European Review for Medical and Pharmacological Sciences 2018; 22: 876-887

Oral management of adult patients undergoing hematopoietic stem cell transplantation

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Abstract. – Chemotherapy and hematopoietic stem cell transplantation (HSCT) are the current treatments for patients with hematological diseases; they result in myelosuppression, and increase the susceptibility of patients to severe infections. The oral cavity is a potential site of complications in HSCT patients, because it is the entrance for agents that can cause systemic infections; it is one of the most frequent locations for side effects deriving from conditioning therapy. The importance of dental pre-chemotherapy and transplant prescription is often stressed, since both therapies depress the immune system and platelets, making each intervention at this stage a high risk. The aim of this article is to review the potential complications of HSCT, and to extrapolate from the scientific literature the treatments and timeframes in which dental therapies can be performed, avoiding important risks for patients.

Key Words:
Stem cell, Transplantation, Oral management, Complications of HSCT, Chemotherapy, Hematopoietic.

Introduction

The feasibility of performing certain dental procedures in patients undergoing hematopoietic stem cell transplantation (HSCT) depends on the overall state of the patient's health, as well as the stage of the disease and/or antineoplastic therapy or HSCT. HSCT is widely used in the treatment of disorders of the hematopoietic system or, most commonly, of malignancies such as lymphoma, myeloma, and leukemia[1,2]. It represents a valid therapeutic option for aplastic anemia congenital immune deficiency states, lysosomal accumulation disorders (Gaucher's disease) and congenital leukocyte affections (Kostmann's syndrome). This procedure has been successfully extended to patients with solid tumors and autoimmune diseases such as multiple sclerosi[s3,4].

HSCT is a complex therapeutic procedure that involves the infusion of healthy hematopoietic cells, following a preconditioning therapy that destroys diseased cells and those no longer functioning; the conditioning therapy is an indispensable step in the transplantation procedure. Conditioning involves the administration of high-dose chemo/radiotherapy associated with antiangiogenetic, cortisone or monoclonal antibody drugs, according to standardized protocols. High doses of therapeutic drugs and/or radiotherapy cause complications and side effects both direct (due to the same administration) and indirect or secondary to the organ toxicity characteristic of these drugs. The indirect effects of preconditioning occur in the gastrointestinal tract (mucositis), liver, lung, and bladder, as well as in other manifestations such as hemorrhagic cystitis and veno-occlusive liver disease, or severe secondary respiratory deficits such as the development of idiopathic pneumonia. In the most severe cases, there is irreversible multi-organ dysfunction. The aplasia phase is characterized by a severe reduction in immune defenses, as well as a decrease in the concentration of hemoglobin and in peripheral blood-cell counts, which exposes the patient to a high risk of hemorrhage and infection[5]. The aplasia phase of variable duration is followed by the digestion phase, consisting of the resumption of bone marrow function: polymorphonucleate nucleation is achieved at neutrophil counts greater than 500/mm3 (for at least three consecutive days) and at platelet counts greater than 20,000-50,000/mm^3 of blood[6].

Hematopoietic Stem Cells (HSC)

In most countries where allogeneic HSCT is a therapeutic procedure available to most patients in need, families have been so small for many decades that a human leukocyte antigen (HLA)-i-

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dentical sibling donor is available for less than a third of patients[7]. Some patients cannot be transplanted because of the lack of an HLA-identical donor. Hence, the vast majority of patients have to rely on alternatives: peripheral blood stem cells (PBSC) or bone marrow from unrelated adult donors or frozen umbilical cord blood units (CBUs)[7]. For several years, bone marrow was the most widely used source of HSC; HSC (CD34+) in the bone marrow represent 1.1% of total nucleated cells, equivalent to about 2-3 × 106/kg body weight of a healthy individual[8]. Today, peripheral blood is the most used HSC source for harvesting stem cells in adults, after administration of granulocyte colony-stimulating growth factor. PBSC has been shown to produce earlier engraftment and recovery of granulocytes and platelets compared with bone marrow[6,8].

