Long-term oral and craniofacial complications following pediatric bone marrow transplantation

Marcio A. da Fonseca, DDS, MS

Dr. da Fonseca is an assistant clinical professor, Department of Orthodontics and Pediatric Dentistry, University of Michigan School of Dentistry, Ann Arbor, Michigan.

Abstract

Bone marrow transplantation (BMT) has become a common form of treatment for childhood diseases and disorders that directly or indirectly affect the production of stem cells which give origin to blood and immune system elements. The pre-transplant protocols include, but are not limited to, chemotherapy and/or radiotherapy, which can cause considerable acute and long-term undesired effects in the oral cavity and the craniofacial complex. This manuscript discusses the sequelae that a pediatric dentist may encounter when treating a BMT survivor. (Pediatr Dent 22:57-62, 2000)

Systemic and oral complications associated with bone marrow transplantation (BMT) may occur months to years after the procedure. Adverse effects during the first three months are considered early complications. After day 100 post-transplant, adverse effects are considered delayed or long-term complications. They can be directly related to the transplant (engraftment failure, chronic graft-vs-host disease, delayed immunologic recovery, B-cell lymphoproliferative disorder), to the conditioning regimen (neuroendocrine and pulmonary dysfunction, growth and development impairment, ocular disorders, dental developmental disturbances, psychological distress, central nervous system (CNS) abnormalities, secondary malignancies), or to the patient’s underlying disease (relapse).

In order to create strategies to facilitate the management of oral complications, Schubert et al. proposed four stages of BMT:

Stage 1: The patient undergoes a series of evaluations, including dental, in preparation for the transplant;
Stage 2: The patient is admitted to the hospital for the conditioning therapy (7 to 10 days of chemotherapy and/or radiotherapy), marrow infusion (“Day 0”) and early engraftment (up to day 35 post-transplant). The patient is likely to be discharged during this period;
Stage 3: Engraftment continues (from day 36 to 100) with outpatient follow-up;
Stage 4: Full immunologic recovery is expected (> day 100).

Because an increasing number of children are receiving BMT and are surviving longer, a variety of late oral complications and craniofacial sequelae are becoming more apparent.

Post-BMT late systemic effects

Immunologic dysfunction is characterized by a lack of sustained transfer of donor-derived lymphocyte immunity, a capitulation of normal lymphoid ontogeny and the effects of graft-vs-host disease (GVHD) and its therapy. The onset of antigen-specific T-lymphocyte function, in patients without chronic GVHD, occurs 3 to 6 months after the transplant with normal restoration of the immune system within approximately one year. Immune deficiency can persist in patients with active chronic GVHD. Relapse of the original disease also occurs, leading to a second transplant, except in cases of solid tumor recurrence.

Pulmonary dysfunction has not been well documented in pediatric BMT recipients. Studies in adults reveal obstructive defects in 10% to 15% of patients with chronic GVHD. Late pulmonary complications contribute to post-BMT morbidity. There is a 6% chance for secondary malignancy development at 15 years post-transplant for patients who received chemotherapy alone, and a 20% probability for those who received total body irradiation (TBI).

Endocrine dysfunction leading to growth and development problems has been documented. Growth hormone deficiency and deceleration in normal growth rates occur in 50% to 60% of patients who received TBI. Children older than 10 years of age may develop primary gonadal failure, requiring hormone supplementation to achieve pubertal development and secondary sexual characteristics. Most prepubertal boys who receive chemotherapy and hyperfractionated TBI enter and progress through puberty normally, and at least 50% of the prepubertal girls enter puberty and menstruate regularly. Factors that impair growth in BMT children include: chronic GVHD, pulmonary dysfunction, general poor health, steroid therapy, direct irradiation effects on skeletal growth, and thyroid function.

CNS abnormalities (neuropsychological deficits, lower IQ scores, problems with visual motor, fine motor, abstract thinking, and spatial processing tasks) are observed especially in children younger than eight years of age who received cranial irradiation. Adult patients treated with an increased TBI dose have cognitive dysfunction (slowed reaction time, reduced attention and concentration, difficulties in reasoning, and problem-solving).
Other long-term effects include systemic GVHD, cardiac, renal, and hepatic problems, cataract development, ocular disorders, genitourinary dysfunction, psychosocial problems, and infections.1,5,6,10

**Post-BMT late oral and craniofacial effects**

**Dental care**

The frequency of oral exams will vary depending on the severity of oral problems, compliance with oral hygiene, and the patient’s overall health.4 The stress of the transplantation process may lead patients to complain of myofascial pain triggered by increased clenching and bruxism.1 Moist heat packs applied to the masticatory muscles, relaxation techniques and anti-anxiety medications may prove helpful.2 Regular dental exams with radiographs can be done routinely, but elective dental work, including prophylaxis, should be avoided for 8 to 12 months after the transplant because of the profound impairment of immune function.3 If a dental emergency arises during that period, the patient’s physician should be consulted before any treatment is instituted. If the patient has a central venous access device, prophylaxis according to the American Heart Association11 must be prescribed before any dental procedure, in addition to the antibiotics the child may be taking. When the patient is fully recovered, routine treatment can be provided.

