School, Via Nizza 230, Turin, Italy; E-Mails: dcamisassa@alice.it; spadafora.andrea88@gmail.com; giulia.rivetti722@gmail.com; martabezz@yahoo.it
4. Department of Surgical Sciences, Dental School, Via Nizza 230, University of Turin, Turin, Italy; E-Mail: stefano.carossa@unito.it

* **Correspondence:** Tiziana Ruggiero; E-Mail: tiziana.ruggiero@unito.it

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Abstract

***Objective*:** Hematopoietic stem cells transplant (HSCT) requires being preceded by chemotherapy and radiotherapy. The neutropenia and thrombocytopenia which follows may be the possible cause of post-transplant complications. It is required that the patient undergoing transplantation is eradicated of any possible infectious focus. Currently, a uniform protocol for the oral management of these patients is unavailable.

***Methods*:** The approach for the dental management of each patient was designed as a more selective protocol, which was based on the type and size of lesions, symptomatology, and the time available. The samples were divided into three groups, depending on the therapy that was to be performed (selective protocol, radical protocol, and no treatment). The

patients were monitored post-HSCT and all the systemic complications that occurred in the first 30 days, 100 days, and 6 months were recorded.

***Results*:** In the duration of four years, 159 patients were visited, while only 139 of these underwent HSCT. No statistically significant differences were observed in the systemic complications post HSCT among the three groups.

***Conclusions*:** The results of the present study demonstrated that there was no difference between radical dental management and a more conservative one in regard to the onset of infectious complications post HSCT. The present study also aimed to provide a novel approach for the oral management of these patients as the conditioning regimen followed was less myeloablative compared to those followed in the past.

Keywords

HSCT; oral-management; prevention; infectious complications; infectious focus

1. Introduction

Since the time it was introduced, hematopoietic stem cell transplantation (HSCT) has become an essential treatment for several patients with malignant and non-malignant hematological diseases, including acute and chronic leukemias, aplastic anemia, myelodysplastic syndromes, and lymphomas [1-3].

In addition to the conditioning regimen, with chemotherapy and/or radiotherapy, the patients undergoing HSCT receive immunosuppressive agents to accomplish engraftment and to prevent the graft-versus-host disease (GVHD). The subsequent immunosuppression increases the patients' susceptibility to infections, including the development of severe septicemia [2, 4, 5].

All infectious foci have to be treated prior to the commencement of HSCT in order to reduce post-transplant complications. The oral cavity is a potential site of infection because it is not a sterile environment and oral bacteria are able to cause systemic infections. In order to prevent these complications, it has been recommended to incorporate pre-transplant comprehensive oral care into the preparatory steps for the patients scheduled to receive HSCT [6-9].

Unfortunately, the guidelines for the management of this kind of patient are ambiguous. As a matter of fact, the dentist has no indications in regard to which oral diseases have to be considered "high risky" and which ones not. Therefore, it remains unclear as to which foci require immediate treatment and which ones could be postponed to the time of discharge from the hospital without increasing the risk of infectious complications.

Finally, it is important to highlight that the oral care protocol being followed must consider the general health conditions of these patients for whom HSCT serves as a life-saving therapy. In this context, in order to avoid failure of transplant, it is necessary that oral foci treatments are performed immediately and safely. Furthermore, changes in the oral cavity of a person may cause physical (mastication, phonetics, and aesthetics) and psychological alterations, which should not be underestimated.

The aim of the present study was to propose a "selective" treatment protocol, for determining which foci have to be considered more dangerous and which ones not. The ultimate aim of the

present study was to implement a less invasive dental care for the patients undergoing HSCT [1, 4, 10].

2. Methods

2.1 Patient Characteristics

In the period between the years 2012 and 2016, 159 candidates were referred, for allogenic HSCT, to the Oral Surgery Department, Dental School, University of Turin, from the division of Hematology, Città della Salute e della Scienza, in order to receive oral foci evaluation and treatment. The inclusion criteria for the present study were as follows:

i) patients of either sex;
ii) age > 18 years;
iii) hematological indication to HSCT;
iv) informed consent and the ability to complete the trial.

