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Stomatologic complications of bone marrow transplantation in a pediatric population

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Bone marrow transplantation (BMT) is associated with numerous complications of multiple organ systems (Thomas et al. 1978). Several studies,[1] regarding oral complications associated with this procedure, have recently been reported. This report details the clinical manifestations and management of oral reactions to marrow transplantation in 41 consecutive pediatric patients at Rainbow Babies and Childrens Hospital (Cleveland).

Methods

Study Population

The study population for this investigation consisted of 41 consecutive pediatric patients presenting to Rainbow Babies and Childrens Hospital for BMT between April, 1981 and July, 1984. The study group (Table 1) consisted of 15 females and 26 males ranging in age from 7 months to 17 years. Fourteen patients had acute lymphocytic leukemia (ALL)—12 were in second remission and 2 in relapse; 10 patients had acute nonlymphocytic leukemia (ANLL)—9 were in first remission and 1 in relapse; 8 presented with Grade 4 neuroblastoma; 3 presented with aplastic anemia (AA); 2 presented with Wiskott-Aldrich syndrome; and 1 each with osteopetrosis, T-cell lymphoma, Burkitt's lymphoma, and stage 5 Wilms' tumor with metasteses. Three neuroblastoma patients and the Wilms' tumor patient received autologous transplants. One neuroblastoma patient received a syngeneic transplant. The remaining 36 patients received allogeneic bone marrow. Thirty-two of these donors were HLA histocompatible and mixed lymphocyte culture nonreactive with their respective recipients. The remaining 4 donors were selected HLA A and/or B loci partial mismatches with DR compatibility and minimally reactive mixed lymphocyte cultures. Marrow ablative therapy regimens varied within the study population based on diagnosis as indicated in Table 1. Donor marrow was infused intravenously within 24 hr after completion of marrow ablative therapy. Thirteen of the 41 patients received methotrexate (MTX) for graft versus host disease (G.V.H.D.) prophylaxis in the immediate post-transplant period.

[1] Berkowitz et al. 1983; Dreizen et al. 1979; Heimdahl et al. 1985; Rakocz et al. 1982; Schubert et al. 1983; Seto et al. 1985.

Oral Evaluation

Each patient received a dental evaluation (consisting of a clinical examination, panorex, bite-wings, and selected periapical radiographs) 14–23 days prior to initiation of marrow ablative therapy. Dental pathology associated with a possible risk for hemorrhage (e.g., exfoliating primary teeth) and/or infection (e.g., dental abcesses) during periods of pancytopenia and immunosuppression were treated prior to initiating marrow ablative therapy. A minimum interval of 10 days was established between completion of dental treatment and initiation of ablative therapy to allow adequate time for healing of extraction wounds.

In addition, all patients (4 years of age and older), their parents, and nurses received instructions regarding dental hygiene procedures. In this regard, daily tooth brushing and flossing were performed when granulocyte counts exceeded 500/mm^3 and platelet counts were above 40,000/mm^3. In contrast, when the granulocyte and/or platelet counts were

TABLE 1. Study Population

Disease	No. of Subjects	Sex (M/F)	Mean Age (years)	Age Range (years)	Type of BMT	Preparative Regimen***
ALL	14*	9/5	7.64	3–13	Allogeneic	A—13 B^1—1
ANLL	10**	6/4	12	2–17	Allogeneic	A—8 B^1—2
Grade 4 neuroblastoma	8	5/3	9.37	2–16	Allogeneic—4 Autologous—3 Syngeneic—1	C^1—7 C^2—1
AA	3	3/0	13.3	11–15	Allogeneic	B^2
Wiskott-Aldrich syndrome	2	2/0	——	0.83–13	Allogeneic	D
Osteopetrosis	1	0/1	0.67	——	Allogeneic	D
T cell lymphoma	1	0/1	13	——	Allogeneic	A
Burkitt's lymphoma	1	1/0	5	——	Allogeneic	E
Stage 5 Wilms' tumor	1	0/1	16	——	Autologous	C^2

* Of the 14 ALL patients, 12 were in remission and 2 in relapse. ** Of the 10 ANLL patients, 9 were in remission and 1 in relapse. *** *Preparative Regimens:* A—Cytosine arabinoside 3 g/m²/dose IV q 12 hr × 12 doses followed by fractionated TBI 200 rads bid × 6 doses. B^1—Cyclophosphamide 60 mg/kg/dose IV q 24 hr × 2 doses followed by TBI 1000 rads/dose × 1 dose; B^2—Cyclophosphamide 50 mg/kg/dose IV q 24 hr × 4 doses followed by fractionated TBI 200 rads/dose × 3 doses. C^1—Melphalan 60 mg/m²/dose IV q 24 hr × 3 doses followed by fractionated TBI 200 rads bid × 6 doses; C^2—same as C^1 without TBI. D—Busulfan 2 mg/kg/dose PO q 24 hr × 4 doses followed by cyclophosphamide 50 mg/kg/dose IV q 24 hr × 4 doses. E—Multi-agent chemotherapy × 4 days followed by fractionated TBI 200 rads bid × 6 doses.