The use of CB provides many theoretical advantages, both for PBSC and spinal cord stem cells, due to the immunity of the cells contained therein. Infant cells are, in fact, primitive stem cells with high regenerative potential when compared with adult stem cells. The main practical advantages of using CB as an alternative source of stem cells are the relative ease with which they can be obtained and cryopreserved, the absence of risks for mother or baby, the reduced likelihood of transmitting infections, particularly CMV (cytomegalovirus), and the ability to store fully tested and HLA-typed transplants, available for immediate use. The volunteer donor, once identified by the register, must still be available for donation, must undergo examination for infection and completion of HLA typing[9,10]. Pooling CB from two donors whose HLA is closely matched to the recipient has resulted in more rapid engraftment in adults for whom unrelated donors are unavailable[8].

HSC transplantation is distinguished as one of two types: autologous or allogeneic. Autologous transplantation is utilized to treat chemosensitive malignancies, such as multiple myeloma, non-Hodgkin and Hodgkin lymphoma[8]. Autologous transplantation consists of the reinfusion, after chemotherapy, of a high dose of HSC from the same patient, previously withdrawn and cryopreserved. Emphasis is increasingly placed on the identification of new phenotypic markers that might be relevant for optimizing discrimination between leukemic and normal cells, and, perhaps more importantly, for the detection of minimal residual disease, as well as post-transplantation monitoring of relapse occurrence[11]. The objective of autotransplantation is to treat a malignant disease in the blood or a solid organ, allowing the patient to survive the administration of myeloablative therapy that eradicates the pathology itself. Benefits arise from administering high doses of chemotherapy without compromising bone marrow function irreversibly: reinfusion allows bone marrow recovery in about 15 days. Autologous transplantation restores immunological tolerance by replacing an immune system reactive against self-antigens, and therefore, no longer functioning[12].

Spleen HSCs are extracted by an extracorporeal procedure consisting of multiple aspirations of medullary blood at the level of the iliac ridges (bilaterally), performed under general or spinal anesthesia. Before the infusion is performed, CD34+cells are counted because the medullary blood undergoes filtration procedures that could reduce the number of HSC in the product being infused. To increase the number of peripheral stem cells, it is possible to resort to a mobilization procedure involving the use of chemotherapies such as cyclophosphamide and/or growth factors. The growth factors used to mobilize HSC in peripheral venous blood are: recombinant human granulocyte colony-stimulating factor (rhG-CSF), recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) and Flt3 ligand (positive lymphoematopoietic development modulator)[13-15]. The side effects associated with mobilization with G-CSF are of little magnitude, and generally represented by headache, bone pain and asymptomatic upsurge of alkaline phosphatase and gamma GT[16].

The biological assumptions underlying the clinical outcome of allogeneic transplantation are the eradication of the underlying disease, followed by the recovery of hematopoiesis by infusing the donor HSC. Eradication is entrusted to the pre-transplant conditioning regimes, which determine the total disappearance of the totipotent stem cell compartment of the patient that will be replaced by donor hematopoietic progenitor cells. The purpose of allogeneic transplantation is the complete replacement of the patient's hematopoietic patency with healthy cells obtained from the donor. Allogeneic stem cell donors may be related (sibling) or unrelated, and should have a matching HLA type. Allogeneic transplantation is a potentially curative cellular therapy for hematologic malignancies, many neoplastic and non-systemic hepatic disorders and bone marrow failure syndromes (congenital or acquired medullary apathy and hemoglobinopathies)[6,8,16-18].

Graft Rejection

Extreme polymorphism of the HLA system within the general population makes it possible to find a compatible donor in the household in only 25% of cases, extending to 33% if family members are incompatible with only one locus[19]. The main complications of allogeneic HSCT are graft rejection and graft-vs.-host disease (GvHD). Rejection is a rare complication that occurs only in 1% of cases, due to the effect of conditioning regimens that make the patient accept the transplant by depressing the immune system heavily1. The ever-increasing indication for allogeneic transplantation, and the use of incompatible HLA donors for patients without a compatible donor, make GvHD one of the major causes of transplant-related morbidity and mortality in HSCT recipients. It is more likely to occur if the host receives a graft from an unrelated donor, or if the host or donor is older[8,20].