**Chronic oral GVHD**

GVHD is a process in which the transplanted T-lymphocytes recognize histocompatibility antigens of host tissues as foreign, causing immune-mediated injury.1,2,12,13 Chronic GVHD occurs as progression of acute GVHD, following resolution of acute GVHD (quiescent) or de novo.12 It is an autoimmune phenomenon where tolerance for host tissues either fails to develop or is lost.2,12 It occurs after day 80 post-transplant and presents with dermal, hepatic, gastrointestinal, ocular, or oral mucosal involvement.12-14 The patient may become thrombocytopenic.14 Chronic GVHD incidence varies with patient’s age, history of previous acute GVHD, and marrow donor type, ranging from 33% in human leukocyte antigen identical sibling transplants to 64% in unrelated donors.1,12 Morbidity and mortality are highest in patients with progressive onset and lowest among those with de novo onset.1,14 Treatment is with prednisone, cyclosporine, tracolimus, azathioprine, and PUVA, and continues for at least 9 months until all clinical and pathological evidence disappears.1,2,12,14

A clue to chronic oral GVHD is increasing mucosal xerostomia and/or generalized stomatitis 100 days or more following the transplant.4 Oral manifestations of chronic GVHD may be confused with infections or residual conditioning regimen effects.12,13 The oral cavity may be the first or only site of chronic GVHD.12 There is a striking similarity between oral chronic GVHD and autoimmune disorders, such as lichen planus and lupus erythematosus.15,16 Mucosal atrophy, erythema, lichenoid changes, pain, and xerostomia have been described as the clinical oral manifestations of chronic GVHD (Fig 1).15 The buccal mucosa, palate, and dorsal surface of the tongue are the most frequent sites for ulcers.12 Lichenoid hyperkeratotic changes are predominantly reticular and papular in the lips, labial, and buccal mucosa, palate, and gingiva.15 Areas of ulceration may be extensive, especially along the lateral tongue borders and posterior buccal mucosa.12,13 Mucosal surfaces often lose their normal architecture, particularly attached gingiva stippling and the tongue papillae (Fig 2).3,4 With severe liver dysfunction, there is a marked icteric discoloration (yellowish orange) of the oral tissues.13 Ulcerations tend to be covered with a heavy grey or yellow pseudomembrane.13 When sclerodermatous changes are present, decreased mouth opening occurs due to perioral fibrosis (Fig 3).3,4,10 Toothpastes, carbonated beverages, acidic foods, and spices cause pain and burning sensations.4 Oral examinations, along with lip biopsies obtained between days 80 and 100 post-transplant, have
been useful in chronic GVHD assessment.\textsuperscript{13} Minor salivary gland involvement is characterized by ductal necrosis, sialadenitis, epithelial lymphocytic infiltration, acinar destruction and epithelial cell necrosis.\textsuperscript{12,13,15,16}

Oral GVHD management is directed toward the specific lesion, pain, and xerostomia alleviation, and oral hygiene maintenance.\textsuperscript{12} Pain and xerostomia significantly affect nutrition and mouth care.\textsuperscript{12} Oral chronic GVHD usually resolves with successful systemic therapy.\textsuperscript{15} At times local measures may be implemented, such as topical steroid gels and elixirs, topical cyclosporine, saline and sodium bicarbonate rinses, topical anesthetics, and analgesics.\textsuperscript{12} Topical steroids have shown mixed results with relief of pain and irritation being more likely than the resolution of the oral lesions.\textsuperscript{3,13}

**Xerostomia and taste dysfunction**

Xerostomia may persist up to 6 to 8 months post-BMT, making the tissues more susceptible to trauma and infection.\textsuperscript{3,4} Alcohol-free rinses are recommended for home use, while sugarless gum and candy may increase salivary flow. If the patient is not allowed to drink fluoridated tap water, then fluoride supplementation must be prescribed accordingly.\textsuperscript{18} Rampant dental caries can become a problem (Fig 4). Optimal oral hygiene must be maintained, with neutral fluoride therapy indicated in cases of moderate and severe xerostomia. Taste disturbances may lead to increased eating difficulties and poor nutrition. In adolescents and adult BMT recipients immediately after the transplant, there may be significant disturbance in taste with recovery of taste acuity by one year post-BMT.\textsuperscript{19,20}

