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Studies on supportive care in oral mucositis: random or randomised?

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During the last decades, measures on supportive care are considered standard in everyday oncology practice. Supportive care measures not only prevent or ameliorate complications of antitumour therapy and thereby increase the patients' quality of life, they also make antitumour therapy in sufficient doses possible. Due to large-scaled clinical trials, the treatment of chemotherapy- and radiotherapy-induced nausea and vomiting has become evidence-based in current practice. The development of guidelines on the use of haematopoetic growth factors in chemotherapy-induced leucopenia and anaemia was also based on clinical trials. For the prevention and treatment of oral mucositis, however, scarcely any evidence exists. A recent review by the Cochrane Collaboration could identify just one measure, the application of ice chips, with some evidence that it could prevent chemotherapy-induced oral mucositis [1]. Nevertheless, the impact of mucositis in clinical practice is great. Approximately 40% of adult patients treated with standard cytotoxic chemotherapy develop oral mucositis. The incidence is higher in children, in patients with advanced cancer of the head and neck treated with concurrent chemotherapy and radiotherapy and in patients treated with high-dose chemotherapy and blood or bone marrow transplantation. A recent study in 92 blood and marrow transplant patients from eight study centres in the United States, Canada and Europe demonstrated that the extent and severity of oral mucositis was significantly correlated with the number of days injectable narcotics, total parenteral nutrition (TPN), and injectable antibiotics were given; and with the risk of significant infection; the number of hospital days; hospital charges; and even mortality. Total hospital charges were almost $43 000 higher among patients with ulceration in contrast to those without [2].

This issue of the *European Journal of Cancer* includes four reports on clinical studies in oral mucositis (Table 1). Because scientific evidence on the prevention and treatment of mucositis induced by antitumour therapy is scarce, these studies are important, although they all include a limited number of patients. The four studies evaluate different interventions for the prevention and treatment of oral mucositis. The study by Cheng and colleagues evaluates a protocol on oral hygiene as a preventive measure in children with haematological malignancies or solid tumours [3]. Two studies, one performed by Hejna and colleagues and the other performed by Sprinzl and colleagues, were set up to evaluate the effect of topical administration of granulocyte-macrophage-colony stimulating factor (GM-CSF) in the treatment of oral mucositis induced by 5-fluorouracil (5-FU)-based chemotherapy and combined chemoradiotherapy, respectively [4,5]. The fourth study, by Awidi and colleagues, evaluates the effect of pilocarpine in the prevention of chemotherapy-induced oralmucositis [6]. The four studies used different instruments for the measurement of the degree of mucositis.

1. Assessment scales

A 'gold standard' for the assessment of the severity of mucositis is not yet available. This absence of a standardised assessment scale which would permit clinical evaluation and allow for a direct comparison of various treatment or prevention approaches has been an impediment to research in this area. Most available diagnostic tools are toxicity scales that emphasise the functional disability, but neglect its anatomical characteristics [7]. These instruments rely on subjective

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Table 1
Summary of studies in mucositis reported in this issue of the *EJC*

	Cheng	Hejna	Sprinzl	Awidi
Study intervention	Oral hygiene	GM-CSF mouthwash	GM-CSF mouthwash	Pilocarpine
Prevention/cure	Prevention	Cure	Cure	Prevention
Patient population	Children	Adults 5 FU-chemotherapy	Adults chemoradiotherapy	Adults various chemotherapy
n	42	31	35	38
Single/multi-centre	Single	Single	Single	Single
Randomisation	−	+		
Open	+	+ open	+ open	+ double-blind, cross-over
Open	+ double-blind, cross-over	+ open	+ open	
Blind assessment	−	−	?	+
Calculation study sample	−	−	−	−
Assessment scales	Eiler's Oral Assessment Guide, Faces Scale	Mucositis±CTC	WHO Pain-VAS	Donnelly WHO
Oral hygiene standard	Object of study	−	+	−

GM-CSF, granulocyte macrophage-colony stimulating factor; 5-FU, 5-fluorouracil; CTC, common toxicity criteria; WHO, World Health Organization; VAS, visual analogue scale.

interpretation with possibly great intra- and interobserver variability. Studies on mucositis, therefore, need a sufficient number of patients to detect possible differences between treatments as measured with subjective rating scales. Before the start of a study, the number of patients needed to detect a defined benefit has to be calculated for the intra- and interobserver variability. However, in none of the four currently published trials on mucositis has the size of the study been planned initially. As mentioned above, the four studies all used different assessment instruments. Before progress in the field of mucositis can be reached, agreement on the standardised assessment scales and sufficiently powered (multicentre) studies are necessary. Furthermore, with the use of subjective rating scales, the evaluation of the severity of mucositis should be performed blindly. To develop an objective, reliable and internationally accepted scale for the measurement of the extent of oral mucositis, a team of oral medicine specialists, oncologists and oncology nurses from the United States, Canada and Europe convened in 1996 (Ciba-Oncogene Consensus Conference). They set up the Oral Mucositis Assessment Scale (OMAS) [8]. OMAS evaluates multiple regions of the oral cavity for erythema (none, mild/moderate, severe) and the presence and size of ulcerations or pseudomembranes (none, <1 cm^2, 1–3 cm^2). The scale may be of value for future clinical trials.