After hematopoietic recovery, donor T-lymphocytes in the graft recognize the host tissues as foreign, and initiate an immune-mediated inflammatory response. This gives rise to GvHD, which is a potentially fatal complication if not treated adequately. This is, in addition, to the direct effects of the disease which are also due to immunosuppressive medicines used for treatment. A certain aspect known as graft-vs.-neoplasia attacks and destroys any remaining cancer cells, and accounts for the highly curative potential of allo-HSCT[21]. One of the major complications of hematopoietic cell transplantation is GvHD differentiation into acute (aGvHD) and chronic (cGvHD) disease in relation to post-transplantation time and various clinical manifestations. By convention, GvHD is considered acute if it arises after the implantation phase (recovery of bone marrow function) within 100 days of transplantation. It is possible to diagnose aGvHD forms even before complete neutrophilization; for this reason, aGvHD is best characterized by clinical manifestations rather than onset timing[8]. cGvHD develops in 25-45% of patients who have received HLA-identical bone marrow transplant, and rises to 50-80% of recipients undergoing allo-HSCT from unrelated donors or HLA-partially compatible family members[8,18]. The clinical presentation of cGvHD is variable, and may include lichen planus-like changes of skin and mucosa, sclerosis of the skin, sicca syndrome secondary to lacrimal and/or salivary gland damage, liver involvement with cholestasis, and a decrease in pulmonary function secondary to bronchiolitis obliterans[20]. Oral involvement may be seen in approximately 80% of patients with cGvHD, and can be a significant source of patient morbidity. Common areas of oral involvement include the tongue and buccal and labial mucosa; oral lesions are often hyperkeratotic, and are considered evident signs for the presence of systemic disease[22,23]. Patients with salivary gland cGvHD report symptoms of xerostomia, hyposalivation, altered taste, limited opening of the mouth, and difficulty eating and tooth brushing. In addition, salivary gland cGvHD can predispose to the risk of caries determined by reduced antimicrobial activity, compromised buffering capacity and a decreased rate of enamel and dentine remineralization[18,24]. Another complication of salivary gland cGvHD is the formation of mucoceles[25]. Immunological reconstitution, starting with the HSC of the donor, takes place in months or years, prolonging the risk of infection over time[5]. In the HSC transplant phase, it being a programmable procedure, the role of the dentist is to evaluate possible odontostomatological pathologies that may interfere with the outcome of the transplant itself, and then to treat all those infectious loci that may cause systemic bacterial transmission, or those pathologies that cause pain and/or discomfort of the oral cavity. GvHD represents, to date, the major complication of allo-HSCT. As a result, timely diagnosis and a multidisciplinary treatment programme are essential for early detection of the oral signs of potential systemic complications, and to improve the quality of life in both adult and paediatric patients[26,27].

Materials and Methods

English language literature was searched for references published from August 1997 up to July 2017 in MEDLINE and PubMed, using the following medical subject headings (MeSH) and terms or combinations: leukemia, stem cell transplantation dental, oral, periodontal, hematological patients, chemotherapy, dental treatment, mucositis. Terms were used together with all their known synonyms.

Results

Patients undergoing immunosuppressive and conditioning therapy have an increased risk of developing oral complications: opportunistic infections, gingivitis, mucositis, and ulcerations

of the oral mucosa. No dental treatment before HSCT is related to a higher rate of these complications[28]. It has been shown that dental treatment prior to chemotherapy/HSCT may prevent the additional death of 1.8/1,000 patients, and reduce systemic infections by 20-25%[29]. The role of the dentist in HSCT mainly occurs in three different phases. The first is preconditioning dental screening; dental care at this stage is based on treatment priority, and is geared to acute phase problems. Conditioning follows the so-called aplasia phase in which, in addition to a reduction in hemoglobin concentration and the number of circulating platelets, there is a drastic reduction in the patient's immune defenses.

Dental care should be planned based on pre-treatment dental evaluation, and management of complications during immunosuppression and after HSCT. There are considerations to be made and limitations regarding certain dental treatments, especially invasive ones, during the various stages of antineoplastic treatment. A simplified myelosuppression grading is considered a useful tool for understanding the myelosuppressive state caused by chemotherapy. It also facilitates communication between medical and dental staff[30]. Considering the risk of bleeding and serious infections associated with invasive oral cavity procedures, there are protocols that underline the importance of evaluating some hematologic indices, especially neutrophil and platelet counts. All potential sources of oral infection should be eliminated before the conditioning phase, but time limitations and the patient's condition can interfere with the treatment protocol. In these cases, some treatments should be postponed until the patient is in a good clinical and hematological condition[1,5,22-24,31]. The US National Cancer Institute[32] argues that oral cavity lesions, endodontic lesions, caries, periodontal disease, and implants should be treated at this stage.

