A Randomized, Controlled Clinical Trial of the Homeopathic Medication TRAUMEEL S® in the Treatment of Chemotherapy-Induced Stomatitis in Children Undergoing Stem Cell Transplantation

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BACKGROUND. Stomatitis is a common consequence of chemotherapy and a condition for which there is little effective treatment. Although the management of patients with other chemotherapy-related toxicities has improved in recent years, the incidence of stomatitis is increasing because of more intensive treatment and is often a dose limiting factor in chemotherapy. The authors assessed the efficacy of a homeopathic remedy, TRAUMEEL S®, in the management of chemotherapy-induced stomatitis in children undergoing bone marrow transplantation.

METHODS. A randomized, placebo-controlled, double-blind clinical trial was conducted in 32 patients ages 3–25 years who had undergone allogeneic (16 patients) or autologous (16 patients) stem cell transplantation. Of the 30 evaluable patients, 15 were assigned placebo, and 15 were assigned TRAUMEEL S both as a mouth rinse, administered five times daily from 2 days after transplantation for a minimum of 14 days, or until at least 2 days after all signs of stomatitis were absent. Stomatitis scores were evaluated according to the World Health Organization grading system for mucositis.

RESULTS. A total of five patients (33%) in the TRAUMEEL S treatment group did not develop stomatitis compared with only one patient (7%) in the placebo group. Stomatitis worsened in only 7 patients (47%) in the TRAUMEEL S treatment group compared with 14 patients (93%) in the placebo group. The mean area under the curve stomatitis scores were 10.4 in the TRAUMEEL S treatment group and 24.3 in the placebo group. This difference was statistically significant ($P < 0.01$).

CONCLUSIONS. This study indicates that TRAUMEEL S may reduce significantly the severity and duration of chemotherapy-induced stomatitis in children undergoing bone marrow transplantation. ***Cancer* 2001;92:684–90.**

KEYWORDS: TRAUMEEL S®, stomatitis, mucositis, autologous, allogeneic, stem cell transplantation, bone marrow transplantation, randomized, placebo-controlled, homeopathy, complementary medicine.

Stomatitis occurs commonly as part of general inflammatory damage to the mucous membranes in patients receiving chemotherapy or radiation therapy to the oropharyngeal region. The overall incidence of reactive stomatitis is about 40%.[1,2] However, it is particularly common in patients receiving 5-fluorouracil (5-FU) treatment[1–4] and is even more common in those undergoing radiation therapy for malignancies of the head and neck, in which approximately 80% of patients are affected.[2] In patients undergoing bone marrow transplantation (BMT), the incidence of stomatitis reaches 95%.[1]

The mechanism of development of stomatitis is primarily cytotoxic,[1,5]

although neutropenia,[1,6] periodontal pathology,[1,7] poor oral hygiene,[1,8] poor nutritional status,[1] and infections also contribute to the condition. Morphologic characteristics can vary from slight erythema and edema of the oral mucosa to severe, focal, or widespread ulceration, bleeding and exudation.[1,5] In addition to pain and discomfort, loss of the mechanical barrier together with the large surface of necrotic mucosa and neutropenia can lead to secondary local infections, sepsis, and even life-threatening systemic infections.[1,6,9,10] Severe cases of stomatitis often necessitate the interruption of chemotherapy treatment or dose reduction and may affect patient compliance with further treatment.[1] Compared with other chemotherapy-related toxicities, such as myelosuppression, the incidence of mucositis and the significance of its toxicity is increasing. Consequently, oral mucositis is becoming the most common dose-limiting toxicity of chemotherapy.[1,2]

The current treatment of patients with stomatitis is essentially symptomatic. This includes stringent oral hygiene, avoiding irritating and abrasive foods, good oral and dental care, and the use of bland rinses, topical anesthetics, and systemic analgesics.[11] Such treatments, however, are of limited value and have shown improvement only in patients with mild to moderate stomatitis.[1,2,12]

