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REVERSIBLE NAIL LOSS AFTER CANCER CHEMOTHERAPY

Most anticancer drugs act by inhibiting cell division. Therefore, rapidly proliferating tissues such as bone marrow, gastrointestinal mucosa, and hair follicles are especially susceptible to the toxic effects of these drugs. Clinical nail symptoms may occur but are rare. We now report a patient with a curious episode of reversible nail loss after cytotoxic treatment.

In Mrs VA, aged 40 years, a left-sided breast cancer (T3N1M0) was diagnosed in January, 1985. She underwent simple mastectomy and received locoregional radiotherapy (50 Gy in 25 fractions). The patient was apparently well till September, 1988, when she presented with a local recurrence—a 3 × 4 cm mass in left outer upper quadrant—and a superclavicular lymph node metastasis. Fine-needle aspiration biopsy of the local mass confirmed recurrence of the disease. She received CMF (cyclophosphamide, methotrexate and 5-fluorouracil) (1). After 2 courses, the finger nails loosened from the nailbed and dropped off within a month. She also had marked alopecia. After the fourth course of CMF in January, 1989, her nails had regrown and they were now looking normal.

Comments. Symptoms and signs from the nails are uncommon manifestations of anticancer drug toxicity. Pigmentary changes (diffuse changes, pigmented bands or horizontal lines) are the most common. These may be seen after doxorubicin, cyclophosphamide, methotrexate, bleomycin, etc. (2). One of the authors has previously described two patients of non-Hodgkin's lymphoma with reversible nail loss after chemotherapy (3). Received drugs common to these two patients were cyclophosphamide, vincristine and prednisolone. Also the now reported patient had received cyclophosphamide, in addition to methotrexate and 5-fluorouracil. This suggests that cyclophosphamide might be mainly responsible for the observed reversible nail loss.

Key words: Cancer, breast, chemotherapy.

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May 1989

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A PROSPECTIVE PILOT STUDY ON THE EFFECT OF SUCRALFATE MOUTH-SWISHING IN REDUCING STOMATITIS DURING RADIOTHERAPY OF THE ORAL CAVITY

Radiotherapy in sufficient dose involving the oral cavity always causes stomatitis, the severity of which is dependent on primary diagnosis, age, oral status and whether concomitant chemotherapy is given or not (1).

The patients complain of oral discomfort, changes in taste, dry mouth, burning sensation and pain. Erythema and, if more pronounced, fibrinous exudation is seen. The radiation reaction may be complicated by local and systemic infections, especially in leukopenic patients (2).

Radiation stomatitis usually appears at a dose level above 20 to 25 Gy, when therapy is given with a daily dose of 2 Gy. After completing radiotherapy the stomatitis as a rule resolves in 2 to 3 weeks (1). Current treatment is ineffective and stomatitis may aggravate pre-existing malnutrition (1). Therefore, efforts are needed to reduce the severity of stomatitis or, if possible, to prevent it.

Sucralfate is a non-absorbable, basic aluminum salt of a sulfated disaccharide which has proven effective in the treatment and prevention of gastric and duodenal ulcers. Sucralfate forms polyvalent bridges to the positively charged proteins present in the mucosa and forms a pasta-like, adhesive substance (3–5), a protective barrier is thus formed against further mucosal damage. The binding of sucralfate is most effective at low pH but may still occur at higher pH (3, 5). In a former study, using sucralfate labeled with $^{99}Tc^{m}$, we found that 20–30% of the initially attached sucralfate remained bound to the oral mucosa $2\frac{1}{2}$ h after the swishing procedure (6).

Moreover, sucralfate has a cytoprotective effect probably mediated through prostaglandin release from the mucosa (7). The result is an increase in mucosal blood-flow, mucus production, mitotic activity and surface migration of cells (5, 8).

A few pilot studies (9, 10) and one randomized trial (6) indicate that patients treated with stomatotoxic chemotherapy may benefit from oral sucralfate suspension. Other pilot studies indicate that sucralfate may be helpful in reducing or preventing the radiation induced toxicity of the mucosal lining in the lower intestinal tract (11, 12).

Thus, mouth-swishing with a sucralfate suspension might be of value in stomatitis induced by radiotherapy.

The aim of the present pilot study was to assess whether mouth-swishing with sucralfate suspension might reduce oral radiation mucositis without disturbing side effects.

Material and methods. Patients receiving radiation therapy encompassing the oral cavity were considered for the study. Patients were not included if permanent systemic treatment with anti-inflammatory drugs was given. Mouth-swishing with the sucralfate suspension was started at the point of time when the patients complained of oral discomfort during radiotherapy, and when objective signs of mucositis were present. Written informed consent was provided by each patient. The trial was approved by the local Ethical Committee.