The local ethics committee approved the clinical protocol followed in the study, and every patient who was enrolled in the present study provided written informed consent for participation in the study.

2.2 Treatment Plan

The patients received a dental visit prior to HSCT, in order to evaluate their suitability for the transplant. In this session, soft and hard tissues of the oral cavity were examined through clinical and radiographical methods (such as panoramic radiograph and periapical radiographies in case of teeth with questionable prognosis).

The status of the oral hygiene of these patients was recorded in terms of the periodontal screening recording (PSR) score, and was subsequently related to the oral treatments conducted during the pre-transplant oral management.

The following diseases were recorded in the patients: caries, periodontal pockets, periapical radiolucencies, and impacted third molars.

In order to define the prognosis for each dental element hit by one or more of these lesions, the following parameters were recorded:

1. Pain: yes/no;
2. Extension of the carious lesion: far from the pulp (>2 mm in rx) or close to the pulp (<2 mm in rx);
3. Periapical lesion size <5 mm or >5 mm;
4. Coronal seal in the endodontically treated teeth: yes/no;
5. Periodontal probing: presence or absence of a periodontal pocket (<5 mm or >5 mm);
6. Poll furcation: degree I, II, and III;
7. Mobility dental element: degree I, II, and III;

Each doubted dental element was assigned a score based on the parameters mentioned above, and the prognosis was established. The treatment planning was then scheduled for each patient according to the protocol presented in Table 1.

According to the general health conditions of these patients, the treatment plan was required to consider the following factors:

1. Time for dental care prior to hospitalization;
2. Priority treatment: the necessity to immediately treat the more compromised teeth, which were considered “at risk”;
3. Healing time: this was dependent on the type of therapy, i.e., for dental extraction, 14 days would be required to allow the formation of an epithelial barrier around the wound in order to avoid dangerous contamination by oral bacteria [11-21];
4. Patient’s compliance and oral hygiene.

Table 1 Baseline characteristics and hematological diagnoses of the patients.

SEX	Male	81
	Female	58
AGE	Average	50
	Min-Max	19–74
PATHOLOGIES	Acute Myeloid Leukemia	58
	Chronic Lymphoblastic Leukemia	17
	Chronic Lymphatic Leukemia	5
	Non Hodgkin's Lymphoma	21
	Hodgkin's Lymphoma	10
	Multiple Myeloma	13
	Myelodysplastic Syndrome	9
	chronic myeloid leukemia	2
	Chronic myeloproliferative	3
	Severe aplastic anemia	1

Finally, the patients visited for follow-up at the time points of 30 days, 100 days (with the implementation of a novel orthopantomography), and six months after the transplantation; during these visits, all the infectious complications (fever, mucositis, acute and chronic GVHD, sepsis, and death by toxicity) were recorded. In addition, any acute episode, involving dental elements which are considered healthy or not at risk during the pre-transplant examination, was recorded.

In order to perform statistical analysis, the samples were divided into three groups:

- Group A: 46 patients (34%) treated by following the protocol, without treating the initial and asymptomatic lesions;
- Group B: 39 patients (27%), for whom it was not possible to treat certain deep and asymptomatic lesions because of lack of time;
- Group C: 54 patients (39%), in whom, after the dental treatment, neither superficial nor deep lesions could be identified.

2.3 Statistical Methods

The results of the present study included continuous as well as categorical variables. The continuous variables were reported in terms of mean and standard deviation. Non-parametric tests were performed: the Wilcoxon's signed-rank test for comparison between two correlated samples involving matched pairs, and the Mann–Whitney test for comparison between two independent distributions. Categorical variables, reported in terms of count and percentage, were arranged in cross-correlation tables, and were compared using the X^2 test with Yates correction when all the expected values were greater than five or by using Fisher's test. Statistical significance corresponded to a probability of less than 0.05; else the differences could be ascribed to chance.

