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Oral Cooling (Cryotherapy), an Effective Treatment for the Prevention of 5-Fluorouracil-induced Stomatitis

Stefano Cascinu, Anna Fedeli, Stefano Luzi Fedeli, and Giuseppina Catalano

Recently, a randomised study demonstrated the utility of oral cooling (cryotherapy) in the prevention of 5-fluorouracil (5FU)-induced stomatitis. In order to verify these results a confirmatory study, using identical treatment regimen, was initiated. 84 patients treated with a 5-FU-containing regimen were randomised to a control arm or to receive oral cryotherapy. End point evaluation was obtained by a global assessment of the physician's judgement and patients' description of mucositis severity graded 0–4. Mucositis was significantly reduced by cryotherapy considering both the first cycle of therapy (the mean toxicity score for cryotherapy was 0.59 and it was 1.1 for the control group, $P \leqslant 0.05$) and all the chemotherapeutic courses (the mean toxicity score for cryotherapy was 0.36 when it was 0.69 for the control group, $P \leqslant 0.05$). In conclusion, the present study confirms that cryotherapy can decrease 5FU-induced stomatitis and should be recommended for patients receiving bolus 5FU-containing regimens.

Keywords: 5FU-induced stomatitis, oral cryotherapy
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INTRODUCTION

ORAL MUCOSITIS is a prominent feature of 5-fluorouracil (5FU) toxicity. It is frequently painful and can interfere with nutrition and quality of life [1, 2]. An effective prophylactic measure for decreasing the incidence of this distressing toxicity can significantly enhance patient comfort and compliance with therapy.

Despite the promising results from two small uncontrolled trials of an allopurinol mouthwash, a randomised placebo-controlled trial was unable to demonstrate any protective effect [3–5].

Recently, oral cooling was proposed to prevent 5FU-induced mucositis. It should cause local vasoconstriction and, thus, temporarily lead to reduced oral mucosal blood flow. On account of the short plasma half-life of 5FU, a reduction in the blood flow to the oral mucosa during the administration of a bolus injection of this drug could reduce the amount of 5FU delivered to these cells and result in less stomatitis. A randomised study on the prevention of 5FU-induced stomatitis showed the efficacy of oral cryotherapy [6]. These results prompted us to verify the activity of cryotherapy in the prevention of 5FU-induced mucositis in a confirmatory study using the identical treatment regimen as described by Mahood *et al.* [6].

Correspondence to S. Cascinu.
The authors are at the Servizio di Oncologia, Ospedali Riuniti, P.le Cinelli 4, 61100 Pesaro, Italy.
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Table 1. Mucositis grading

Grade	Degree of toxicity
0	No toxicity
1	Painless ulcers, erythema or mild soreness
2	Painful erythema, oedema or ulcers but can eat
3	Painful erythema, oedema or ulcers and cannot eat
4	Requires parenteral or enteral support

PATIENTS AND METHODS

Patients eligible for the study had to receive their first ever course of chemotherapy with a 5FU-containing regimen. Prior to therapy, patients were stratified by age, chemotherapeutic regimen and whether or not they had dentures. They were then randomised to a control arm or to receive cryotherapy. The cross-over to the alternative protocol arm was not allowed. The control arm consisted of no intervention at the time of 5FU administration. Cryotherapy consisted of patients placing ice chips in their mouths 5 min prior to each dose of 5FU. Patients were instructed to continuously swish the ice around their oral cavities and to replenish the ice chips before the previous ice had completely melted, for a total of 30 min. Patients were asked to remove dentures if present. End point evaluation was obtained by a global assessment of the physician's judgement and patients' description of mucositis severity, graded 0–4 as reported in the Mahood's study (Table 1) [6]. Patients were checked every week and the final

Table 2. Patients' characteristics

	Cryotherapy ($n=44$)	Control ($n=40$)
Sex		
Male	30	28
Female	14	12
Age, years		
Median	60	58
Range	(38–73)	(44–72)
Performance status*		
0	22	20
1	14	14
2	8	6
Primary tumour		
Colon-rectum	36	30
Pancreas	2	3
Stomach	5	6
Prostate	1	1
Chemotherapy		
5FU (370 mg/m^2)+ LV/IFN (every 3 weeks)	6	5
5FU (500 mg/m^2)+ LV/IFN (weekly)	7	5
5FU (370 mg/m^2)+LV	26	24
5FU (500 mg/m^2)+ LV/VP16	5	6

*Eastern Oncology Cooperative Group. LV = leucovorin; IFN = interferon; VP16 = Vepesid.

judgement on mucositis grade was performed on the day of the next chemotherapy course.

The primary outcome variable in this study was the intensity of mucositis registered in each group and expressed by a score, that sum up the degree and the number of patients who complained of this side-effect. This scoring method was chosen on the basis of previous studies and because, in the clinical evaluation of a toxic effect induced by therapy, we consider it important not only to record the number of patients who experience the side-effect but also the degree of severity. The scoring method can help to summate both of these aspects.

