Support Care Cancer (2000) 8:55–58
DOI 10.1007/s005209900076

ORIGINAL ARTICLE

N. Serdar Turhal
S. Erdal
S. Karacay

Efficacy of treatment to relieve mucositis-induced discomfort

Published online: 5 October 1999

N.S. Turhal, M.D. · S. Erdal, R.N.
S. Karacay, M.D.
Department of Medicine, Division of Oncology, Marmara University Hospital, Istanbul, Turkey

N.S. Turhal M.D. (✉)
Tophanelioglu Cd. 13/15, Altunizade, Üsküdar 81190, Istanbul, Turkey
e-mail: turhal@superonline.com
Tel.: +90-542-4312760
Fax: +90-216-3275181

Abstract To determine the efficacy of a mouthwash in relieving mucositis-induced discomfort in patients receiving chemotherapy, 31 (16 male, 15 female) with a mean age of 45 (range 16–80) were given an in-house three-drug (lidocaine, diphenhydramine and sodium bicarbonate in normal saline) mouthwash when they developed mucositis of any severity. The complications were assessed on the CALGB (Cancer and Leukemia Group B) scale. The response to the mouthwash was reported on a self-assessment scale. Patients' response data were analyzed with reference to: (1) relief throughout the duration of mucositis and (2) relief during the worst stage (for each episode) of mucositis. Five patients with fungal, viral or bacterial oral infection were excluded from study. Overall, 4 patients had grade I, 16 patients had grade II, 10 patients had grade III and 1 patient had grade IV mucositis. The average duration of mucositis was 7.9 days (range 3–23 days), and the mean duration of the worst stage of mucositis was 4.81 days (range 2–13 days). The mean mucositis severity score was 1.9 (range 1–4), and the average self-assessment (response) score was 0.81 (range 0–2). The mean mucositis score during the worst stage of mucositis was 2.25 (range 1–4), and the average self-assessment (response) score during the worst stage of mucositis was 0.91 (range 0–2.7). These results suggests that this three-drug mouthwash provides effective symptomatic relief in patients with chemotherapy-induced mucositis.

Key words Mucositis · Palliation · Chemotherapy

Introduction

Oral mucositis is a frequent and often severe complication following cytostatic chemotherapy and is assumed to be due primarily to cytotoxicity. The oral mucosa is comprised of membranes that have a high mitotic index, with rapid epithelial turnover and maturation rates. This causes the mucosa to be vulnerable to the adverse effects of chemotherapy. Chemotherapy alters the integrity of the mucosa, the microbial flora that normally inhabit the oral cavity, salivary quantity and composition, and the epithelial maturation. The mucosal damage might be the result of synergy between the irradiation and chemotherapy. Several schemes have been devised to score mucositis in cancer patients on the basis of the presence of signs, e.g. erythema, lesions, alone or together with symptoms, e.g. pain and difficulty in swallowing.

Various agents studied to date for prevention and treatment of mucositis

GM-CSF appears to be effective in recuperation once mucositis has occurred after chemotherapy or radiation [8, 19]. Both povidone iodine [1, 18] and oral glutamine

supplementation [2, 20] have given promising results in prevention and treatment of mucositis in some studies. Sucralfate trials, especially in radiation-induced mucositis, showed a trend toward improved symptom relief, but this was not statistically significant [13], and another trial for chemotherapy-induced mucositis failed to show any benefit [12]. Steroids have also been tried, especially in radiation-induced mucositis, and a recent trial found a trend favoring shorter treatment interruptions in the prednisone arm, but not a reduction in the intensity or duration of mucositis [11]. Also, trials of a chamomile mouthwash [7] and nonabsorbable antibiotic lozenges [16] failed to show any compelling evidence of benefit. One recent promising agent has been the use of mucosa-adhesive water-soluble polymer film containing topical anesthetics and antibiotics; initial studies confirmed this agent as useful to alleviate pain caused by acute radiation-induced oral mucositis, maintain good peroral feeding, and prevent secondary oral infections, without inducing adverse reactions [15]. On the other hand, immunoglobulin has recently been studied for both treatment and prevention of radiation-induced mucositis, but its role in this is also not yet clear [14]. Use of the low-energy helium–neon laser for prevention of oral mucositis is a new treatment modality for this old problem, but optimal laser treatment schedules still need to be defined [4].