All the patients were informed regarding the possible use of their health data for clinical studies and were asked to sign an informed consent form. The patient data were anonymized prior to performing analysis. The analysis was performed in accordance with the standards of the local institutional review board and conformed with the Declaration of Helsinki of 1975 and its subsequent modifications.

3. Results

Among the 159 patients with hematological malignancies, only 139 underwent HSCT; the other 20 patients did not undergo HSCT because either no appropriate donor could be found or because of poor general health conditions or premature death.

These 139 patients were subsequently enrolled in the prospective trial. Among the subjects, 81 were male and 58 were female, with the mean age of the group being 50 years (age range: 19–74 years). Among these 139 patients, 126 underwent HSCT with an allogenic donor, while 12 underwent autologous transplantation (3 in group A, 5 in group B, and 4 in group C). Patients were observed to have been affected by 10 different hematological malignancies; Table 1 presents the baseline characteristics and hematological diagnosis of the patients.

The first dental visit, which evaluated the patients' dental status, occurred, on an average, in 47 days (DS ±16; range 1–378 days), prior to the conditioning regimen, while the time duration between the hematological diagnosis and HSCT was, on an average, 23 months (DS ±34). Hospitalization lasted, on average, for 37 days (DS ±16). Dental treatment was required to be completed 14 days prior to hospitalization, in order to allow the patients time to heal prior to the commencement of the conditioning regimen [1].

According to the protocol followed in the present study, dental treatments performed prior to HSTC were: 214 tooth extractions, 128 mechanical scaling, 13 manual root scaling, 41 tooth fillings, and 16 endodontic therapies.

Teeth were extracted because of the following pathologies: 57% patients having caries, 37% having periodontitis, and 5% periapical lesions in the teeth that were already treated endodontically. One element was because it was involved in BRONJ (Biphosphonate Related Osteonecrosis of the Jaw) in a female patient suffering from multiple myeloma.

Owing to the lack of time between the first dental visit and the hospitalization in the case of 39 patients, the following asymptomatic lesions were not treated: 13 periodontal pockets with PD >5 mm and 12 deep decays. The following infectious foci were not treated because they were not

considered “at risk” according to this protocol: eight periapical lesions in already Non-Hodgkin's treated teeth with intact coronal seal, 51 periodontal pockets with PD <=5 mm, and 33 initial decays.

In regard to the third molars, six third molars in full bone inclusion and 16 third molars partially erupted were documented; one of these teeth was symptomatic and was, therefore, extracted in order to ensure suitability to the HSCT therapy. The other 15 molars were not treated, although these were controlled clinically and radiographically, prior to and post HSCT.

In the first dental visit, the level of periodontal health was assessed through the PSR score, with the mean value of the sample obtained to be 2.45. On the basis of the PSR score, the study sample was divided into two groups:

- Group 1: 78 patients with PSR 1–2;
- Group 2: 61 patients with PSR 3–4.

Extractions, root planing, fillings, and endodontic therapies were observed to be associated with the oral hygiene of the patients. It was observed that there was a statistically significant difference ($p < 0.05$) between the requirement for dental care and the level of oral hygiene of the patients in the study sample, as presented in Table 2.

Table 2 Differences between Group 1 with good oral hygiene and Group 2 with poor oral hygiene in the number of treatments.

	Oral treatments				
	Yes	**No**	**Tot**		
Group 1 PSR 1–2	20	58	78	RR=1,59	p= 0,04
Group 2 PSR 3–4	25	36	61		
Total	45	94	139		

Data from the three groups (A, B, C) were observed to be linked to oral and systemic infectious complications (such as fever, mucositis, GVHD, sepsis, and toxicity death), and were analyzed during the follow-up visits at 30, 100, and 180 days post-HSCT. Table 3 presents the results obtained; no statistically significant differences were observed among the three groups, in all the complications recorded in the first six months after the transplant. Sepsis episodes were recorded during the six months in 12 cases (26%) in Group A, 7 cases (19%) in Group B, and 12 cases (22%) in group C, with a p-value of 0.73 which represented a non-significant difference.