TRAUMEEL S® is a homeopathic-complex remedy that has been sold over the counter in pharmacies in Germany, Austria, and Switzerland for over 50 years. It contains extracts from the following plants and minerals, all of them highly diluted (10^{-1}–10^{-9} of the stem solution): Arnica montana, Calendula officinalis, Achillea millefolium, Matricaria chamomilla, Symphytum officinale, Atropa belladonna, Aconitum napellus, Bellis perennis, Hypericum perforatum, chinacea angustifolia, Echinacea purpurea, Hamamelis virginica, Mercurius solubilis, and Hepar sulfuris. Information from the manufacturer indicates that TRAUMEEL S is used normally to treat trauma, inflammation, and degenerative processes.

Informal experience in patients with chemotherapy-related stomatitis suggests that the condition may respond to treatment with TRAUMEEL S homeopathic-complex remedy. Based on this and subsequent positive results from a preliminary open study in 20 patients with stomatitis who were treated with TRAUMEEL S compared with 7 untreated, randomly selected patients,[13] we decided to conduct the randomized, placebo-controlled, double-blind clinical trial reported here.

MATERIALS AND METHODS

Patients

Thirty-two consecutive patients who were admitted to Schneider Children's Medical Center, ages 3–25 years, suffering from malignant diseases and underwent BMT were enrolled. Patients had undergone allogeneic or autologous stem cell transplantation.[14] The study was approved by the ethical committee at the Rabin Medical Center, and informed, written consent was obtained from parents and/or guardians of all children prior to their enrolment in the study after a full explanation of the benefits, potential hazards, and procedures involved in the study to the patients and their parents and/or guardians.

Study Medication

For this study, both TRAUMEEL S and placebo were provided by the HEEL Company (Baden-Baden, Germany) in sterile, 2.2-mL ampoules. Solutions of TRAUMEEL S were prepared by diluting the active substance in saline, according to the German Homeopathic Pharmacopoeia (HAB). The placebo consisted only of saline. The active medication and placebo did not differ in color, taste, or odor.

TRAUMEEL S is manufactured according to the European Union Guidelines on Good Manufacturing Practice for Medicinal Products[15] and in accordance with the HAB. The physical and microbiologic controls of the medications were according to the European Pharmacopoeia specifications.

Extensive safety data from a large survey of TRAUMEEL S showed adverse events in only 0.0035% of patients, despite its use in over 3.5 million patients (manufacturer's own survey). Adverse effects reported were mostly skin reactions to the cream or local pruritus as a reaction to injection. However, because TRAUMEEL S contains dilutions of substances that may be regarded as toxic, we calculated the content of one of the most toxic substances, a mercury salt, in the medication. Assuming that a patient will have to be treated with TRAUMEEL S for 1 week, he or she will receive 35 ampoules. The mercury concentration of one ampoule is 0.5 ng/mL, giving a total amount of ingested mercury of approximately 17.5 ng per week. This compares favorably with the permitted mercury content of drinking water according to German law (0.001 mg/L).[16] Thus, a 1-week treatment of TRAUMEEL S contains approximately 10^{-3} of the amount of mercury deemed permissible in 1 L of drinking water.

Study Procedures

Thirty-two patients received various conditioning regimens for 5–8 days followed by autologous (16 patients) or allogeneic (16 patients) stem cell infusion on Day 0. Patients were randomized to receive either placebo or TRAUMEEL S on Day 2 of the study in addition to twice-daily mouth washes with chlorohexamide, oral amphoterin B, and gentle tooth brushing

TABLE 1
World Health Organization Grading System for Mucositis

Grade	Status
0	No change
1	Soreness/erythema (painless)
2	Erythema (painful), ulcers; can eat solids
3	Ulcers; requires liquid diet only
4	Alimentation not possible