2. Oral hygiene

Oral care protocols have long been propagated for the prevention of chemotherapy-induced oral mucositis, especially in the nursing literature [9]. As Cheng and colleagues state, randomised clinical trials on programmes for oral care are difficult to perform, because patients in a control and an experimental group will interact and exchange information when they are treated at the same time. Moreover, they are cared for by the same nursing staff. Therefore, most studies on programmes for oral care were descriptive or they used a trend analysis over a specified time period in which such a programme was introduced. Furthermore, studies were performed in adult patients only. The study of Cheng and colleagues was aimed at improving the scientific evidence on the traditional idea of oral hygiene. The prospective study was carefully designed in a paediatric patient population, although the number of patients needed to detect a predefined difference in outcome variables, had not been calculated before the start. The incidence and severity of mucositis was significantly reduced in children who were taught the oral care protocol compared with a group of children who were prospectively followed just before the introduction of the study programme. After a follow-up period of 21 days the pain scores in the two groups of patients still differed. The study strengthens the idea of oral hygiene as an important preventive measure for chemotherapy-induced oral mucositis.

However, the choice of the measures included in protocols on oral hygiene is still a matter of debate. Cheng and colleagues included a 0.2% chlorhexidine mouth rinse after waking up and before bedtime. Two earlier, randomised, placebo-controlled, multicentre studies failed to demonstrate an effect of 0.12% chlorhexidine mouthwashes in the prevention and the treatment of chemotherapy-induced oral mucositis [10,11]. All the patients who were studied in these two trials also followed an oral hygiene programme, as did the experimental group of patients in the study of Cheng and colleagues. The oral hygiene programmes included brushing the teeth. This intervention has indeed been demonstrated to be feasible and to diminish the severity

of mucositis [12]. Further research on the different measures which have to be included in programmes on oral hygiene is necessary before standard advice can be given. Considering the low cost of oral hygiene and the fact that a programme on oral hygiene promotes the responsibility of the individual patient, the development of a scientifically proven set of measures on oral hygiene seems paramount for future studies. In future studies, protocols on oral hygiene should be included as a standard preventive measure above which newer and, mostly, much more expensive preventive or therapeutic measures should be tested.

3. GM-CSF mouthwashes

The use of GM-CSF in the treatment of mucositis is pathophysiologically interesting, as laboratory studies have shown that both granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage colony-stimulating factor (GM-CSF) influence the migration and proliferation of human endothelial cells and keratinocytes [13]. It was found that non-myeloid tissue can respond to GM-CSF or express GM-CSF receptors [14]. For these reasons, it is speculated that both growth factors act as regulatory signals outside the haemopoietic system and have a direct stimulatory effect on the growth or regeneration of the oral mucosa.

A possible beneficial effect of GM-CSF on the regeneration of the oral mucosa seemed to be supported by two controlled trials on GM-CSF. A significant reduction in both grade 3 and 4 mucositis was seen in patients with haematological malignancies treated with myeloablative chemotherapy randomised to be supported by systemically administered GM-CSF compared with the placebo group [15]. A cross-over study in 20 patients with advanced head and neck cancer treated with combination chemotherapy showed a reduced incidence of oral mucositis in the cycles supported by GM-CSF subcutaneously (s.c.) compared with those without support [16]. As the incidence and severity of neutropenia was the same in the cycles with or without support of GM-CSF, the reduction of oral mucositis did not appear to be related to the granulocyte-stimulatory action of the growth factor. However, a recent study of sucralphate mouth washings with or without s.c. GM-CSF in the prevention of radiation-induced mucositis in 40 patients with head and neck cancer showed no reduction of mucositis in the patients treated with GM-CSF [17]. Moreover, the toxicities in the sucralphate plus GM-CSF group consisted of skin reactions at the GM-CSF injection site (65%), fever (30%), bone pain (25%), and nausea (15%), whereas the toxicity of sucralphate given alone was nil.

