Gelclair: managing the symptoms of oral mucositis

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Oral mucositis is a common side-effect of oncology therapies and other diseases. This article gives an overview of the issues associated with oral mucositis, and an outline of a new product, Gelclair, that may address some of these issues.

Oral mucositis, ulceration and inflammation are common complications in patients receiving radiotherapy or chemotherapy, and human immunodeficiency virus (HIV) patients, and they are also primary symptoms of Behçet's disease.

The term 'oral mucositis' is often used interchangeably with 'stomatitis'. Technical differences between the two definitions may include aetiology (chemotherapy *vs* ionizing radiation) or the presence of infection. In this article inflammation and ulceration of the oral mucosa is referred to as oral mucositis.

Reviewing oral mucositis in oncology, Dr Douglas Peterson (1999) wrote:

> **'The data highlight the clinical importance that this lesion exerts relative to infections risk, quality of life and cost of care. Oral mucositis has a direct impact on duration of disease, remission, cure rates and long-term survival.'**

This impact may be exerted in part because oral mucositis can result in the need for dose reduction, or occasionally cessation, of chemotherapy or radiotherapy. This could potentially reduce the effectiveness of the chosen therapy (Pico et al, 1998). As oncology therapies are advancing, and other side-effects such as neutropenia from chemotherapy are being addressed more successfully, oral mucositis is emerging as a major non-haematological toxicity that limits therapy (Karthaus et al, 1999).

Oral mucositis must therefore be considered not only as a distressing and painful condition for the patient, but also as a side-effect to be managed carefully.

> **'Oral mucositis has a direct impact on duration of disease, remission, cure rates and long-term survival' (Peterson, 1999).**

WHAT IS MUCOSITIS?

Oral mucositis usually starts with erythema of the oral mucosa. This develops into discrete pseudomembraneous lesions which then become confluent. Finally, the mucosa becomes deeply ulcerated and necrotic. Nearly all radiotherapy episodes involving irradiation of the oral cavity result in oral mucositis (Ohrn et al, 2001), approximately 30–40% of standard dose chemotherapy episodes (Sonis et al, 1978) and up to 75% of high-dose chemotherapy episodes (McGuire et al, 1993; Woo et al, 1993). The pattern is more predictable in patients receiving radiotherapy than in those receiving chemotherapy, where mucositis may be more intermittent and unpredictable.

Mucositis is also associated with infection. The impaired mucosal barrier may become colonized by abnormal bacterial flora (Karthaus et al, 1999), particularly in patients with reduced immune responses.

As well as causing patients discomfort and distress, extreme pain while eating or drinking can lead to dehydration and malnutrition. Many patients will need enteral nutrition and intravenous fluids, and patients with the most severe mucositis (often high-dose chemotherapy) may need total parenteral nutrition. Difficulty in speaking and interrupted sleep also spoil patients' quality of life.

The need for help with nutrition and hydration often leads to decisions to reduce, delay or stop therapy. According to the National Institutes of Health in the United States, a 'significant number' of patients develop mucositis of such severity that their medical management is changed (National Institutes of Health Consensus Development Conference, 1990). Dose limitation because of oral mucositis can lead to a worse than predicted outcome of cancer therapy.

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MEASUREMENT OF ORAL MUCOSITIS

Most oral mucositis scales combine gradings of signs and symptoms. In common use are the Radiotherapy Oncology Group (RTOG) and World Health Organisation (WHO) gradings, and a new system has been introduced by the US Mucositis Study Group (Sonis et al, 1999).

However, a total score may not be as useful as the separate signs and symptoms of the patient's mucositis in judging their impact on the cancer therapy plan. Patients with identical levels of ulceration may differ in their ability to tolerate eating and drinking: one may need to reduce the chemotherapeutic dose, while the other may not.

CHEMOTHERAPY-INDUCED MUCOSITIS

Cytotoxic agents targeting tumours may also hit other high-turnover cells such as the oral epithelium, so that oral mucositis is a significant toxic effect of many chemotherapeutic regimens. It occurs in about 40% of all standard-dose chemotherapy (Sonis et al, 1978; Carl, 1995; Mueller et al, 1995), and its incidence increases further, to more than 50%, with higher doses.