A Wilcoxon–Mann Whitney test and a χ^2 test with Yates correction were used to assess the difference in mucositis scores and in incidence, respectively, between the two groups [7].

Informed consent was obtained from all participants after the nature of the study has been fully explained.

RESULTS

84 patients were entered onto this clinical trial, all of whom were eligible. Patients' characteristics are summarised in Table 2.

In the first cycle the mean toxicity score for cryotherapy was 0.59 and 1.1 for the control group ($P \leqslant 0.05$) (Table 3). Accounting for all the chemotherapeutic courses the mean toxicity score for cryotherapy was 0.36 and 0.69 for the control group ($P \leqslant 0.05$) (Table 4). Even considering the overall incidence of stomatitis in the two groups, a difference was present, although not statistically significant. It occurred in the 50% of patients in the control group versus 30% of the treated patients in the first cycle of chemotherapy ($P=0.14$) while, accounting for all the cycles, it was present in 30% of the control group and in 20% of the treated patients ($P=0.06$). The number of days of mucositis was 70 for cryotherapy and 95 for the control patients.

Table 3. Results (initial cycle only)

Mucositis grade	Cryotherapy ($n=44$)	Control ($n=40$)
0	30	20
1	6	6
2	4	4
3	4	10
4	0	0
Mean score	0.59	1.1 $P \leqslant 0.05$

Table 4. Results (all the cycles)

Mucositis grade	Cryotherapy ($n=154$)	Control ($n=140$)
0	122	97
1	13	10
2	13	13
3	6	19
4	0	1
Mean score	0.36	0.69 $P \leqslant 0.05$

Table 5. Mean mucositis grade during the first cycle of chemotherapy according to smoking history and cryotherapy treatment

	Cryotherapy	Control
Non-smoker	0.2 ($n=28$)	0.44 ($n=24$)
Smoker	0.5 ($n=16$)	0.63 ($n=16$)

The incidence of other side-effects (diarrhoea, vomiting and leukopenia) was virtually identical in both arms.

Of interest, we failed to confirm the protective effect of smoking, as shown in Table 5.

The cryotherapy was well tolerated by most patients. 2 patients only noted an "ice cream" headache which caused them to refuse this technique after the second and third cycle of chemotherapy, respectively.

DISCUSSION

Up to the report of Mahood *et al.*, on the prevention of 5FU-induced mucositis by mouth cooling with ice chips, this side-effect continued to be a prominent clinical problem with no adequately documented preventive therapy [6]. Nevertheless, the lack of a double-blind study, as a consequence of the modality of this technique, with the possibility of investigator biases, as well as the absence of other studies convinced us that further trials were necessary before considering cryotherapy as routinary prophylactic treatment for 5FU-induced stomatitis.

On this basis a confirmatory study using the identical treatment regimen as described by Mahood, was initiated in our institution. Our trial was different from Mahood's study in two points: the cross-over design and the 5FU chemotherapeutic treatment. Unlike the previous study, we did not cross over to the alternative protocol arm. This allowed us to evaluate the overall protection from mucositis in subsequent courses and not only in the first cycle of chemotherapy. 5FU toxicity is unpredictable in different courses even in the same patient. In our opinion the evaluation of the activity in several chemotherapeutic courses result in a better definition of protection from 5FU-mucositis. Furthermore, cross-over studies can determine some problems in the interpretation of the results as already suggested by the Biometric and Epidemiologic Advisory Committee of the Food and Drug Administration [8].

The other difference is that our patients received different bolus 5FU-containing regimens, whereas in the Mahood's study patients received 5FU and low dose leucovorin combination only.

Despite these differences, the results derived from the present trial confirmed data obtained in Mahood's study, demonstrating that cryotherapy can reduce significantly the severity of mucositis (Tables 3, 4).

On the contrary, we did not find a statistical difference in the overall incidence of mucositis episodes between the two groups, considering both the first cycle only ($P=0.14$) or all the chemotherapeutic courses ($P=0.06$). This could be due to the small number of patients or even to the fact that cryotherapy is effective in reducing the severity rather than the overall incidence of mucositis. In our opinion, a different analysis of our results can contribute to demonstrating this hypothesis. In fact, a significant difference ($P=0.01$) in incidence between the two arms was found comparing the patients with absence of mucositis and grade 1 (asymptomatic patients) versus patients with higher degrees of mucositis.

It is of interest also that the efficacy of cryotherapy was irrespective of the 5FU-containing regimen. Cryotherapy determined also a reduction of the number of days where patients complained of stomatitis (95 versus 70 days).

The relationship between smoking habit and incidence of mucositis seems to be a more debated question. Our data in fact, did not show a lower incidence of mucositis in the patients who smoked (Table 5) as reported by Mahood *et al.* [6]. However, the number of patients is probably too small in both studies to identify subsets for prognostic factors and a greater number should be considered before a correct assessment can be made of this aspect.

In conclusion, because this treatment is simple, inexpensive, well tolerated and the activity has been substantially confirmed we think that it should be recommended for patients receiving a bolus 5FU-containing regimen, who are at risk of developing 5FU-induced mucositis.

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