(institutional standard for mouth care). Packages of TRAUMEEL S and placebo were prepared by the HEEL Company and were identified by serial number only. The code showing the treatment corresponding to each serial number was kept by the company, the study coordinator (M.O.), and the statistician (L.S.F.). The code was not broken until the completion of the trial. Treatment was started on Day 2 after stem cell transplantation, so that treatment began before the first symptoms of stomatitis (e.g., dryness and/or soreness of the mouth) were observed. The peak incidence of mucositis is typically 5–7 days after transplantation. Fifteen evaluable patients received placebo, and 15 evaluable patients received TRAUMEEL S. Patients were instructed to rinse their mouths vigorously with the solution for a minimum of 30 seconds before swallowing. In addition, patients were directed to keep the liquid as long as possible on particularly troublesome lesions in their mouth. This procedure was repeated five times daily.

The World Health Organization (WHO) grading system for mucositis (Table 1) was used to evaluate stomatitis in each patient.[17] In addition, a subjective scoring system was used in which either the patient or the parents were asked to judge the degree of oral pain and discomfort, dryness of mouth and tongue, dysphagia, and ability to swallow. A five-grade system was used (Grade 0, no complaints; Grade 4, very severe complaints, unable even to swallow liquids). The time to worsening of stomatitis was evaluated as the time from randomization to the day when the mucositis score increased from that recorded at baseline. Patients were evaluated at least once every 2 days. All evaluations were performed blind by the same observer (the study nurse). The trial continued until the patient symptomology had been scored as Grade 0 on 2 consecutive days or until a minimum of 14 days after the start of TRAUMEEL S or placebo treatment in patients in whom no symptoms developed.

The trial was carried out at the Bone Marrow Transplantation Unit, The Schneider Children's Medical Center of Israel, Rabin Medical Center, Petach Tikva, Israel. All study forms were collected, stored, and transferred to computer for analysis by the study coordinator (M.O.). Statistical analysis was performed at the Department of Mathematics, Statistics, and Computer Sciences, Bar-Ilan University, Ramat-Gan, Israel (L.S.F.). The randomization code was prepared by the manufacturer (HEEL Company) and was revealed only on completion of the study. Neither the manufacturer, the study coordinator, nor the statistician was involved in any aspect of the treatment of participating patients.

Statistical Analysis

All statistical analyses were done on an intent-to-treat basis unless indicated otherwise. That is, each patient was considered to be allocated randomly to a group regardless of the treatment actually received. The two main treatment comparisons, as specified in the protocol, were of the *area under the curve* (AUC) for stomatitis symptoms, and the *time to first worsening* of stomatitis symptoms. Both are based on the WHO grading system.

The AUC is equivalent to the sum of the grade on each day from the start of TRAUMEEL S or placebo treatment. It therefore incorporates both severity and duration of symptoms. When grades were recorded every other day, we used linear interpolation to estimate the stomatitis score on those days when evaluation did not occur. Because the AUC score distribution was not normal, statistical comparison was performed using the two-sample Wilcoxon rank-sum test.

Most patients (77%) started TRAUMEEL S or placebo treatment before the onset of symptoms. In these patients, therefore, the time to worsening of symptoms was the same as the time to the start of symptoms. Consequently, the time to worsening differed from time to first development of symptoms in only 23% of patients (17% with Grade 1 symptoms and 6% with Grade 2 symptoms). The statistical comparison of this endpoint was performed using the log-rank test. All P values reported are two-sided.