Diphenhydramine HCl 12.5 mg/5 ml (Benadryl) is an antihistamine with anticholinergic and sedative properties. This agent is used in the mouthwash for its antihistaminic effect at the local injury site. Caution should be exercised in its use in elderly patients with respiratory tract disease, hyperthyroidism, hypertension, narrow-angle glaucoma, stenosing peptic ulcer disease, pyloroduodenal obstruction and symptomatic prostatic hypertrophy or bladder neck obstruction, because of its atropine-like action. The maximum dose in our patients would be 50 mg/day if they swallowed the mouthwash instead of spitting it out as they are instructed. Lidocaine HCl 2% (Aritmal ampule) is an amide-type local anesthetic and a parenteral antiarhythmic agent. This agent used in the mouthwash for its local anesthetic properties. Side effects include central nervous system irritation- or depression-related effects, hypotension and bradycardia, especially in patients with heart block. The maximum dose in our patients would be 50 mg/day if they swallowed the mouthwash instead of spitting it out. Sodium bicarbonate 8.4% molar ampule is an alkalotic agent. This agent is used in the mouthwash for its neutralizing effect on salivary acids. It is contraindicated in metabolic or respiratory alkalosis. At the doses used in the mouthwash no side effects were expected to occur.

The hypothesis underlying this trial was that combination of the local anesthetic lidocaine, sodium bicarbonate and diphenhydramine would provide good symptomatic relief in patients with chemotherapy-induced mucositis.

Patients and methods

Patients selected for study were receiving chemotherapy for various kinds of tumors and included patients with hematological malignancies receiving high-dose chemotherapy and stem cell rescue ($n=9$) and patients with solid tumors receiving chemotherapy ($n=22$). This mouthwash is not intended for prophylaxis or treatment of chemotherapy-induced mucositis, but only for the relief of symptoms until the natural course of healing occurs. During the study period (June to September 1998) all patients entered on study if they developed any degree of mucositis. Therefore, all patients with mucositis without a demonstrable cause after receiving chemotherapy were included in the trial, no selection criteria besides a reversible cause for mucositis other than the chemotherapy being used. The patients were appropriately worked up for reversible causes of mucositis and were excluded from the study if they had documented viral, bacterial or fungal infection of the oral mucosa. Patient characteristics are shown in Table 1. Mouthwash was prepared by adding 125 ml (100 mg) of diphenhydramine, 1 ampule of 2% (100 mg) lidocaine and 2 ampules of 8.4% sodium bicarbonate to 1000 ml of sterile saline. The mouthwash was kept at the bedside Örevauth1Örevdttm-969485263 at room temperature, and the patients are told to swish 20 ml round inside their mouths and spit it out every 2–3 h as needed. Inpatients were questioned daily by a nurse or physician to record scores. Outpatients were seen initially by a physician and then contacted every other day by the same physician to record their scores, and seen personally again by the same physician every time it was deemed appropriate or the symptoms were perceived to have progressed. Scores for mucositis, bleeding, WBCs, infection, taste, and metabolism scores are shown in Table 2, graded according to cancer and leukemia group B (CALGB)'s expanded common toxicity criteria. The CALGB assessment scale for stomatitis was the only scale used for mucositis assessment. Mucositis was graded as 0 none, 1 painless ulcers, erythema or mild soreness, 2 painful erythema, edema, or ulcers, but can eat, 3 painful erythema, edema, or ulcers, and cannot eat, 4 requires parenteral or en-

Table 1 Patient characteristics

Age (years)	45	16–80
Sex	Male	16
	Female	15
Diagnosis	Gastrointestinal malignancy	12
	Acute lymphoblastic leukemia	4
	Acute myeloid leukemia	3
	Chronic myeloid leukemia	2
	Non-Hodgkin lymphoma	2
	Melanoma	2
	Others	6
Treatment	Fluorouracil based	13
	5 days, bolus	11
	5 days, infusion	2
	Radiotherapy	4
	Alone	1
	With Adriamycin	1
	With cisplatin	1
	With docetaxel/Adriamycin	1
	Cyclophosphamide-based pre-BMT regimen	4
	Others	10

Table 2 Toxicity characteristics

Toxicity	0 (%)	1 (%)	2 (%)	3 (%)	4 (%)	Unknown
Bleeding	23 (74)	7 (22)	1 (3)	–	–	-
WBC	4 (12)	1 (3)	2 (6)	1 (3)	9 (29)	14 (45)
Infection	19 (61)	–	3 (9)	7 (22)	2 (6)	-
Taste	1 (3)	16 (51)	14 (45)			-
Metabolic score	21 (67)	3 (9)	6 (19)	1 (3)		-

Table 3 Mucositis characteristics

	Mean (SE)	Range
Average mucositis duration	7.9 (±0.85) days	3–23
Average mucositis severity	1.9 (±0.59)	1–3.27
Best self-score of all stages	0.32	0–1
Average self-score of all stages	0.81	0–2
Worst stage mucositis duration	4.81 (±0.41) days	2–13
Worst stage mucositis score	2.25	1–4
Best self-score at worst stage	0.58	0–2
Average self-score at worst stage	0.91 (±0.13)	0–2.7

teral support. Response to the treatment solution was graded by the patients themselves, assessed during the first hour after they washed their mouth with mouthwash, as: total relief of their symptoms (0), some improvement of symptoms (1), no difference (2), some worsening (3), significant worsening (4). The characteristics of mucositis are shown in Table 3. Bone marrow transplant (BMT) patients were collected for a historical control group, since they were the only patients for whom proper mucositis assessment data were recorded, but the data compiled for these patients' ages and the duration and severity of their mucositis were found to be statistically very different from those recorded in the study group and are therefore not presented in the paper.