Because of these toxicities of systemically administered GM-CSF, trials were developed with local application of GM-CSF as mouthwashes. A study in 45 patients with breast cancer during the first cycle of a combination chemotherapy regimen showed no effect from treatment with GM-CSF mouthwash compared with placebo [18]. The mouthwashes were administered four times daily starting within 24 h of chemotherapy and were continued until the end of the cycle. The dose-finding character of the study brought along the use of different concentrations of the GM-CSF mouthwash (0.01, 0.1, 1.0 or 10 μg/ml). Very recently, the results were published of a study with locally applied GM-CSF, 300 μg, in a 2% methylcellulose gel daily versus a 2% methylcellulose gel alone performed in 36 patients undergoing a stem cell transplantation [19]. No beneficial effect of GM-CSF was found on the incidence, severity and duration of oral mucositis. In both studies, the GM-CSF mouthwashes were well tolerated without any oral discomfort or systemic side-effects.

The two studies reported in this journal on GM-CSF mouthwashes for the treatment of chemo- or chemoradiotherapy-induced mucositis demonstrate conflicting results. In the study of Hejna and colleagues, therapy with GM-CSF mouthwashes, given in a concentration of 400 μg/250 ml thrice daily, resulted in a significantly faster resolution of mucositis than therapy with povidone-iodine mouthwashes combined with amphotericin B. In the study of Sprinzl and colleagues, no significant difference in the severity of mucositis was found between patients treated with GM-CSF mouthwashes, 400 μg/250 ml once daily and patients treated with mouthwashes of hydrocortisone and pantocain. All patients in the last study were also instructed to maintain strict oral hygiene. The choice of the GM-CSF dose is not explained in either study and this is regrettable, because there is no information available concerning the optimal dose. Furthermore, as already stated above, a proper calculation on the number of patients needed to detect a specified difference in effect between the GM-CSF mouthwash and the 'conventional' treatment was not reported for either study. Both studies were stopped prematurely: the study of Hejna and colleagues because of a highly significantly shorter duration of symptoms in the patients treated with GM-CSF mouthwashes and the study of Sprinzl and colleagues because no superiority in effect of GM-CSF could be found. However, it is generally accepted that interim analyses have to be planned before the start of the study. Premature termination is only allowed when differences with adjusted, predefined P values are found. Therefore, conclusions on the possible effectiveness of GM-CSF mouthwashes for the treatment of mucositis are not yet possible due to major methodological flaws in the two studies. In the study of Hejna and colleagues, discrepancies related to age, performance status at the beginning of treatment,

oral hygiene, consumption of cigarettes and ingestion of alcohol between the two treatment arms make conclusions even more difficult. These differences in patient characteristics between the two arms may well explain the differences in the results between the two arms. The consumption of cigarettes and the ingestion of alcohol has not been proven to exert an impact upon chemotherapy-induced oral mucositis [20], but in combination with poor oral hygiene this may be influential [21].

4. Pilocarpine

The use of oral pilocarpine to prevent chemotherapy-induced oral mucositis has not been studied before. Pilocarpine is a parasympathetic stimulant of exocrine secretion. It produces clinically significant benefits in the management of radiation-induced xerostomia [22,23]. The drug was also found to be effective in the reduction of xerostomia in patients with advanced cancer [24]. With a dose of 5 mg three times daily adverse effects are usually mild and limited to increased sweating.

In this issue, Awidi and colleagues report on a double-blind placebo-controlled cross-over study on pilocarpine for the prevention of chemotherapy-induced oral mucositis. They do not give a hypothesis on the pathophysiological mechanism of effect. The dose regimen chosen is similar to that used for the management of xerostomia. The study was performed in a heterogenous patient population with respect to the underlying malignancies and the chemotherapy regimens used. The authors do not report on mean individual mucositis scores, but on total scores for courses in which patients were treated with placebo and pilocarpine, respectively. According to the total scores, mucositis must have been mild in most patients. This study also did not make a calculation on the number of patients needed to detect a clinically significant effect of pilocarpine. Therefore, several shortcomings can be demonstrated in the design of the study. Nevertheless, if the preventive effect of pilocarpine can be proven in a new and adequately powered study, this would offer a simple preventive measure with major clinical implications. Up till now, new strategies in the prevention of chemotherapy-induced mucositis may be tested for feasibility in small clinical studies. Larger studies have to be planned for definite conclusions to be drawn.

5. Conclusion

In conclusion, progress is being made in the field of antitumour therapy-induced oral mucositis. Sufficiently powered clinical trials on the prevention and treatment of mucositis are awaited. Internationally accepted assessment scales for measuring the severity and impact of mucositis are of paramount importance for these studies. Protocols on oral hygiene should be the standard intervention in addition to which special therapies will be developed. Up till now, however, oral hygiene is not yet standardised, as scientific evidence on the different measures included in protocols on oral hygiene is lacking.

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