RESULTS

Patients

A total of 32 patients were enrolled in this trial. However, two patients (one in the TRAUMEEL S treatment group and the other in the placebo group) received a single dose of study drug but then refused further treatment, complaining of nausea. These patients were not evaluated subsequently for stomatitis and, thus, cannot be included in this analysis. Fifteen patients each remained in the TRAUMEEL S group and the placebo group. The distribution of patient characteristics for each group is shown in Table 2. The groups were comparable with regard to age, gender, type of BMT, granulocyte-colony stimulating factor

TABLE 2
Patient Characteristics

Characteristic	TRAUMEEL S®	Placebo
Patients (no.)	15	15
Age (yrs)		
Mean (SD)	10.1 (7.0)	9.7 (5.7)
Distribution		
3–4	3	5
5–9	6	3
10–14	2	3
15–19	3	3
20–25	1	1
Gender (no. of men) (%)	8 (53)	9 (60)
Diagnosis (%)		
AML	3 (20)	7 (47)
ALL	1 (7)	2 (13)
CML	1 (7)	1 (7)
Lymphoma	3 (20)	0 (0)
Other[a]	7 (47)	5 (33)
BMT (%)		
Allogeneic	8 (53)	7 (47)
Autologous	7 (47)	8 (53)
GCSF	4 (27)	4 (27)
GVHD prophylaxis (%)		
CSA only	1 (7)	2 (13)
CSA + methotrexate	3 (20)	4 (27)
CSA + steroids	3 (20)	1 (7)
None	8 (53)	8 (53)

AML: acute myelogenous leukemia; ALL: acute lymphoblastic leukemia; CML: chronic myelogenous leukemia; BMT: bone marrow transplantation; GCSF: granulocyte-colony stimulating factor; GVHD: graft versus host disease; CSA: cyclosporin A; SD: standard deviation.

[a] Other diagnoses in the TRAUMEEL S® group: one neuroblastoma, one aplastic anemia, one thalassemia, one Ewing sarcoma, and one medulloblastoma. Other diagnoses in the placebo group: one neuroblastoma, one Wilms tumor, two aplastic anemia, one thalassemia, one Ewing sarcoma, and one Fanconi syndrome.

TABLE 3
Stomatitis Area Under the Curve Scores and Time to First Worsening of Symptoms by Allocated Treatment

TRAUMEEL S®			Placebo		
Patient	AUC[a]	Time to worsening (days)[b]	Patient	AUC[a]	Time to worsening (days)[b]
1	9	> 8	2	27.5	4
3	0	> 18	4	16	4
6	4	> 9	5	16	2–3
7	20	4–5	8	36	1–2
9	11	3–5	10[c]	4	6–7
12[d]	38	20	11	56	4
13	0	> 13	14	14	2–3
15	0	> 13	16	20	2–3
17	0	> 5	18	31	10–11
19	17	5	20	21	3
22	0	> 10	21	0	> 6
23	17	4–7	24	26.5	5
25	3	> 8	26	45	4
28	5	7	27	35	10
30	26.5	2–3	29	16	4
Mean	10.4	6.9[e]	—	24.3	4.3[e]
Median	5.0	4.7[e]	—	21.0	4.0[e]

AUC: area under the curve.

[a] Test for difference in AUC: Wilcoxon rank sum score, 167.5; expected score, 232.5 ($P < 0.01$).

[b] Test for difference in time to worsening: chi-square test, 13.4 with 1 degree of freedom ($P < 0.001$).

[c] The patient received TRAUMEEL S® accidentally.

[d] There was doubt regarding the AUC score and time to worsening. An alternative interpretation would be AUC, 0; time > 19 days.

[e] Means and medians of uncensored times only are shown.

treatment and prophylaxis against graft versus host disease (GVHD). However, there were some differences in the distribution of diseases between the groups: There were seven patients versus three patients with acute myelogenous leukemia (AML) and zero patients versus three patients with lymphoma in the TRAUMEEL S and placebo groups, respectively. In addition, the three patients who underwent a higher risk BMT (haploidentical or cord blood) all were allocated randomly to the TRAUMEEL S treatment group. The use of concomitant medication, including analgesic treatment, was comparable in both treatment groups.