below these levels tooth brushing and flossing were discontinued to avoid gingival hemorrhage and bacteremia. Dental hygiene procedures during pancytopenia were restricted to wiping off the teeth with moistened gauze sponges or toothettes. In addition, all patients were evaluated on a daily basis during their hospital course by a member of the Division of Pediatric Dentistry. The duration of hospital admission varied within the study population from 35 days to several months. All surviving patients received an oral re-evaluation on a regular basis after discharge from the hospital (at least once every 3 months).

Oropharyngeal Candidiasis (OPC) Prophylaxis

Three OPC prophylaxis regimens were employed. Regimen 1 consisted of unsupervised "swishing and swallowing" of nystatin (500,000 units qid). Regimen II, referred to as the multi-agent regimen (Berkowitz et al. 1985), consisted of the following:

1. Debriding all mucous membrane surfaces within the oropharyngeal cavity with 1 povidone-iodine swabstick (PDI) 4 times per day.
2. Swabbing all mucous membrane surfaces within the oropharyngeal cavity with 1 large cotton pledget saturated with 500,000 units of nystatin 4 times per day.
3. Ketaconazole—given by mouth once per day at the following dosages: 50 mg (weight < 20 kg), 100 mg (weight 20–40 kg), and 200 mg (weight > 40 kg).

The povidone-iodine debridement immediately preceded the nystatin application. These procedures were performed by pediatric dental residents and the nursing staff. Regimen III consisted of multi-agent regimen therapy with 1 modification—deletion of the ketaconozole.

The distribution of patients with regard to type of OPC prophylaxis employed was: Regimen I—13 patients; Regimen II—16 patients; Regimen III—12 patients. OPC prophylaxis began on the day of initiation of marrow ablative therapy and was continued until the patient's absolute neutrophil count (ANC) recovered to 500/mm³ for 3 consecutive days.

Findings

Pre-BMT Dental Evaluation

Dental evaluation prior to initiating marrow ablative therapy indicated that 28 of the 41 patients comprising the study group had no periodontal disease, active dental caries, osseous lesions of the maxilla or mandible, and/or intraoral soft tissue lesions. Of the remaining 13 patients, 9 patients presented with a total of 15 necrotic primary teeth, 1 necrotic permanent tooth, and 7 large caries lesions involving permanent molar teeth. Two additional patients presented with a total of 5 exfoliating primary molars. The necrotic and exfoliating teeth were extracted and the carious teeth restored under local anesthesia at least 10 days prior to the initiation of ablative therapy. One patient presented with generalized gingivitis and periodontitis. Treatment included local debridement and antibiotic therapy (Tetracycline HCl 250 mg qid × 10 d). The remaining patient had 4 soft tissue impacted third molars removed under local anesthesia and IV diazepam 15 days prior to initiating ablative therapy. Review of this patient's past medical history revealed that her clinical course during remission

induction for ANLL was complicated by a left facial cellulitis secondary to a pericornitis associated with the mandibular left third molar tooth. None of these procedures were associated with any postoperative complications.

Oral Complications During Marrow Ablative Therapy

Seven of the 36 patients receiving total body irradiation (TBI) developed xerostomia and thick, ropy saliva immediately after their second or third dose of fractionated TBI. Three of these 7 patients also developed a unilateral or bilateral parotitis that manifested as a tender, mumps-like swelling at the angle of the mandible that resolved spontaneously in 48 hr. The xerostomia persisted in all 7 patients for approximately 1 week and was palliated by the use of a synthetic saliva substitute. In addition, all 7 of these patients were postpubertal adolescents. The 29 prepubertal patients who received TBI as well as the 5 patients who did not receive TBI did not develop any oral complications during ablative therapy.

Oral Complications During the Immediate Post-Transplant Period: Mucositis

The most common oral complication in the immediate post-transplant period was mucositis. All of the patients experienced some degree of mucositis. The onset of the mucositis usually occurred 4–6 days post-transplant at the nadir of the white blood cell count (WBC) and resolved when the absolute neutrophil count (ANC) recovered to approximately 500/mm^3.