While the study was being conducted, ten patients died; three due to toxicity and seven because of the recurrence of the disease. It must be underlined that no acute oral episodes were recorded during the observation period of six months post-transplant and that there were no cases of death due to toxicity resulting from an oral infectious focus. Systemic complications, such as fever, oral mucositis, GVHD, and death by toxicity, appeared to occur in the same proportion in all the groups.

Table 3 Outcome of HSCT according to the dental management protocol. Differences between the infectious complications (fever, mucositis, GVHD, pneumonia, and toxicity death) in the period 1–30 days, 31–100 days, and 101–180 days after HSCT. Grade of mucositis: 3 and 4 of the WHO scale [23].

30 days				
	Group A	Group B	Group C	
Fever	21 (46%)	18 (46%)	33 (61%)	p=0.21
Grade 3–4 mucositis	11 (24%)	7 (18%)	13 (24%)	p=0.74
Graft versus host disease (GVHD)	11 (24%)	10 (26%)	15 (28%)	p=0.90
Pneumonia	2 (4%)	1 (2%)	1 (2%)	p=0.75
Transplant related mortality (TRM)	2 (4%)	1 (2%)	2 (4%)	p=0.90
100 days				
	Group A	Group B	Group C	
Fever	12 (26%)	3 (8%)	12 (22%)	p=0.07
Grade 3–4 mucositis	2 (4%)	4 (10%)	1 (2%)	p=0.18
Graft versus host disease (GVHD)	11 (24%)	7 (18%)	14 (26%)	p=0.63
Pneumonia	0%	1 (2%)	1 (2%)	p=0.58
Transplant related mortality (TRM)	1 (2%)	1 (2%)	1 (2%)	p=0.95
180 days				
	Group A	Group B	Group C	
Fever	5 (11%)	3 (8%)	8 (15%)	p=0.55
Grade 3–4 mucositis	0%	0%	1 (2%)	p=0.99
Graft versus host disease (GVHD)	6 (13%)	7 (18%)	10 (19%)	p=0.74
Pneumonia	1 (2%)	2 (4%)	1 (2%)	p=0.61
Transplant related mortality (TRM)	1 (2%)	3 (8%)	3 (6%)	p=0.50

P<0,05 *statistically significant.

4. Discussion

Pre-HSCT dental screening for the identification and treatment of the potential oral sources of infection has become a standard treatment in the patients scheduled for allografting. The principal aim of this screening is to reduce morbidity and mortality which may arise from the oral

complications associated with HSCT during the period of immunosuppression [1]. Although all potential sources of oral infection should be eliminated by dental treatment prior to HSCT conditioning, factors such as time limitations and the disease status of the patient frequently interfere with performing a complete treatment [1, 22, 23]. Owing to the restriction of the time factor, extraction of the potentially diseased teeth may often be the only option that remains. However, this treatment may not be consistent with the long-term oral requirements of the patients, because the removal of multiple teeth may compromise nutrition during and after HSCT [24]. Furthermore, dental extraction has been reported to be associated with an increased risk of infection, bleeding, or delayed wound healing, which could result in the requirement of postponing the scheduled HSCT [1].

One of the most important aspects of the present study was the analysis of the huge difference in the time between the date of diagnosis of the hematological pathology and the time available to the dentist for oral management. The availability of a longer period for dental treatment would allow for a less invasive treatment for the patient, in addition to a more predictable degree of healing and reclamation at the time of transplantation. Therefore, greater cooperation between hematologists and dentists is recommended in order to ensure better management of these patients. The analysis of the PSR score in relation to the requirement of therapies revealed how treatments are required in all kinds of patients, including the ones with acceptable oral hygiene as well as the ones with poor oral hygiene. It is recommended that dental advice must be provided to all the patients waiting for HSCT, regardless of their oral health.