Table

Patient	Age	Sex	Site of cancer	Former CT	Radiation dose at start of sucralfate (Gy)	Total radiation dose (Gy)	Subjective change in symptoms
1	66	M	Nasal cavity		48	60	Decrease
2	66	F	Mouth	Cis, 5-Fu	10	60	Decrease
3	61	F	Larynx	Cis, 5-Fu	12	58	Decrease
4	27	F	Hodgkin	COPP	16	37	Decrease
5	51	F	Tonsilla	Cis, 5-Fu	38	62	NC
6	71	F	Larynx		22	62	Decrease
7	49	M	Pharynx	Cis, 5-Fe	21	55	NC
8	33	M	Melanoma		36	40	NC
9	77	F	Sinus	Cis, 5-Fu	30	60	NC
10	74	M	Skin		56	62	Decrease
11	37	M	Melanoma		16	58	Decrease
12	64	M	Mouth	Cis, 5-Fu	20	48	NC
13	64	F	Mouth	Cis, 5-Fu	14	56	Decrease
14	66	M	Pharynx		18	60	Decrease

CT = Cytotoxic therapy. Cis, 5-Fu = Cisplatin day 1, and 5-fluorouracil as 5 day continuous infusion. COPP = Cyclofosfamide, vincristine, procarbazine, prednisolone.

A single score covering erythema, edema, erosion, and ulceration was created to record the findings at inspection of the mouth. The score ranged from 0 to 12. Erythema covered the range from 1 to 3, edema 4 to 6, and erosion 7 to 9. The maximum scores, 10 to 12, were recorded for ulceration.

Each patient was instructed to swish for at least 2 min and then either spit out or swallow 15 ml (1 g) of sucralfate suspension 4 times a day, i.e. after the main meals and at bedtime.

Objective and subjective signs were recorded before start of radiotherapy and once weekly during irradiation. Assessment of food intake was made by asking the patients whether mouth complaints interfered with food intake. Patients with score 0 had no complaints. Patients with score 1 to 3 had complaints but were some days able to consume normal food (score 1), soft food (score 2) or liquids (score 3). Patients with score 4 experienced at least one day with no food or liquid consumption at all. Assessment of oral discomfort was made using a 100 mm visual analog scale (VAS) (13, 14) and patients' judgement of oral discomfort compared. After radiotherapy the patients were asked whether mouth-swishing with sucralfate did change the subjective symptoms. All registrations were terminated concomitantly with the irradiation.

Between March 1987 and January 1988, 16 consecutive patients (9 male and 7 female) were considered for the study. Excluded from the study were two patients, one who never developed oral discomfort and one who stopped the treatment with sucralfate because the swishing procedure aggravated the radiotherapy induced nausea.

The remaining 14 evaluable patients (Table) had a median age of 64 years (range 27 to 77 years). All patients swished the mouth at least three times a day. The primary diagnoses were head and neck carcinoma in 10 patients, malignant melanoma in 2, Hodgkin's disease in 1, and basal cell carcinoma in 1 patient. Eight patients had prior treatment with chemotherapy, which was stopped at least 3 weeks before start of radiotherapy. In all cases the oral cavity was irradiated with 4 MV photon beams. The target dose was 2 Gy a day 5 days a week, except in one patient who received 37 Gy in 21 fractions for Hodgkin's disease. The total dose ranged from 37 Gy to 62 Gy (median 59 Gy). Mouth-swishing was started after a median time of 2 weeks (range 1 to 5 weeks) and at a median dose of 20 Gy (range 10 to 56 Gy).

The change in objective signs and subjective complaints during the week before compared to the change during the week after sucralfate swishing started was tested using the Wilcoxon's matched-pairs signed-rank test. Two-sided p-values less than 0.05 was considered to be statistically significant.

Results. Fig. 1 shows the objective score, subjective score, and oral discomfort before and during treatment with sucralfate. Mouth-swishing with sucralfate was started at a time when objective signs of stomatitis was minimal but present. A steep rise in symptoms and signs was seen before the start of mouth-swishing (time '0'). After initiation of sucralfate treatment no further increase in objective signs and subjective complaints was seen for the next 3 to 4 weeks despite continuation of radiotherapy. This holds for the objective scale, the subjective score as well as the VAS-scale. When comparing the change in objective signs ($p = 0.05$) and change in assessment of food intake ($p = 0.02$) during the week before and after the time '0', one hardly significant and one significant difference were found. Difference in VAS did not reach significant difference ($p = 0.2$).

Nine patients experienced subjective relief of the oral complaints during sucralfate-swishing, whereas no patient indicated aggravation due to the treatment ($p = 0.004$). Five patients found that sucralfate did not influence the symptoms.

Patient No. 13 had severe aggravation of stomatitis after an initial relief lasting almost 5 weeks and stopped medication. Patient No. 14 had a pause of one week at the end of treatment but continued therapy with sucralfate. Except for these two patients everyone had their treatment as planned.