The severity and duration of mucositis varied in the study population. Therefore, a multiple stepwise regression analysis (Fleiss 1973) was utilized to determine whether a relationship existed between the severity and duration of mucositis and the following variables: methotrexate (MTX); cytosine arabinoside (ARA-C); cyclophosphamide (CYC); melphalan (M); total body irradiation (TBI); and oropharyngeal candidiasis prophylaxis regimen (OPCP).

Duration of mucositis was significantly related statistically to MTX administration for graft versus host disease (G.V.H.D.) prophylaxis (multiple correlation = 0.77; $F = 55.69$, df = 1 and 39, $P < 0.001$). Those patients (N = 13) receiving MTX for G.V.H.D. prophylaxis had mucositis for 9–23 days (mean = 14.33 days) whereas the mucositis persisted for 6 to 18 days (mean = 8.46 days) in those patients (N = 28) not receiving MTX. Stated differently, MTX administration was associated with a statistically significant 6-day increase in the mean episode duration, which represents almost a doubling of the duration. None of the other variables (ARA-C, CYC, M, TBI, or OPCP) demonstrated a statistically significant association with duration of mucositis.

TABLE 2. Grading of Mucositis—Criteria of the East Coast Oncology Group

Degree of Stomatitis	*Clinical Observations*
0	None
1	Oral soreness, ≤ 3 ulcers
2	Oral soreness, > 3 ulcers, can eat and swallow
3	Many ulcers, cannot eat
4	Hospitalization and IV alimentation required

The severity of the mucositis for each of the 41 patients was graded according to the criteria of the East Coast Oncology Group (Table 2). The severity of mucositis was best predicted by a combination of indicator variables corresponding to M administration and TBI (multiple correlation coefficient = 0.61, $F = 11.4$, df = 2 and 38, $P < 0.001$). In particular, patients graded on a severity scale of 0–4 (Table 2) tended to be at least 1.5 categories worse if M was administered ($F = 17.76$, df = 1 and 38, $P < 0.001$) and were an additional category worse if they received TBI ($F = 5.06$, df = 1 and 38, $P < 0.05$). Thus M and TBI contribute independently to severity. In addition, none of the other variables (ARA-C, CYC, MTX, or OPCP) demonstrated a statistically significant association with severity of mucositis.

Oropharyngeal Candidiasis (OPC)

A diagnosis of OPC was based on the presence of characteristic white mucosal patches coupled with the presence of positive *Candida* cultures from debris obtained from those lesions. Utilizing these criteria, 11 of 13 patients on Regimen I developed OPC. In contrast, 3 of 16 patients on Regimen II and 2 of 12 patients on Regimen III developed OPC. The observed differences in the OPC frequencies between Regimen I vs. Regimen II and Regimen I vs. Regimen III were statistically significant ($\chi^2 = 12.46$, $P < 0.001$; $\chi^2 = 11.54$, $P < 0.001$). However, the difference in the OPC rate for Regimen II vs. Regimen III was not statistically significant. The sampling techniques, cultivation procedures, and discussion of these experimental findings have been reported earlier (Berkowitz et al. 1985). Finally, resolution of the OPC usually paralleled resolution of the mucositis. None of the 41 patients developed a documented *Candida* sepsis.

Oral Complications in the Postengraftment Period: Graft Versus Host Disease (G.V.H.D.)

Acute G.V.H.D. developed in 25/36 patients receiving allogeneic marrow transplants, as evidenced by liver dysfunction, generalized dermatitis, diarrhea, enterocolitis, and/or recurrent stomatitis. Five

of the 25 patients with acute G.V.H.D. developed recurrent stomatitis approximately 1 week after their pancytopenia-associated mucositis resolved. The recurrent stomatitis presented as an ulceration of the buccal mucosa, tongue, palate, and/or chelitis. These oral lesions usually resolved rapidly with systemic steroid therapy.

Eight of the 25 patients with acute G.V.H.D. developed chronic G.V.H.D. None of the patients developed chronic G.V.H.D. without having antecedent acute G.V.H.D. All of the patients with chronic G.V.H.D. had minor salivary gland and labial mucosa histology characteristic of G.V.H.D. (Sale et al. 1981). All of the 8 patients with chronic G.V.H.D. presented with clinical oral findings which included: lichen planus-like lesions (1 of 8 patients), mucosal erythema (7 of 8 patients), and xerostomia (4 of 8 patients). The lichenoid reaction presented as an asymptomatic, fine, white, reticular striae on otherwise normal-appearing mucosa. This lesion, which was noted on day 68 post-BMT, completely resolved by day 180 post-BMT. The discomfort associated with the mucosal erythema was controlled adequately with anesthetic mouth rinses. The onset of this lesion was associated with premature tapering of steroid therapy. This lesion resolved rapidly by increasing systemic steroid dosages. The xerostomia was palliated with the use of a synthetic saliva substitute. In addition, as xerostomia is associated with the development of rampant dental caries (Dreizen et al. 1977), the 4 xerostomic patients were prophylaxed with caries preventive measures which included daily use of topical fluoride gels (0.4% stannous fluoride), carbohydrate restriction diets, meticulous oral hygiene, and regular dental evaluation (at least once every 2 months). The use of a daily topical fluoride gel was discontinued when the xerostomia resolved. In this regard, the xerostomia resolved in 2 of the 4 patients within 6 months of onset and persisted in the other 2 patients for 10 and 14 months, respectively. None of these 4 patients developed dental caries during their observation periods (16 to 25 months).