Moreover, in a previous study, comparison between the patients with no dental foci or those who have received a complete dental treatment and the ones with dental foci or no dental interventions demonstrated that the impact of dental foci on the occurrence of post-HSCT infections was not statistically significant [25]. The patients with chronic dental pathology were reported to be safe to proceed with chemotherapy without dental intervention, as the conversion of chronic dental disease into an acute state during chemotherapy occurs infrequently. These reports suggested that intensive pre-HSCT dental treatment is not a necessity. Furthermore, patients should avoid the additional morbidity or mortality associated with needless treatment. Consequently, the minimal dental intervention has been recommended, even by several other studies conducted in past [1, 4, 10].

The clinician should classify the oral infectious lesions on the basis of the extension defined by the clinical and radiological evaluation and symptoms, as reported above. The dentist should not treat low-risk lesions if there is not an increased risk of post-HSCT infectious complications. In order to design a treatment plan, the clinician also requires considering the time available prior to hospitalization and the patient's compliance and oral hygiene. Oral hygiene is, in fact, fundamental to reducing and controlling the bacterial flora in the oral cavity. Therefore, in addition to the management of oral diseases, dentists and dental hygienists should provide adequate instructions on oral care during immunosuppression. Prior to dental treatment, all the patients included in the present study were educated in regard to exfoliating dental plaque which produces dental caries and marginal periodontitis. The extent to which dental care instruction influenced the absence of oral infection observed in the present study is unknown, although it is believed that the instruction was beneficial, as reported in a previous study as well [1].

5. Conclusions

The combination of sessions of professional oral hygiene and motivation to oral self-care and the application of a selective protocol, proposed in the present study, may lead to a novel approach to the treatment of these patients. A more conservative approach has considerable advantages for such patients, as it avoids interference with their health, either physical or psychological, which has already been severely compromised by the diagnosis of the oncohematology disease, without exerting a significant impact on infection complications.

Author Contributions

Tiziana Ruggiero: coordinating study and writing article; Renato Pol: enrolled, visited and curing patients; Luisa Giaccone: coordinating hematologic unit; Davide Camisassa: enrolled, visited and curing patients; Andre Spadafora: enrolled, visited and curing patients; Giulia Rivetti: enrolled, visited and curing patients; Marta Bezzi: writing article and review; Stefano Carossa: coordinating study.

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Competing Interests

All authors disclose any financial and personal relationship with other people or organizations that could inappropriately influence (bias) their work.

References

1. Yamagata K, Onizawa K, Yanagawa T, Hasegawa Y, Kojima H, Nagasawa T, et al. A prospective study to evaluate a new dental management protocol before hematopoietic stem cell transplantation. Bone Marrow Transplant. 2006; 38: 237-242.
2. Appelbaum FR. The current status of hematopoietic cell transplantation. Annu Rev Med. 2003; 54: 491-512.
3. Bortin MM, Horowitz MM, Gale RP, Barrett AJ, Champlin RE, Dicke KA, et al. Changing trends in allogeneic bone marrow transplantation for leukemia in the 1980s. JAMA. 1992; 268: 607-612.
4. Yamagata K, Arai C, Sasaki H, Takeuchi Y, Onizawa K, Yanagawa T, et al. The effect of oral management on the severity of oral mucositis during hematopoietic SCT. Bone Marrow Transplant. 2012; 47: 725-730.
5. Center for International Blood and Marrow Transplant Research (CIBMTR), National Marrow Donor Program (NMDP), European Blood and Marrow Transplant Group (EBMT), American Society of Blood and Marrow Transplantation (ASBMT), Canadian Blood and Marrow Transplant Group (CBMTG), Infectious Disease Society of America (IDSA), et al. Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: A global perspective. Bone Marrow Transplant. 2009; 44: 453-558.