There was doubt regarding the stomatitis score of Patient 12 as a result of an administrative error. Our policy in areas of doubt was to take the value less favorable to the TRAUMEEL S treatment group. In this instance, the choice was between an AUC score of either 38 or 0, and we used the score of 38. In addition, one patient who was allocated to the placebo group inadvertently received TRAUMEEL S. However, this patient was still considered part of the placebo treatment group, and it is interesting to note that this patient had the second lowest stomatitis AUC score in the placebo treatment group. This patient was included in the analysis according to the intent-to-treat principle and to guard against any bias in the study. Exclusion of this patient from the analysis would have increased the difference between the treatment groups (in favor of TRAUMEEL S). In view of the double-blind design and the intention-to-treat analysis used, it seems unlikely that these irregularities would have substantially affected the results of the study.

Efficacy

The stomatitis AUC scores, together with the times to first worsening, are summarized in Table 3. Stomatitis AUC scores range from 0 to 56. Five patients (33%) allocated to the TRAUMEEL S group did not develop stomatitis (AUC score, 0) compared with 1 patient (7%) from the placebo group. The mean AUC scores were 10.4 in the TRAUMEEL S group and 24.3 in the placebo group. This difference was statistically signif-

icant (Wilcoxon rank-sum score, 167.5; expected score, 232.5; $P < 0.01$) and suggests that TRAUMEEL S treatment reduced the severity and/or duration of stomatitis compared with placebo.

In the group of 22 patients age < 15 years, the mean AUC score for stomatitis was 11.0 in the TRAUMEEL S group and 25.9 in the placebo group. The Wilcoxon rank-sum test for the difference remained statistically significant (Wilcoxon rank-sum score, 93.0; expected score, 126.5; $P < 0.01$). Thus, the difference remains only if younger patients are considered.

Seven patients (47%) in the TRAUMEEL S treatment group and 14 patients (93%) in the placebo group experienced worsening of symptoms during treatment. The log-rank test indicated that there was a statistically significant difference (chi-square test, 13.4 with 1 degree of freedom; $P < 0.001$) between the two groups in the time to worsening of symptoms. In those patients whose symptoms worsened, the median time to worsening was 4.7 days in the TRAUMEEL S group and 4.0 days in the placebo group. These results indicate that symptoms were much less likely to worsen in patients receiving TRAUMEEL S treatment than in those receiving placebo, but that, among those whose symptoms did worsen, there was little difference in the median time to worsening of stomatitis between the two treatment groups.

Subjective Symptom Score

The maximum symptom scores for dryness of mouth, oral pain, and eating difficulty over the first 7 days of TRAUMEEL S and placebo treatment are shown in Figure 1. These data were recorded at regular intervals over the 7-day treatment period. These results are very similar to the stomatitis AUC score results: Patients in the TRAUMEEL S group showed a clear reduction in severity of symptoms in all three categories, as indicated by changes in the symptom grading system, compared with the placebo group.

Safety and Tolerability

There was a high incidence of serious complications but with no significant difference between the groups, as expected in a group of patients undergoing BMT. GVHD occurred in three patients in the TRAUMEEL S group compared with six patients in the placebo group, sepsis occurred in three patients in the TRAUMEEL S group compared with eight patients in the placebo group, and gastrointestinal complications occurred in no patients in the TRAUMEEL S group compared with five patients in the placebo group. Four patients with venous-occlusive disease occurred in the TRAUMEEL S group compared with none in the placebo group, and pneumonitis occurred in four patients in the TRAUMEEL S group compared with none in the placebo group. Some patients developed more than one of these complications. There was no difference in the incidence or duration of severe neutropenia between the two treatment groups.

There was no significant difference in the number of deaths between the TRAUMEEL S and placebo groups in a follow-up of 44 weeks. Only one death occurred during the study period (to Day 20).