Results

Thirty-six patients entered on this clinical study between January 1998 and November 1998. Five patients were excluded from the study because of fungal (2) and herpetic (3) causes of their mucositis. The 31 evaluable patients' average duration of mucositis episode was 7.9 days (range 3–23 days), and the average severity of mucositis during these episodes was 1.9 (range 1–4). The average duration of the worst-stage mucositis episode was 4.81 days (range 2–13) and the worst-stage mucositis severity during these episodes was 2.25 (range 1–4). As far as responses are concerned, the best self-score with mouthwash at any stage of mucositis was very high, at 0.32 (range 0–1). We then looked to see the best self-score during the worst stage of mucositis, and it was 0.58 (range 0–2), lower, as expected, than the best self-score at any stage of mucositis. The average self-score at any stage of mucositis was 0.81 (range 0–2), but a bias might have occurred if self-scoring was very variable during the worst stage of mucositis; to avoid that we calculated the average self-score during the worst stage of mucositis, and it was 0.91 (range 0–2.7). We concluded that average self-score during the worst stage of mucositis can reliably be used to assess patient response to this mouthwash. This score of 0.91 points to an average response somewhere between some improvement and total relief of mucositis symptoms.

Patients were further grouped into those with solid tumors ($n=22$) vs those with leukemias ($n=9$), and their response data were analyzed. Solid tumor patients were older. Their average duration of mucositis episodes was 7.9 vs 7.88 days ($P>0.05$), and their average duration of worst stage mucositis episodes were 5.1 vs 4.0 days ($P>0.05$; not statistically significant). Interestingly, average mucositis severity, 2.1 vs 1.3 ($P<0.001$), and the worst-stage mucositis severity during these episodes, 2.45 vs 1.77 ($P<0.05$), were worse for the solid tumor group. The explanation for these results could be that since leukemia patients were observed as inpatients their early-stage mucositis was detected sooner, and also they were observed and kept in the study longer during the healing phase. As far as responses were considered the best self-score at any stage of mucositis was significantly better for the solid tumor group, with 0.18 vs 0.66 ($P<0.01$), and the same also holds true for the best self-score during the worst stage of mucositis: 0.36 vs 1.11 ($P<0.01$). The average self-scores at any stage of mucositis were 0.53 vs 1.5 ($P<0.0001$), and average self-scores during the worst stage of mucositis were 0.6 vs 1.64 ($P<0.0001$). These subgroup analyses indicate the usefulness of this combination in the outpatient setting for solid tumor chemotherapy-induced mucositis but the small number of patients at each subset makes these conclusions weak.

Discussion

Mucositis is a common toxicity of cancer chemotherapy [5, 9, 22]. Antimetabolites, antitumor antibiotics, alkylating agents and various other agents besides radiation can damage the rapidly dividing cells of the oral mucosa, resulting in inflammation of the oral and intraoral soft tissue, which can progress to painful ulceration and infection [21]. This problem is particularly problematic if combined-modality therapy is used for treatment, for example in head and neck cancers. There is no known method of predicting precisely which patients will develop this condition, although some mouth awareness programs [10] and surveillance cultures have been studied [6], and there is as yet no consensus on assessment and management of this condition other than new and effective means of administering pain medications [3].

We studied this old concoction regimen because of its simplicity for preparation, widespread availability of ingredients, ease of administration and low cost. There is not a single recent phase III trial assessing the efficacy of this three-drug combination regimen in chemoradiotherapy-induced oral mucositis against other new and expensive promising agents. Effective scoring of mucositis is an old problem with few new solutions [17]. We attempted to test the feasibility and applicability of a combined scoring system for such a trial. It is obvious that assessing the effect of a drug in a disease like this has to use a lot of subjective data, but we believe that until we develop a way of measuring pain, the CALGB-supported evaluation method we used here is an adequately way of assessing patients. Phase III trials for randomization with other commercially available mouthwashes or promising study agents would be helpful to assess whether any regimen is superior to any other.