Time Limitations

The appropriate duration between referral for assessment and transplant is under discussion, and may differ between authors[33]. In the preconditioning phase, all dental treatment needs to be completed before the patient initiates over-peak chemotherapy and immunosuppressive therapy. Neutropenia and thrombocytopenia create a limited period for dental treatment.

All dental treatments should be carried out at least 3 days before the onset of chemotherapy (approximately 10 days before granulocyte count falls below 500 cells/mm^3). When hematologic parameters have values lower than those considered minimal, dental treatments should be postponed. Surgical procedures should be as atraumatic as possible and should be completed at least 7-10 days before the initiation of radio/chemotherapy[8,33-36].

A neutrophil count of at least 1000-1500/mm3 and a platelet count of at least 40,000-50,000 cells/mm3 are required to perform invasive procedures (periodontal probing or dental extraction)[32,37,38].

Given the high proportion of interproximal and rampant caries in patients with cGvHD, it is recommended that patients should undergo routine dental examinations with bitewing radiographs in the early follow-up period, no later than 6 months to 1 year after allo-HSCT[18]. Lastly, in the long-term survival phase, it is necessary to have a video protocol for dentistry inserted in the context of the multidisciplinary approach to the transplant patient. After treatment of acute phases, other procedures may be performed, such as restoring restorations, restoring fractured teeth or prosthetic assessments.

The US National Cancer Institute emphasizes that immune system reconstitution time in transplanted patients may vary from 6 to 12 months, and that routine dental care, including calculus removal procedures, should not be carried out during this period. This is because ultrasounds and other instruments that produce an aerosol can cause pneumonia in these patients, by accidental aspiration of bacteria and debris[39,40]. Preventive manoeuvres should be used, and antibiotic prophylaxis is required. The use of corticosteroids and/or platelet transfusion is recommended before invasive procedures[40].

Dental Treatment Needs

Dentists and oral hygienists have important roles in managing the oral health of myelosuppressed patients[8,30]. The aim of dental assessment and treatment prior to HSCT is to identify potential sources of infection and trauma, and to reduce the morbidity derived from oral complications which themselves can compromise chemotherapy protocols. Many dentists have incomplete knowledge of the disease and the HSCT procedure, the correct dental care that should be provided before and after HSCT, and the dental care provided in hospital[41].

Toljanic et al[39] conducted a prospective study to evaluate a pre-chemotherapy dental treatment protocol. The study was conducted on 48 patients

with odontogenic pathologies classified as mild, moderate or severe, considering the probability of developing acute processes during chemotherapy. Acute processes were analyzed on the basis of clinical signs such as edema, abscess and radiographic alterations, whereas the clinical symptoms mainly considered were pain and fever. Acute pathologies were removed before chemotherapy, and in cases of chronic disease, no treatment was done. Odontogenic chronic lesions were present in 79% of patients (of these, 44% were considered serious); 4% showed fever due to odontogenic infection, and antibiotic therapy was administered without interruption of chemotherapy. The authors postulated that patients with mild or moderate chronic lesions can safely undergo chemotherapy without dental treatment, as it has been shown that exacerbation is rare. When it has occurred, patients have been treated effectively without interruption of chemotherapy. The authors argued that it is more important to initiate chemotherapy rapidly because tooth extraction could be a source of a possible infection that would delay the repair of the wound. The authors concluded that the treatment of chronic odontogenic lesions can be safely postponed until the end of chemotherapy, considering the therapeutic benefits.