6. Overholser CD, Peterson DE, Williams LT, Schimpff SC. Periodontal infection in patients with acute nonlymphocyte leukemia. Prevalence of acute exacerbations. Arch Intern Med. 1982; 142: 551-554.
7. Barker GJ. Current practices in the oral management of the patient undergoing chemotherapy or bone marrow transplantation. Support Care Cancer. 1999; 7: 17-20.
8. Peterson DE. Pretreatment strategies for infection prevention in chemotherapy patients. NCI Monogr. 1990; 61-71.
9. Sonis S, Kunz A. Impact of improved dental services on the frequency of oral complications of cancer therapy for patients with non-head-and-neck malignancies. Oral Surg Oral Med Oral Pathol. 1988; 65: 19-22.
10. Yamagata K, Onizawa K, Yanagawa T, Takeuchi Y, Hasegawa Y, Chiba S, et al. Prospective study establishing a management plan for impacted third molar in patients undergoing hematopoietic stem cell transplantation. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011; 111: 146-152.
11. Friedman S, Mor C. The success of endodontic therapy--healing and functionality. J Calif Dent Assoc. 2004; 32: 493-503.
12. Sjogren U, Hagglund B, Sundqvist G, Wing K. Factors affecting the long-term results of endodontic treatment. J Endod Ottobre. 1990; 16: 498-504.
13. Bystrom A, Happonen RP, Sjogren U, Sundqvist G. Healing of periapical lesions of pulpless teeth after endodontic treatment with controlled asepsis. Endod Dent Traumatol. 1987; 3: 58-63.
14. Van der Weijden GA, Timmerman MF. A systematic review on the clinical efficacy of subgingival debridement in the treatment of chronic periodontitis. J Clin Periodontol. 2002; 29: 55-71; discussion 90-91.
15. Echeverria JJ, Caffesse RG. Effects of gingival curettage when performed 1 month after root instrumentation. A biometric evaluation. J Clin Periodontol. 1983; 10: 277-286.
16. Non-surgical pocket therapy: Mechanical, pharmacotherapeutics, and dental occlusion. J Am Dent Assoc. 1998; 129: 34S-39S.
17. Lindhe J, Westfelt E, Nyman S, Socransky SS, Heijl L, Bratthall G. Healing following surgical/non-surgical treatment of periodontal disease. A clinical study. J Clin Periodontol. 1982; 9: 115-128.
18. Suvan JE. Effectiveness of mechanical nonsurgical pocket therapy. Periodontol 2000. 2005; 37: 48-71.
19. Feliciani C, Gupta AK, Sauder DN. Keratinocytes and cytokine/growth factors. Crit Rev Oral Biol Med. 1996; 7: 300-318.
20. Deodhar AK, Rana RE. Surgical physiology of wound healing: A review. J Postgrad Med. 1997; 43: 52-56.
21. Adeyemo WL, Ladeinde AL, Ogunlewe MO. Clinical evaluation of post-extraction site wound healing. J Contemp Dent Pract. 2006; 7: 40-49.
22. Elad S, Garfunkel AA, Or R, Michaeli E, Shapira MY, Galili D. Time limitations and the challenge of providing infection-preventing dental care to hematopoietic stem-cell transplantation patients. Support Care Cancer. 2003; 11: 674-677.

23. Elad S, Thierer T, Bitan M, Shapira MY, Meyerowitz C. A decision analysis: The dental management of patients prior to hematology cytotoxic therapy or hematopoietic stem cell transplantation. Oral Oncol. 2008; 44: 37-42.
24. Akintoye SO, Brennan MT, Graber CJ, McKinney BE, Rams TE, Barrett AJ, et al. A retrospective investigation of advanced periodontal disease as a risk factor for septicemia in hematopoietic stem cell and bone marrow transplant recipients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002; 94: 581-588.
25. Melkos AB, Massenkeil G, Arnold R, Reichart PA. Dental treatment prior to stem cell transplantation and its influence on the posttransplantation outcome. Clin Oral Investig. 2003; 7: 113-115.