References

1. Adamietz IA, Rahn R, Böttcher HD, Schäfer V, Reimer K, Fleischer W (1998) Prophylaxis with povidone-iodine against induction of oral mucositis by radiochemotherapy. Support Care Cancer 6:373–377
2. Anderson PM, Schroder G, Skubitz KM (1998) Oral glutamine reduces the duration and severity of stomatitis after cytotoxic chemotherapy. Cancer 83:1433–1439
3. Coda BA, O'Sullivan B, Donaldson G, Bohl S, Chapman CR, Shen DD (1997) Comparative efficacy of patient-controlled administration of morphine, hydromorphone, or sufentanil for the treatment of oral mucositis pain following bone marrow transplantation. Pain 72:333–346
4. Cowen D, Tardieu C, Schubert M, Peterson D, Resbeut M, Faucher C, Franquin JC (1997) Low energy Helium-Neon laser in the prevention of oral mucositis in patients undergoing bone marrow transplant: results of a double blind randomized trial. Int J Radiat Oncol Biol Phys 38:697–703
5. Eisen D, Essell J, Broun ER (1997) Oral cavity complications of bone marrow transplantation. Semin Cutan Med Surg 16:265–272
6. Feld R (1997) The role of surveillance cultures in patients likely to develop chemotherapy-induced mucositis. Support Care Cancer 5:371–375
7. Fidler P, Loprinzi CL, O'Fallon JR, Leitch JM (1996) Prospective evaluation of a chamomile mouth wash for prevention of 5-FU-induced oral mucositis. Cancer 77:522–525
8. Ibrahim EM, al Mulhim FA (1997) Effect of granulocyte-macrophage colony-stimulating factor on chemotherapy-induced oral mucositis in non-neutropenic cancer patients. Med Oncol 14:47–51
9. Kennedy L, Diamond J (1997) Assessment and management of chemotherapy-induced mucositis in children. J Pediatr Oncol Nurs 14:164–174
10. Larson PJ, Miaskowski C, MacPhail L, Dodd MJ, Greenspan D, Dibble SL, Paul SM, Ignoffo R (1998) The PRO-SELF Mouth Aware program: an effective approach for reducing chemotherapy-induced mucositis. Cancer Nurs 21:263–268
11. Leborgne JH, Leborgne F, Zubizarreta E, Ortega B, Mezzera J (1998) Corticosteroids and radiation mucositis in head and neck cancer. A double-blind placebo-controlled randomized trial. Radiother Oncol 47:145–148
12. Loprinzi CL, Ghosh C, Camoriano J, Sloan J (1997) Phase III controlled evaluation to alleviate stomatitis in patients receiving fluorouracil based chemotherapy. J Clin Oncol 15:1235–1238
13. Meredith R, Salter M, Kim R, Spencer S, Weppelmann B, Rodu B, Smith J, Lee J (1997) Sucralfate for radiation mucositis: results of a double-blind randomized trial. Int J Radiat Oncol Biol Phys 37:275–279
14. Mose S, Adamietz IA, Saran F, Thilmann C, Heyd R, Knecht R, Böttcher HD (1997) Can prophylactic application of immunoglobulin decrease radiotherapy-induced oral mucositis? Am J Clin Oncol 20:407–411
15. Oguchi M, Shikama N, Sasaki S, Gomi K, Katsuyama Y, Ohta S, Hori M, Takei K, Arakawa K, Sone S (1998) Mucosa-adhesive water-soluble polymer film for treatment of acute radiation-induced oral mucositis. Int J Radiat Oncol Biol Phys 40:1033–1037
16. Okuno SH, Foote RL, Loprinzi CL, Gulavita S, Sloan JA, Earle J, Novotny PJ, Burk M, Frank AR (1997) A randomized trial of a nonabsorbable antibiotic lozenge given to alleviate radiation-induced mucositis. Cancer 79:2193–2199
17. Parulekar W, Mackenzie R, Bjarnason G, Jordan RC (1998) Scoring oral mucositis. Oral Oncol 34:63–71
18. Rahn R, Adamietz IA, Boettcher HD, Schaefer V, Reimer K, Fleischer W (1997) Povidone-iodine to prevent mucositis in patients during antineoplastic radiochemotherapy. Dermatology 195:57–61
19. Rosso M, Blasi G, Gherlone E, Rosso R (1997) Effect of granulocyte-macrophage colony-stimulating factor on prevention of mucositis in head and neck cancer patients treated with chemo-radiotherapy. J Chemother 9:382–385
20. Skubitz KM, Anderson PM (1996) Oral glutamine to prevent chemotherapy induced stomatitis: a pilot study. J Lab Clin Med 127:223–228
21. Sonis ST (1998) Mucositis as a biological process: a new hypothesis for the development of chemotherapy-induced stomatotoxicity. Oral Oncol 34:39–43
22. Symonds RP (1998) Treatment-induced mucositis: an old problem with new remedies. Br J Cancer 77:1689–1695