Melkos et al[28] conducted a prospective study in 58 patients undergoing allogeneic or autologous HSCT, analyzing pre-existing odontogenic lesions, dental care and the effect of both on the medical procedure. Patients were divided into two groups: Group I = absence of infectious outbreaks or patients fully treated prior to transplantation, and Group II = presence of infectious outbreaks while undergoing transplantation, without dental surgery. All patients were subjected to dental screening before transplantation, through objective and radiographic examination (panoramic radiographs and periapical radiographs of symptomatic teeth). Dental elements with periapical lesions and periodontal pockets were considered infectious loci. The type of dental treatment prior to transplantation, and the appearance of post-transplant complications (mucositis, infections, GvHD development and disease relapse) were evaluated for an average of 25-75 weeks after the date of transplantation. The protocol before HSCT consisted of conservative treatment of carious lesions, and extraction of non-recoverable teeth. Non-vital teeth and those with periapical lesions were treated by performing endodontic therapy, apicectomy or extraction. Post-HSCT complications were observed in 75% of patients in Group I and in 95.4% of patients in Group II. The main post-operative infections were cytomegalovirus reactivation and *Staphylococcus epidermidis* bacteraemia. aGvHD was significantly associated with teeth in inclusions or with periapical lesions. A higher number of complications was observed in Group II patients, highlighting the importance of oral examination and dental treatment prior to transplantation. The authors concluded that dental treatment prior to HSCT should not be radical, but it should be an integration of restorative and preventive protocols that should be tailored to each individual case.

Yamagata et al[15] conducted a prospective study on 41 patients with hematological malignancies and who were scheduled for HSCT. The authors designed a protocol for minimal intervention, in which the treatment modality was decided according to the severity of the disease, and only symptomatic and heavily compromised teeth were extracted. The dental status was evaluated between 7 and 240 days before HSCT therapy by clinical and radiographic examination. Thirty-six patients required one or more kinds of dental treatment. All therapies were performed up to 10 days before transplantation, without alteration or delay in transplant planning. No patient had signs or symptoms of odontogenic infection during the immunosuppression period. The authors concluded that a conservative protocol seems to be suitable for patients who are to undergo HSCT.

Durey et al[36] assessed the treatment needs of 116 patients undergoing pre-HSCT; 93.6% of patients had signs of mucosal and/or dental disease. There was an overall incidence of periodontal disease of 79.5%, ranging from gingivitis to periodontal pockets greater than 6 mm. The authors concluded that assessment within a specialized hospital center has the advantage of providing direct access to an expert dentist and sedation facilities.

Endodontic Treatment

Periapical lesions should be treated because they are a risk factor for acquisition of viridians bacteremia after transplant[42]. The oral bacterial flora changes before and following chemotherapy; an increase of oral colonization with potentially pathogenic microorganisms (*Enterococcus faecalis and Candida* spp.) is observed. Root canal infections among autologous and allogeneic HSCT patients can be associated with a substantial increase in morbidity, and with significant impairment of the patient's quality of life[25]. The

research of Braga-Diniz et al[43] investigated the relationship between the epidemiological and clinical profiles of 188 patients before and after HSCT, and the need for endodontic treatment. Patients were subjected to an HSCT conditioning dental regimen based on a thorough clinical and radiographic evaluation. Intraoral periapical and bitewing X-rays were obtained; after evaluation, specific dental treatment was planned and performed. A total of 103 patients were in the pre-transplantation stage, and 85 were in the post-transplantation stage. The systemic conditions of the patients referred for dental treatment were compromised, especially for those in the pre-transplantation stage. The frequencies of endodontic treatment were 24.3% and 24.7% before and after HSCT, respectively, corresponding to 23.2% of the targeted sample.

Periodontal Treatment

Assessment of periodontal and oral hygiene status should be performed in patients undergoing HSCT, because prolonged neutropenia may be associated with oral complications. Laine et al[40] have shown a higher incidence of febrile episodes during chemotherapy in patients with untreated periodontal disease compared to those with healthy periodontal status[44]. Teeth with advanced periodontal disease may potentially cause bacteremia during neutropenia. In a retrospective study on 77 subjects who received a pre-transplant dental evaluation, Akintoye et al[45] reported that the high incidence of septicemia (64%) was related to bacteria typically found in the periodontal crevice or oral cavity, and many patients had poor periodontal health during transplantation. Raber-Durlacher et al[44] studied the correlation between gingivitis/periodontitis and the development of bacteremia during the neutropenia period following HSCT. Eighteen patients were examined and classified into two groups: the first group (28% of total) without periodontal disease (PPD $\leq$ 4 mm and BOP $\leq$ 10%), and the second group consisting of patients with gingivitis (PPD $\leq$ 4 mm and BOP > 10%) or periodontitis (PPD > 4 mm and BOP $\geq$ 10%). Two-thirds (67%) of patients developed bacteremia (diagnosed by blood samples taken twice a week), and Group 2 had more frequent episodes during the neutropenia phase than Group 1. The authors suggested that gingivitis and periodontitis may represent a risk factor for the development of bacteremia, also demonstrated in other studies[46,47]. Dental/periodontal infections can be misdiagnosed, particularly when inflammation symptoms are masked by neutropenia.