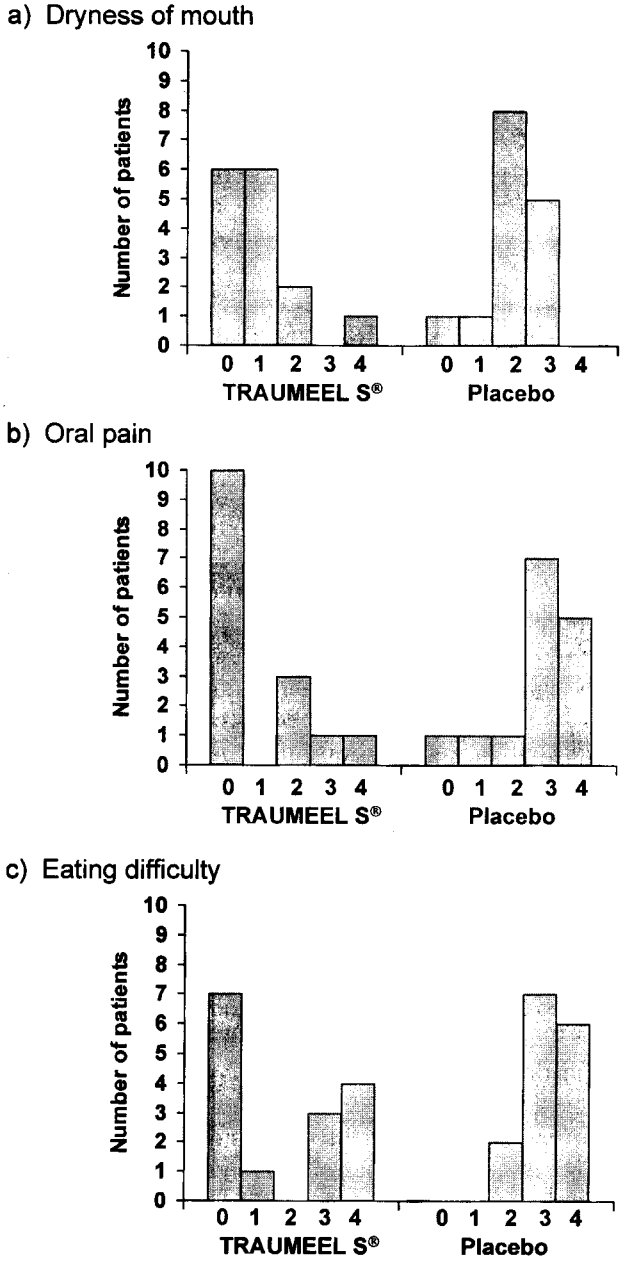

FIGURE 1. The maximum subjective score (0, no complaints; 4, very severe complaints/parenteral nutrition necessary) during the first 7 days of study treatment with TRAUMEEL S® (n = 15 patients) or placebo (n = 15 patients) for dryness of mouth (a), oral pain (b), and eating difficulty (c).

DISCUSSION

Currently available treatments for chemotherapy-induced stomatitis are of limited efficacy in preventing or ameliorating it. The effect of local treatment is short lived, and the medications often have an unpleasant taste. Moreover, the risk of absorption limits the frequency with which some of these drugs may be used in small children and in the elderly. For these reasons, the potential benefits of treatment with TRAUMEEL S are of particular interest.

This study demonstrated a statistically significant and clinically relevant difference in efficacy between TRAUMEEL S and placebo in the treatment of stomatitis in children undergoing stem cell transplantation. The strategy of analysis employed in this trial protects against any bias toward TRAUMEEL S. For example, a patient who developed stomatitis on the day that TRAUMEEL S was discontinued (Day 20) was classed as having stomatitis despite developing the condition after treatment was stopped. Patient 10, who accidentally received TRAUMEEL S instead of placebo, still was considered part of the placebo group and, in fact, had the second lowest stomatitis AUC score in this group. In addition, there was an excess of patients with lymphoma and a deficit of those with AML in the TRAUMEEL S group. Because it was observed that AML patients had, on average, slightly lower AUC scores compared with other patients in this trial (data not shown), any resulting bias would not benefit the TRAUMEEL S group. Finally, the three transplant patients who were at the highest risk were allocated randomly to the TRAUMEEL S group. These patients subsequently died, two of them within 3 months of BMT. This may account for the somewhat higher number of deaths among patients in the TRAUMEEL S group. Because the AUC scores for these three patients were 0, 17, and 38, there is no evidence that these higher risk transplantation patients had less severe stomatitis.