Infections

One patient developed herpes labialis on day +65. The herpetic lesions resolved without complication after 5 days of topical acyclovir therapy.

Dental Caries

Three patients (2.5, 4, and 5 years of age) developed rampant dental caries. Only 1 of the 3 patients had chronic G.V.H.D. The onset of the dental caries occurred 6 to 13 months post-BMT. None of these patients complained of "dry mouth" or had evidence of xerostomia during their entire clinical course. In addition, parental interview indicated that eating habits were not of a cariogenic nature (e.g., excessive carbohydrate consumption and frequent feedings). However, all 3 patients were taking nystatin elixir (500,000 u qid) for OPC prophylaxis. In this regard, elixirs of nystatin are viscous liquids that contain 50% sucrose (Barnhart 1985) and therefore may have significant cariogenic potential. Dental therapy included restoration of carious teeth, biweekly use of topical 0.4% stannous fluoride gels (2 patients over 4 years of age), restriction of nystatin intake to mealtime to decrease the frequency of daily carbohydrate exposure, meticulous oral hygiene, and regular dental follow up (at least once every 2 months). None of these 3 patients developed recurrent dental caries during their follow-up observation periods of 16 months, 8 months, and 3 months.

Discussion

Pre-BMT Dental Evaluation

Infection is a major cause of morbidity and mortality during myelosuppressive therapy (Winston et al. 1979). Many of these infectious complications are caused by organisms which are residents of the patient's oral flora (Dreizen et al. 1974). In particular, necrotic teeth (Shapiro et al. 1950) and periodontal infection (Anolik et al. 1981) represent microbial reservoirs available for bacteremia. Collectively, this information implies that elimination of dental infection prior to initiating marrow ablative therapy would decrease the patient's risk for infectious complications. This approach was employed for the study population of the present report and none of the 41 patients developed an infectious complication of dental origin.

Dental hygiene procedures were performed regularly by most of the patients. As daily removal of dental plaque prevents gross accumulation of bacteria on dental surfaces, it appears likely that this approach may reduce the patient's risk for bacteremia. Specific data to support such a hypothesis are lacking, however. Finally, it was noted by the nursing staff that daily dental hygiene helped to nurture an optimistic outlook for the patients and their parents.

Oral Complications During Marrow Ablative Therapy

Seven of 36 patients receiving TBI developed xerostomia and thick, ropy saliva immediately after their second or third dose of fractionated TBI. Three of these 7 patients also developed parotitis. In contrast, Dreizen et al. (1979) and Seto et al. (1985) reported that almost every transplant patient in their series (which was restricted to adolescents and adults) presented with parotitis and xerostomia after TBI. The observed differences between these 2 reports may relate to the age of the patients. In this regard, all of

the adolescent patients (N = 7) conditioned with fractionated TBI developed xerostomia, thick, ropy saliva, and/or parotitis; however, none of the 29 prepubertal patients prepared with fractionated or single fraction TBI presented with these complications. Collectively, this information suggests that salivary gland tissue may be less radiosensitive in prepubertal children.

Oral Complications During the Immediate Post-transplant Period

Mucositis was the most common oral complication in the immediate post-transplant period. The onset of the mucositis usually occurred 4–6 days post-BMT at the nadir of the WBC and resolved when the ANC recovered to approximately 500/mm^3. The duration and severity of the mucositis varied in the study population. Those patients (N = 13) receiving MTX for G.V.H.D. prophylaxis experienced a statistically significant 6-day mean increase in the duration of mucositis as compared to those patients (N = 28) who did not receive MTX. This difference may relate to MTX's toxicity for oral epithelium. However, it was of interest to note that statistical analyses of the data indicated that there was no relationship between the severity of mucositis and the MTX variable. In this regard, the statistical analyses indicated that there was a significant relationship between the severity of mucositis and 2 variables—TBI and melphalan administration. None of the other variables (ARA-C, CYC, MTX, or OPCP) were statistically significantly associated with the severity of mucositis. However, the clinical impressions of the authors indicated that those patients who were on Regimens II and III for OPC prophylaxis had less severe mucositis than those patients on Regimen I with 1 exception—namely, all 7 patients (Table 1) receiving melphalan and TBI experienced Grade 4 mucositis (Table 2) regardless of the type of OPC prophylaxis employed.