Septicemia frequently occurs during HSCT, and can be fatal. A loss of integrity in the alveolar bone around the teeth suggests that an intact alveolar barrier is also important in preventing viridans streptococcal bacteremia, which occurs in 61% of bacteremia patients during the period of post-transplant neutropenia[42]. Domestic oral hygiene should be based on the use of chlorhexidine-based mouthwashes, in addition to dental floss and toothbrushes, for the prevention of possible infections.

Protocol

Non-invasive procedures do not require an additional cure, and can be performed at any stage of the disease or chemotherapy; they are classified as Type I (objective examination, X-rays, and oral hygiene instructions) or Type II (simple and atraumatic restorations, prophylaxis and supragingival scaling)[1]. There are non-surgical procedures (Type III), such as complex restorations, scaling/root planning and endodontic treatments, whose implementation requires special attention before and during chemotherapy, considering the patient's overall health status and the risk/benefit ratio[46,47]. Execution of invasive treatments such as simple (Type IV) and multiple extractions (Type V) may be performed, but always considering the risk/benefit ratio and the patient's state of health[48].

In high-risk patients (active phase leukemia with bone marrow suppression), dental surgery is limited to emergency care. In patients at moderate risk (maintenance phase), the peak of myelosuppression is most apparent usually after 14 days of chemotherapy administration. At this stage, dental treatments should be avoided; before or 21 days after the onset of chemotherapy, treatments may be performed.

1. Eliminate potential sources of traumatic injury to the mucous membrane.
   a) Orthodontic appliances, ill-fitting prostheses, deficient/rough restorations and fractured and/or chapped teeth[8,49]. Orthodontic devices that do not irritate soft tissue can be maintained if the patient maintains a good oral hygiene status. After 2 years of health from completing the therapy, orthodontic treatment that was discontinued can be restarted[8,50].
2. Teeth with mild or moderate caries: restore 5.
3. Residual roots and unrestorable teeth: extract.

4. Symptomatic periodontal tooth or probing on depth > 8 mm or severe periodontitis: extract.
   a) It is important that the dentist is aware of the signs and symptoms of periodontal disease, since these may be difficult to highlight when the patient is immunosuppressed[47].
5. Asymptomatic tooth with probing on depth < 8 mm: scaling.
   a) The patient should undergo scaling and root planning, to check for periodontal disease and related bacterial infection[38,44,51,52]. Some authors suggest that bleeding caused by scaling and root planning can cause bacteremia[31,46,47].
6. Pulpitis: endodontic treatment.
   a) It should be performed at least 1 week before chemotherapy begins, so that there is enough time to evaluate periapical infection resolution[1].
7. Asymptomatic apical periodontitis > 5 mm: endodontic treatment or extraction (if there is insufficient time)[5].
8. Symptomatic partially erupted third molar (PEM): extract.
   a) PEMs can be a source of infection due to pericoronitis; if the gingival tissue partially covering the tooth is a potential factor for infection, it should be surgically removed if hematologic levels allow it. Asymptomatic PEMs do not increase the risk of developing a local infection, even though in 36% of patients local infections frequently occur during HSCT treatment. Complications may be avoided by frequent monitoring of the patient[53].

Antibiotic prophylaxis: For invasive procedures such as extraction and periodontal causal treatment that can cause significant bleeding and spread of bacteria in the blood, antibiotic coverage must be performed. Systemic antibiotic prophylaxis reduces the occurrence of febrile episodes, clinically or microbiologically documented infection and bacteremia, without significantly affecting all-cause mortality or infection-related mortality[54]. Antibiotic prophylaxis during oral and maxillofacial surgery should be performed until 6 months after the completion of chemotherapy, even though some authors do not recommend routine antibiotic prophylaxis in patients undergoing chemotherapy[1,38,52]. Invasive procedures should, therefore, be planned and agreed upon with a multidisciplinary approach[38], and patients should be treated with 2 g amoxicillin orally 1 h before treatment[33]. Antimicrobial prophylaxis is recommended when the neutrophil count is less than 2,000 cells/mm^3 of blood, or in patients with increased susceptibility to endocarditis[32,46,55]. When there is an odontogenic infectious outbreak, intravenous antibiotics should be administered to high-risk patients[48,49].