**Infections**

The head and neck are the most frequent sites of infections in BMT patients after 100 days post-transplant, with the incidence of oral infections mostly linked to chronic GVHD development.\textsuperscript{1,4} Gingivitis and periodontal and dental abscesses become more active in this phase of recovery.\textsuperscript{3,4} Opportunistic infections occur due to systemic immunosuppression, xerostomia, and long-term steroid and antibiotic use.\textsuperscript{3,12}

Herpes simplex (HSV) infections are usually more localized and typical in presentation because of improved local tissue resistance and engraftment.\textsuperscript{3,12,21} However, with slow engraftment or graft failure, herpetic lesions will be widespread and destructive.\textsuperscript{21} Several patients being treated for presumed GVHD had pseudomembranous tongue ulcerations which were refractory to therapy but resolved during treatment of cytomegalovirus (CMV) pneumonia with ganciclovir.\textsuperscript{22} In these types of cases, the lesion biopsy should include the ulcer bed because CMV is located in muscle tissue fibroblasts and in endothelial cells of small vessels.\textsuperscript{12} A segment of the intact epithelial surface should be submitted for possible identification of HSV infection. CMV culture of oral lesions and biopsies may lead to false positive results due to asymptomatic viral shedding.\textsuperscript{23,24} Ganciclovir is the therapeutic choice in CMV infections, with foscanet used in those who have ganciclovir-associated marrow suppression or drug resistance.\textsuperscript{13} Varicella-zoster and Epstein-Barr virus infections may also occur.\textsuperscript{24}

Patients with persistent granulocytopenia are at risk for bacterial and fungal infections.\textsuperscript{4} Candida remains the most common oral infection but aspergillosis can also be observed.\textsuperscript{3} Antifungal agents are available for topical application while intravenous amphotericin B is used for invasive and systemic infections.\textsuperscript{7} The high sugar content of nystatin rinses and clotrimazole troches increases the risk for dental caries. Azole antifungal agents (ketoconazole, clotrimazole, fluconazole) are most effective for antifungal prophylaxis.\textsuperscript{25} Nystatin is usually not successful for prevention of fungal infections.\textsuperscript{26-28}

With the use of broad spectrum antibiotics and penicillinase-resistant drugs, a large number of oral bacterial infections are caused by opportunistic aerobic gram-negative bacilli (Pseudomonas, Enterobacter, Proteus, E. coli) that typically do not cause problems in patients with an intact defense system.\textsuperscript{29} Pseudomonas lesions initially present as a dry, raised, whitish-yellow center that later becomes necrotic.\textsuperscript{30} Other gram-negative bacterial infections are clinically indistinguishable, with a raised, non-purulent, creamy to yellow-white, and moist presentation. They have a smooth-edged growth seated on painful, red, superficial erosions and ulcers.\textsuperscript{30} The tongue, palate, lips, and gingiva are the most common sites although any part of the oral cavity may be affected.\textsuperscript{30} Bacterial infections have decreased today because of the routine use of systemic antibiotics and growth factors. However, despite these advances, serious infections continue to occur.\textsuperscript{29,31} Risk assessment, selection of patients for prophylaxis, accurate diagnosis, and appropriate therapy are hallmarks of infection management.\textsuperscript{11,32}

Oral infection prevention should focus on elimination or reduction of nonendogenous microorganisms and the maintenance of mucosal integrity.\textsuperscript{2} Immunosuppressed patients with oral lesions need to be carefully evaluated to identify the causative agent and avoid further complications.\textsuperscript{24} Cultures and/or biopsies of lesions should be performed to guide therapy. Before delivering regular dental care or invasive procedures in patients with active GVHD and/or on high dose of immunosuppressants, the pediatric dentist should discuss the need for systemic antibiotics with the physician.\textsuperscript{4}

**Non-gingival soft tissue growths**

Pyogenic granulomas on the tongue have been described in chronic GVHD.\textsuperscript{3,11,33,34} Several cases of reactive proliferations of fibrous and granulation tissue in BMT recipients receiving cyclosporine for treatment of systemic GVHD have presented as rapidly growing non-gingival soft tissue masses, with chronic GVHD around the mass.\textsuperscript{35} These growths may be a combination of GVHD-related chronic inflammation and an exaggerated proliferative response of the connective tissue to...
cyclosporine. These lesions are typically painless but bleed when traumatized and may regress spontaneously or be treated with surgical excision or topical steroids (Fig 5a and 5b).