Finally, 1 study (Meyers and Thomas 1981) demonstrated a relationship between chemotherapy-associated mucositis and oral herpes simplex infection. As the 41 patients in this report were not monitored with oral viral surveillance cultures, the potential role of oral herpetic infection to severity and duration of mucositis cannot be assessed. However, the authors currently are obtaining oral viral surveillance cultures on all of their BMT patients. In this regard, the authors have had 2 BMT patients with severe mucositis and positive oral herpes simplex cultures. Both of these patients' mucositis responded within 48–72 hr to IV acyclovir therapy. Collectively, these observations indicate that the potential role of herpes simplex virus to mucositis needs further clarification.

The risk for oral infection was highest during this period secondary to the leukopenia, immunosuppression, and loss of mucosal barriers and 16 of the 41 patients developed oropharyngeal candidiasis. However, segregation of the OPC data according to the type of OPC prophylaxis employed indicated that Regimens II and III were most effective in preventing OPC. Preliminary findings have been reported earlier (Berkowitz et al. 1985). However, this approach for OPC prophylaxis (Regimens II and III) is time-consuming and painful. Less invasive and more cost-effective approaches for OPC prophylaxis are needed. Finally, none of the patients in this report presented with oral bacterial infections in the immediate post-transplant period. The possibility of oral infection by such organisms as Klebsiella, Pseudomonas, and Staphylococcus has been reported, however (Dreizen et al. 1979).

Oral Complications in the Postengraftment Period: Graft Versus Host Disease (G.V.H.D.)

Previous studies[2] indicate that oral involvement in the postengraftment period is frequently associated with G.V.H.D. Oral complications of G.V.H.D. include stomatitis, xerostomia, and a variety of mucocutaneous lesions that mimic such diseases as lichen planus, scleroderma, and lupus erythematosis. The findings of this report are similar with those of earlier investigations—namely, 5 (20%) of the 25 patients with acute G.V.H.D. developed recurrent stomatitis and 8 (100%) of the 8 patients with chronic G.V.H.D. presented with oral involvement that included: lichen planus-like lesions (1 of 8 patients), mucosal erythema (7 of 8 patients), and xerostomia (4 of 8 patients). The clinical characteristics and management of these complications have been described earlier in this report.

Dental Caries

Three of the 41 patients in this report developed rampant dental caries. However, had the 4 xerostomic patients with chronic G.V.H.D. not been prophylaxed with caries-preventive measures, the number of cases of rampant dental caries probably would have increased. These observations suggest that BMT is associated with an increased risk for rampant dental caries. In this regard, a recent Swedish study (Heimdahl et al. 1985) reported that 37% of their BMT patient population presented with rampant dental caries during their first year post-transplant. Collectively, these findings indicate that all BMT patients should be informed of the caries risk and have frequent dental follow-up, especially during the first year post-transplant.

In summary, the authors' experiences indicate that pre-BMT dental evaluation and treatment min-

[2] Berkowitz et al. 1983; Dreizen et al. 1979; Heimdahl et al. 1985; Rakocz et al. 1982; Schubert et al. 1983; Seto et al. 1985.

imizes the risk of infections and hemorrhagic complications of dental origin. In addition, daily oral evaluation and multi-agent regimen therapy (with or without ketoconozale) coupled with appropriate therapeutic intervention during periods of pancytopenia and immunosuppression reduces the potential morbidity and mortality associated with oral complications. Finally, regular dental evaluation is indicated in the postengraftment period to minimize the potential morbidity associated with oral complications of G.V.H.D. and the risk for dental caries.

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AFDH approves grant for AIDS research

The AFDH recently awarded a $22,500 grant to the School of Dentistry at the University of California, San Francisco, for the first year of a 2-year research project on AIDS and its risk to patients. The project is aimed at decreasing the dental practitioner's risk in dealing with AIDS patients. The objective is to increase the dentist's diagnostic skills and encourage infection-control procedures through the development and testing of an educational program. A national information system designed to update dentists on the latest news regarding AIDS and its control also is planned. The study will enlist the support of randomly selected practitioners representing population areas that exhibit both a high and low incidence of AIDS, and will be conducted in 3 phases.