Management of oral bleeding: A platelet count of at least 60,000 cells/mm^3 is acceptable for oral surgery. When spontaneous bleeding is observed, the dentist should perform oral hygiene motivation procedures. If these measures are not sufficient, platelet transfusion can be considered[32]. Oral bleeding can be controlled by the use of vasoconstrictor agents (adrenaline), clot-forming agents (topical thrombin and/or hemostatic collagen agents) and tissue protectants: cyanoacrylate products help seal bleeding sites and protect organized clots[32]. Epsilon-Aminocaproic acid (EACA) may be useful in patients with unstable clots; a notable reduction in post-operative bleeding is evidenced following dental extraction when either EACA or tranexamic acid is used[56]. Tranexamic acid as a topical hemostatic agent is considered effective in reducing the incidence of post-operative bleeding in patients receiving oral anticoagulants; 500 mg tranexamic acid/5 ml saline solution mouthwash minimizes gingival bleeding[33,52].

Oral complications of HSCT

Mucositis

Oral mucositis (OM) occurs in most patients treated with high-dose therapy and stem cell transplantation. It has been associated with an increased need for total parenteral nutrition, opioid analgesics and prolonged hospitalization with intensive attendant care[57,58]. OM is an inflammatory-driven process of the oral mucosa; it is induced by radiation therapy and/or chemotherapy, and is characterized clinically by mucosal damage ranging from mild inflammation (erythema) to extensive ulcerations penetrating the submucosa. Mucositis is associated with an increased risk of systemic infection resulting from bacteremia associated with the breakdown of mucosal barriers. In general, these alterations occur within 2-3 weeks. After completion of radiotherapy, they heal over a similar period of time; resolution coincides with engraftment. Vascular damage and epithelial atrophy make the mucosa susceptible to trauma, and even mild trauma can cause the onset of an ulcer that can take months to heal[59]. The main initiating factor is the presence of reactive oxygen species (ROS) that damage cells, tissues and

blood vessels directly. It is postulated that histamine attenuates tissue damage by decreasing the generation and release of ROS, and suppresses the release of pro-inflammatory cytokines[60].

In HSCT patients, mucositis is not limited to the oral cavity but may occur along the entire oro-digestive tract[25]. The prevalence of OM is between 30-70% after chemotherapy, and can reach 90% after HSCT[61,62]. Conditioning regimens are the most important parameters determining OM risk, but patient-related factors are also involved. Genetic polymorphisms associated with the expression of inflammatory mediators such as tumor necrosis factor (TNF)-α have been implicated in OM risk in patients undergoing allogeneic HSCT[63]. Identification of populations at higher risk for OM is needed to begin intense prevention for patients undergoing conditioning for allo-HSCT. It is hypothesized that patients who carry the MTHFR 677TT genotype are associated with a higher risk of developing OM, and the use of multivitamins before transplantation has a potential protective effect on the development of OM. Concurrent folic acid supplementation does not change the effectiveness or toxicity of methotrexate in this patient population[58,64].

Oral ulcerative mucositis is a significant, common and important risk factor for alpha-hemolytic streptococcal bacteremia in autologous transplant patients with myelosuppression. The extent and severity of OM is significantly correlated with the number of days for which injectable narcotics, total parenteral nutrition, and injectable antibiotics are administered, as well as the risk of significant infection, days spent in hospital and mortality[57,65].