**Dental hypersensitivity**

Some patients report dental sensitivity after the transplant. This may be a neurotoxicity reaction caused by the conditioning regimen or due to gingival recession exposing cement. The patients are advised to use a neutral fluoride gel, and a desensitizing toothpaste, and to avoid foods that trigger discomfort. Reassurance that this is a transient problem is important.

**Dental and craniofacial developmental abnormalities**

Late effects of chemotherapy and radiotherapy on the craniofacial development have become apparent due to improved survival in pediatric BMT recipients. The extent and severity depend on patient’s age at the time of initiation of treatment (many children only undergo BMT after being treated for the baseline disease for months or years), and the protocol used (chemotherapy alone or in conjunction with radiotherapy). The younger the child is at the beginning of treatment (especially before six years of age), the greater the risks for craniofacial and dental disturbances.

Radiotherapy destroys cells during their mitotic phase. At very high doses, it can affect even non-proliferative cells. Enamel and dentin formation can be disturbed not only when craniofacial radiation is administered but also during TBI. Chemotherapeutic agents are selectively toxic to actively proliferating cells by disrupting DNA synthesis and replication, RNA transcription and cytoplasmic transport mechanisms. Non-proliferating cells are not affected. Chemotherapeutic and radiation effects on dental development include tooth agenesis, complete or partial arrest of root development with thin, tapered roots, early apical closure, globular and conical crowns, dentin and enamel opacities and defects, microdontia, enlarged pulp chambers, taurodontism, and abnormal occlusion (Figure 6). It is not unusual to observe delayed eruption of permanent teeth, although some children with hematological...
malignancies who received chemotherapy alone do not have abnormalities in dental maturity or eruption of their permanent dentition. Reduction in lower face height in BMT patients correlated with impaired dental development. Vertical growth of the condyles, and the alveolar and molar heights are adversely affected by pre-transplant conditioning. Children who receive TBI show more severe disruptions in the dental development than those who receive only chemotherapy. Children who receive growth hormone after TBI have greater mandibular length growth increments, which may be triggered by the hormonal stimulation of the chondral growth plate in the condyles.

It is important to discuss these possible sequelae with both the patient and the caretakers during the pre-transplant oral/dental evaluation because many physicians are not aware of these potential problems and may not inform the family. With this information, the patient and the caretakers become aware of the importance of good oral and dental care in decreasing the chances of oral complications. A panoramic radiograph should be obtained before the transplant and yearly afterwards to monitor dentition development, particularly in children at high (<6 years) and moderate risk (<10 years).

References

ABSTRACT OF THE SCIENTIFIC LITERATURE

The purpose of this investigation was to evaluate the performance of a dentin bonding agent applied to carious and noncarious primary dentin in vivo. Following human subjects committee approval 28 children, ages 7-11 years, were enrolled in the study. A total of 48 Class I or II restorations were placed in primary molars using posterior composite restorative material (Z100, 3M Dental). The teeth were randomly assigned to the control or experimental groups. In the control group, using a caries-detecting solution the investigators removed all identified irreversibly infected dentin prior to placement of the restorative material. For the experimental group, the investigators removed carious dentin from the dentinoenamel junction but left visibly moist and soft carious infected dentin on the pulpal and axial walls. The restorations were evaluated clinically at 24 hours, 3, 6, 9 months, and 1 year after initial placement. Radiographic evaluation was completed at 24 hours and 1 year. Forty of the prepared teeth were recovered following exfoliation and processed for examination using scanning electron microscopy. At 1 year the marginal integrity was described as undetectable with an explorer in 95.7% and 100.0% of the restorations in the control and experimental groups, respectively. The radiographic findings for the experimental group after 1 year were as follows: 11 of the 24 restorations exhibited regression of the radiolucency, there was progression of the radiolucent area in 6 restorations, and the radiolucent area was unchanged in 7 restorations. At 1 year all restorations in the experimental group (partial caries removal) were retained and presented good marginal integrity. There were no clinical symptoms, such as spontaneous or elicited sensitivity, nor clinical or radiographic signs indicating degeneration of pulp tissue with the teeth in the experimental group. The authors report that one tooth from the control group was excluded from the study because of pulpal necrosis and fistulization.

Comments: Within the limits of this study the results suggest that similar to other restorative materials, as long as the margins of the composite restoration remain sealed the caries process will not progress.


Address correspondence to: Jorge Perdigão, Associate Professor, Department of Operative Dentistry, School of Dentistry, University of North Carolina at Chapel Hill, CB #7450 Brauer Hall, Room 306, Chapel Hill, North Carolina 27599-7450, E-Mail: jorge_perdigao@dentistry.unc.edu

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