One patient had obstipation during treatment but continued treatment due to subjective relief of the stomatitis. No other side effects were observed.

Discussion. The present study constitutes the first report dealing with a possible effectiveness of sucralfate mouth suspension for the treatment of radiation induced oral mucositis.

In a randomized study of the efficacy of sucralfate in the prevention of chemotherapy induced stomatitis we found that aggravation of nausea was a major problem (6). Seven out of 40 patients did not complete the treatment with sucralfate since the swishing procedure aggravated the chemotherapy related nausea. However, in the present study only one patient felt that

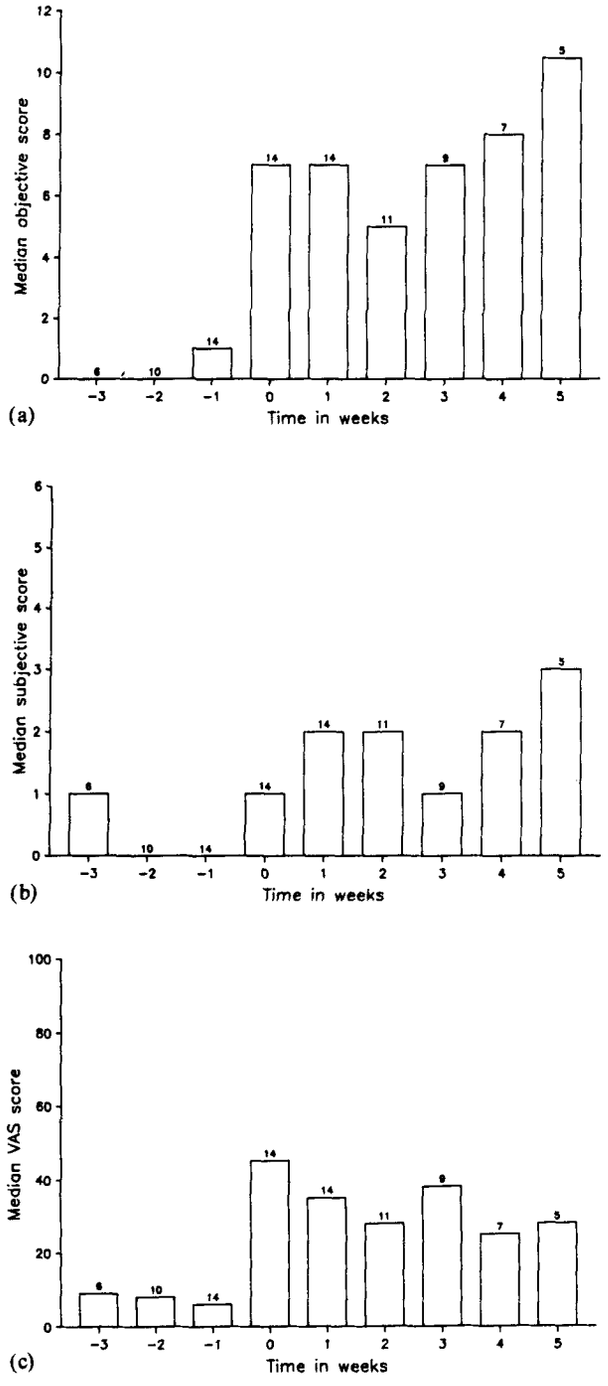

Fig. 1. Sucralfate treatment during radiation of the oral mucosal lining. Median scores prior to and after starting mouth-swishing. a) Median objective score. b) Median subjective evaluation of food intake. c) Median subjective complaints (VAS-scale). Initiation of mouth-swishing is indicated on the curves as time '0'. (The figure above bars indicates the number of patients.)

mouth-swishing with sucralfate aggravated radiotherapy induced nausea.

The present study suggests a positive effect of sucralfate on oral mucositis during radiotherapy. Whether local treatment with sucralfate actually did influence the natural course of the mucositis is difficult to say. In a randomized study (14) all patients reported increasing oral discomfort throughout radiation therapy, reaching its maximum at the end of treatment. However, it is a clinical observation that subjective symptoms of radiation stomatitis often spontaneously pass a maximum during ongoing treatment and that subjective symptoms diminish during continued radiotherapy. Regression towards the mean could also explain some of the reduction in objective score after treatment was initiated.

In conclusion, the present open study suggests that oral sucralfate suspension is a useful agent in preventing or relieving radiation induced oral mucositis. Randomized double-blind trials are needed to confirm these preliminary results.

Key words: Radiotherapy, stomatitis, sucralfate treatment.

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May 1989

ACKNOWLEDGEMENT

We thank Durascan, Odense, Denmark for placing the Sucralfate suspensions at our disposal.

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