A descriptive study was carried out by Recolons et al[66] on 97 patients who received treatment with chemotherapy or conditioning prior to HSCT; oral hygiene and dental, plaque and gingival index were evaluated and related to mucositis. Patients with a high plaque index presented a high percentage of mucositis. Patients with healthy gums, good oral hygiene and no visible plaque presented a reduced prevalence of mucositis (26.7%). In the study of Coracin et al[67] on 97 patients (56% male and 44% female) who underwent HSCT, dental plaque and periodontal status, causative factors in oral inflammation, were determinant of the incidence of OM. The grade of mucositis was seen to be influenced by the number of missing teeth and by the DMFS index; this might be due to the trauma determined by tooth friction[68]. The presence of *Porphyromonas gingivalis*, a strictly anaerobic Gram-negative bacterium associated with periodontitis, has been shown to have a predictive value for mucosal ulcerations in HSCT patients[49].

The presence of plaque and calculus increases the risk of bacteremia, even in neutropenic patients, while good oral hygiene reduces the occurrence and severity of mucositis[66,69]. Sepsis in 25–50% of immunosuppressed patients derives from the oral cavity, and tooth brushing does not increase bacteremia.

Indications

Dental brushing 2-3 times a day[66]. Some authors recommend replacement of the toothbrush after each neutropenic cycle. Toothpaste containing sodium dodecyl sulfate should be avoided if it irritates the mucosa[49].

Chlorhexidine mouthwash: not recommended, due to the possibility of irritation of the oral mucosa. In cases of oral infection, non-alcoholic and non-flavored chlorhexidine may be tolerated during neutropenia[49].

Aloe vera solution: a statistically significant reduction in severe mucositis is found[70].

Caphosol® + 1% fluoride gel: reduces the frequency and intensity of OM[71].

High-power laser therapy: faster healing of lesions, reduced inflammation, decrease in pain 3 days after the first application, and complete healing after 11 days[62,72].

Mucormycosis

Zygomycoses are infections caused by fungi of the class Zygomycetes, comprised of the orders Mucorales and Entomophthorales. Mucormycosis is a fungal infection due to fungi of Mucorales species that may become opportunistic pathogens in immunocompromised patients[73], as for example in the case of HSCT. Mucormycosis confined to the periodontium is uncommon, and few cases have been reported[74]. Prolonged and profound neutropenia due to chemotherapy for an underlying hematologic malignancy, and HSCT in recipients with severe GvHD are other significant risk factors for this form of the disease. Mucormycosis is an aggressive and frequently fatal opportunistic fungal infection in these patients, with mortality rates ranging from 69% to 77%[75]. The most common oral sign of mucormycosis is ulceration of the palate. Differential diagnosis may include odontogenic or periodontal infection and maxillary sinusitis. Organisms may be identified on biopsy using periodic acid Schiff stain or methenamine silver stain[76]. Recently, Epstein et al[76] described

a case of gingival mucormycosis after 25 days of HSCT. The authors emphasize the importance of early detection and treatment of post-transplant oral infections by a multidisciplinary team.

Indications

Amphotericin B deoxycholate: 1-1.5 mg/kg/day.
Granulocyte transfusion: at least 1×10^{10}.

Osteonecrosis and Osteoporosis

Long-term corticosteroid therapy may contribute to the loss of bone density, which may affect alveolar bone and temporomandibular joints, and may be associated with an increased risk of avascular necrosis of bone. Bisphosphonate therapy can increase osteonecrosis of the jaw[8].

Conclusions

The purpose of this work was to evaluate when perform dental interventions in patients waiting for transplantation, and what interventions can be performed safely. Even if large-scale longitudinal studies are absent, dental treatment is preferred to the strategy of no dental treatment, as underlined by Elad et al[29]. The oral health of patients undergoing HSCT should be evaluated for oral infections that should be eliminated, before initiation of the conditioning phase. The role of the dental practitioner occurs during the chemotherapy phase and during the phase preceding the transplant, to allow the patient to achieve good oral health, and increase the success rate of the transplant.

The conditions most reported in different studies are about periodontal pathology. This highlights the importance of the dental hygienist collaborating with the dentist; both of them must educate the patient about the importance of maintaining oral health for the prevention of unwanted complications during and after treatment with chemotherapeutic agents. The patient must be informed about any possible dental-related complications that may occur after transplantation. During the various phases of chemotherapy, emergency dental interventions are always possible; the dentist should be assisted by specialist medical staff. A dedicated dental service within the hospital appears to be effective for better communication between the dentist and the oncologist. Dental care cannot always be done in the hospital in a short time, hence the need to create guidelines for the private dentist.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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