Stomatitis, by definition, is any form of inflammation or ulceration of the oral mucosa. The knowledge that chemotherapy often may prevent the physician from planning such treatment because chemoradiotherapy is both toxic and immunosuppressive. The pain and discomfort accompanying stomatitis can exacerbate the malnutrition due to anorexia or malabsorption. When irritation is compounded by a secondary infection, life-threatening sepsis may ensue.

INTRODUCTION

In general, the higher the mitotic index for malignant cells, the greater the effect of the cytotoxic agent. This applies not only to cancer cells but also to normal, rapidly-dividing cells, such as bone marrow cells and mucosal cells. Therefore, in malignant cells, chemotherapy damages the barrier formed by the mucosa. In patients receiving continuous infusions or in those with renal insufficiency, for example, methotrexate can cause severe mucositis. Fluorouracil causes stomatitis when given in high, aggressive doses or when administered via intra-arterial infusion. Other drugs which cause stomatitis include actinomycin D, bleomycin, cytarabine, doxorubicin, daunorubicin, and bleomycin. Stomatitis often develops following the administration of protocols containing TBI (total body irradiation), busulfan, VP16, or thiotepa (Table 1).

As can be expected, the myelosuppressive and stomatotoxic effects of many drugs are similar and overlap, and when combined, one drug may potentiate the side effects of the other. The greater damage from to the oral mucosa and the mucosa lining the alimentary canal is the loss of the mechanical barrier to the entry of bacteria. When combined with granulocytopenia, the absence of this barrier is an important causal factor for suppurative defense mechanisms and malnutrition. Besides causing discomfort, large particles of necrotic mucosa that are exposed to bacterial infection during a bout of granulocytopenia can serve as a reservoir for mucosal infection, thereby allowing bacteria and fungi to invade the body and multiply. For example, among patients who are hospitalized for treating acute leukemia or chronic leukemia in the last stage, 35% develop oral infections, with about half caused by Candida albicans, and 15% caused by the herpes simplex virus.

Additionally, 10% of patients with non-hematologic carcinoma and 10% of patients with hematologic malignancies develop stomatitis. The high rate of stomatitis among patients treated with antibiotics is due mainly to the suppression of the orally normal bacterial flora, allowing other pathogens to invade. Systemic fungal infection is one of the main causes of post-bone marrow transplantation morbidity and mortality. Immunosuppressed patients with fungal infections in the mouth or conjunctiva or both, develop systemic infections. Clearly, the risk for developing systemic infections and the accompanying mortality can be decreased by providing adequate nutrition, including foods rich in proteins, vitamins, and about 90% of children receiving antracancer chemotherapy suffer from nosebleeds. In children resulting from the especially intensive chemotherapy in this patient population. Bone marrow suppression alone can exacerbate such chronic oral problems as gingival disease, existing ulcers, and other problems.

CHEMOTHERAPEUTIC AGENTS COMMONLY ASSOCIATED WITH MUCOSITIS

Methotrexate

Fluorouracil

Actinomycin D

Doxorubicin (Adriamycin)

Bleomycin

Vinblastine

Frequent ulceration.

 FUNCTIONAL DRUGS AND THEIR MODE OF ACTION

Medical

MUCOSITOTOGENIC DRUGS

Stomatitis can appear in patients with bone marrow suppression before the bone marrow becomes severely suppressed. The first symptoms of mucositis (inflammation of all mucous membranes of the mouth) are expressed by stomatitis. The mucous membranes of the mouth are more sensitive than those of the intestine, possessing a much smaller surface area. Therefore, the mouth are more sensitive than those of the intestine, possessing a much smaller surface area. Therefore, the mouth are more sensitive than those of the intestine, possessing a much smaller surface area. Therefore, the mouth are more sensitive than those of the intestine, possessing a much smaller surface area. Therefore, the mouth are more sensitive than those of the intestine, possessing a much smaller surface area. Therefore, the mouth are more sensitive than those of the intestine, possessing a much smaller surface area. Therefore, the mouth are more sensitive than those of the intestine, possessing a much smaller surface area. Therefore, the mouth are more sensitive than those of the intestine, possessing a much smaller surface area. Therefore, the mouth are more sensitive than those of the intestine, possessing a much smaller surface area. Therefore, the mouth are more sensitive than those of the intestine, possessing a much smaller surface area. Therefore, the mouth are more sensitive than those of the intestine, possessing a much smaller surface area. Therefore, the mouth are more sensitive than those of the intestine, possessing a much smaller surface area. Therefore, the mouth are more sensitive than those of the intestine, possessing a much smaller surface area. Therefore, the mouth are more sensitive than those of the intestine, possessing a much smaller surface area. Therefore, the mouth are more sensitive than those of the intestine, possessing a much smaller surface area. Therefore, the mouth are more sensitive than those of the intestine, possessing a much smaller surface area.