Initial observations of treatment with TRAUMEEL S suggest that it is almost free from adverse effects. In addition to the patients in this trial, TRAUMEEL S has been given to over 80 patients receiving chemotherapy on an outpatient basis at the Schneider Children's Medical Center. With the exception of one patient in the trial who stopped treatment on the first day and two other children who complained of nausea, no other acute adverse effects have been reported.

The mechanism of action of TRAUMEEL S remains unknown. It also is unclear whether only one of its components is biologically active or whether the effects are due to the action of several components. The marked effects seen in this study were achieved using a solution of TRAUMEEL S containing ingredients in very low concentrations. Some of the ingredients of TRAUMEEL S are regarded by homeopaths as remedies with anti-inflammatory properties (Belladonna, Aconitum, Mercurius, Hepar, and Chamomilla) or mucoprotective properties (Calendula and Hamamelis). Arnica is one of the main remedies used in homeopathic treatment of trauma. Arnica, Calendula, Hamamelis, and Milefolium are believed to have antihemorrhagic properties. Echinacea angustifolia and Echinacea purpurea are thought to be immunostimulatory. Hypericum has been used in patients with neural injury. This suggests that several components may play a role in the mechanism of action of TRAUMEEL S. Indeed, the observation that such a strong response is associated with such small quantities of the different remedies in TRAUMEEL S suggests that a synergistic effect may be involved. However, further research is needed to identify which component(s) are the active compound(s).

The effect of orally administered TRAUMEEL S seems to be isolated to the oral mucosa. Patients with mucositis of other areas of the alimentary tract, for example, esophagitis, enteritis, or proctitis as assessed by subjective complaint (diarrhea and rectal or esophageal pain), did not respond to the TRAUMEEL S administered orally in our trial. Furthermore, there was no difference between the two groups in the median number of days with severe neutropenia. This supports the hypothesis that the effect of this homeopathic drug is a local one.

The localized effect of TRAUMEEL S also is important for another reason, which has relevance to the general problem of complementary medicine in the treatment of patients with malignant disease. If complementary medical treatment in reality has no biologic effect, then at least it will do no harm. However, if it does have a biologic effect, and given our lack of understanding of the mechanisms of action of TRAUMEEL S and homeopathic medicine in general, concerns may be raised about deleterious systemic effects, for example, increasing the resistance of the malignant cells to chemotherapy. Because the effect of TRAUMEEL S appears to be only local, this concern becomes less relevant.

In conclusion, this double-blind, controlled study showed that TRAUMEEL S significantly reduces the severity and duration of chemotherapy-induced stomatitis in children undergoing BMT. TRAUMEEL S appears capable, at least in part, of ameliorating a problem that not only causes considerable suffering to patients but often limits the possibilities of aggressive treatment with chemotherapy. Because there are few effective, conventional treatments for patients with chemotherapy-induced stomatitis currently available, the significance of treatment with TRAUMEEL S be-

comes apparent. An effective treatment for stomatitis would allow more aggressive chemotherapy treatments, particularly in children, and, consequently, would be likely to improve the success rates of many chemotherapy programs. Our study population is small and includes patients with a variety of diagnoses who received several different forms of conditioning regimens. Confirmation of our results in a larger trial in patients receiving BMT or other intensive chemotherapy protocols is needed. Therefore, we are planning to extend our investigations to a large-scale, multicenter study to evaluate the efficacy and safety of TRAUMEEL S in the treatment of adults who are at risk for chemotherapy-induced stomatitis.

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