The most common form of mucostatis is stomatitis, in which the patient complains of a burning sensation, which begins about a week after the beginning of the treatment and is followed by the appearance of ulcers that coalesce. The lesions in the oral cavity appear everywhere on the oral mucosa, including the tongue, gums, and lips. The ulcers cause constant pain that is exacerbated by eating, drinking, and swallowing. A cytological examination reveals epithelial hyperplasia, dropout, atrophy, and degeneration of the glandular structures. The Disease Staging of the World Health Organization (WHO) classification for stomatitis is as follows:

- Stage 0: no ulcers
- Stage 1: oral pain with no ulcers
- Stage 2: oral pain with ulcers but the ability to eat is retained
- Stage 3: liquid diet only
- Stage 4: inability to eat or to drink

The information gained from reading anecdotal reports on the efficacy of standard treatments provided the rationale to perform a randomized clinical trial to assess the ability of a complex homeopathic preparation, Traumeel®, for treating chemotherapy-induced stomatitis. Traumeel® Oral Liquid in Vials is a non-prescription drug developed in Germany, which has been sold for nearly a half-century in pharmacies in Germany, Austria, and Switzerland. Other dosage forms include oral drops, tablets, ointment, and ampules for injection. Traumeel® Oral Liquid in Vials contains the following ingredients in 100 ml of isotonic saline: Arnica 2X, Calendula 2X, Millefolium 3X, Chamomilla 3X, Symphytum 6X, Belladonna 2X a/a 0.1 ml, Asimilum 2X 5.00 ml, Bells perennis 2X 0.95 ml, Hypericum 2X 0.05 ml, Echinacea angustifolia 2X, Echinacea purpurea 2X a/a 0.05 ml, Hamamelis 1X 0.01, Mercurtius sol. 0X, 0.05 mg, and Hep esulpir, 6X 0.1 g. Trauma, inflammation, and degenerative processes are the main causes of mucositis.
LIMITED CLINICAL TRIAL WITH TRAUMEEL® IN CHEMOTHERAPY-INDUCED STOMATITIS

We studied 27 subjects between the ages of 6 and 18 years to evaluate the feasibility of using Traumeel® Oral Liquid in Vials for treating chemotherapy-induced stomatitis. Twenty patients received Traumeel® and seven children who did not receive Traumeel® were chosen at random for a prospective follow-up to compare the duration of symptoms in study participants to untreated patients. We assessed the distribution of ulcer severity in all participants according to WHO staging. The age distribution (Table 2), stages of disease (Table 3), and anatomic sites treated (Table 4) were similar in both groups. In the untreated group, however, opiate use was higher, although the difference was not statistically significant (see Table 5). All statistical analyses were carried out using BMDP Statistical Software.

In all treated children, each treatment was followed by an immediate decrease in pain, which continued for 30 minutes to 2 1/2 hours. In children with Stage 1-2 stomatitis, the pain reduction lasted between 24-72 hours until the stomatitis disappeared. Children that began with Stage 3-4 stomatitis required 6-8 days of treatment. In two children with GVHD (graft versus host disease)-associated stomatitis, the pain was significantly reduced for several hours, and then 24 hours later the children ceased to complain about pain. Nevertheless, the basic process that had caused the stomatitis in these two children continued, so the children continued to receive treatment 2-3 times per day for another 5-10 days. Only one participant, a patient with Stage 4 stomatitis, according to the WHO definition, was receiving morphine at the beginning of the trial. Immediately after the first dose of Traumeel®, the morphine dosage was reduced by half. No other participant required treatment with narcotics, and those with Stage 1-2 stomatitis at the beginning of the trial no longer required analgesic treatment.

Table 6 shows the product-limit survival analysis that we used to compare symptom duration. From this table it can be seen that the difference between the two groups is highly significant according to stringent statistical analysis. The median symptom duration in the treated group was 6 days, compared with 13 days in the untreated group.

CONCLUSION

We conducted this small preliminary study to gain a first impression about the effectiveness of Traumeel® Oral Liquid in Vials on mucositis. Obtaining positive results in such a study is a prerequisite to performing a large clinical trial according to strict scientific standards, although we did not conduct this study as a randomized, double-blind trial, and the number of participants was small, the results reported are still impressive. Even if we presume that part of the success was due to the placebo effect, which is known to be very small in a hyperacute system, such encouraging results led us to believe that Traumeel® Oral Liquid in Vials has genuine biological activity. In addition to its biological activity, the onset of action of Traumeel® was remarkable, with patients reporting a strong amelioration of pain within minutes. Some patients also reported a mood improvement. Such rapid action is unusual because the mucosa does not regenerate within minutes. Notably, the improvement persisted. Although the decreased use of opiates as analogues in the Traumeel®-treated group was not significant, we recognized a clear tendency toward such a decrease, so we speculate that the results of a study on a larger group of patients might show a difference in favor of the Traumeel®-treated group. The results of this limited, preliminary trial support the feasibility of performing a prospective, double-blind trial to assess whether positive results will be obtained under more stringent, scientific conditions, and whether Traumeel® treatment can reduce the duration of pain in stomatitis patients. Such a study is currently taking place in two medical centers in Israel.

REFERENCES


8. Euphorbium compositum S Nasal Spray (5% significance level, p = 0.016). Improvement was most evident within the sub...