Some chemotherapeutic agents carry a higher risk than others. Methotrexate, 5-fluorouracil, doxorubicin, bleomycin and the taxanes lead to high rates of mucositis, which is therefore particularly associated with the treatment of leukaemia, lymphoma and colorectal cancer. Patients receiving stem cell transplantation as part of dose-intensified treatment are at high risk, with about 75% developing oral mucositis (Stiff, 2001).

Mucositis usually starts about 5 days after chemotherapy is first given. It may last for about 5–10 days after the treatment has finished, and longer if the oral mucosa is infected. Symptoms often appear a few days before patients develop neutropenia, and can resolve before the neutrophils recover (Karthaus et al, 1999).

RADIOTHERAPY-INDUCED ORAL MUCOSITIS

Ionizing radiation to the head and neck is one cause of damage to the oral mucosa. When the treatment field includes the oral mucosa, the patient will almost certainly experience oral mucositis (National Institutes of Health Consensus Development Conference, 1990). Patients receiving concomitant chemotherapy are likely to experience symptoms to a more severe degree (Pico et al, 1998).

Symptoms start after 1–2 weeks of radiation, and continue for 1–3 weeks after the last dose if there are no complicating factors. In a similar sequence to chemotherapy-induced mucositis, the first symptom is erythema of the oral mucosa, which develops into ulceration that may become infected.

Patients with tumours in the oral cavity who are receiving radiotherapy to the head and neck region have often already had oral surgery. These and indeed all head and neck patients need scrupulous attention to oral hygiene during and after therapy.

CLINICAL AND ECONOMIC BURDEN OF ORAL MUCOSITIS

Oral mucositis significantly increased the burden of care in several reported studies. One study showed that patients with standard-dose chemotherapy-induced mucositis were hospitalized for 3–6 days longer per cycle of therapy (Manzullo et al, 1998) than patients without mucositis (who often do not need admission). Another study (Sonis et al, 2001) found that in patients having high-dose chemotherapy, a 1-point increase in grade of mucositis was associated with:

- 1 additional day of fever
- a 2.1-fold risk of additional infection
- 2.7 days of additional total parenteral nutrition
- 2.6 days of injectable narcotic therapy
- 2.6 more days in hospital.

Most economic analyses have been performed in the USA. They have shown various levels of added costs from oral mucositis:

- Mean hospital charges US$42 749 higher for patients with evidence of oral ulceration than for those without it (Sonis et al, 2001)
- One higher grade of mucositis cost an average of US$25 405 (Sonis et al, 2001)
- The average cost of a grade 1 or 2 oral mucositis episode was US$913 (Bonomi et al, 1999)
- The average cost of a grade 3 or 4 oral mucositis was US$4543.

UK analyses have shown the costs associated with enteral and parenteral nutrition:

- Insertion of nasogastric tube estimated at £36–59 in materials plus time, plus several pounds a day for nutritional costs (Cummin et al, 2000)
- Insertion of percutaneous gastrostomy tube approximately £41 in materials plus time. Trusts may charge up to £582 for this service on a day-patient basis or up to £1295 on an inpatient basis (Cummin et al, 2000). Nutritional costs are extra
- Total parenteral nutrition is estimated to cost between £23 000 and £44 288 (Bissett et al,

1992; Richards and Irving, 1996) at home or up to £93 000 as an inpatient. This is only likely to affect high-dose chemotherapy patients.

Although these data are from studies with varying countries and criteria, which makes it difficult to generalize from their results, it is evident that oral mucositis is an expensive complication to manage.

CURRENT MEASURES

Increasingly in the UK, multidisciplinary teams are involved in oral care of cancer patients. They may include a dentist, dental hygienist, dietician or one of the growing number of oral medicine specialists.

All patients should be advised in advance that oral hygiene is particularly important before and during their cancer therapy, and they should practise using dental floss, regular toothbrushing and use of saltwater mouth rinses where possible.

Although various therapies are available, none have been shown to be uniformly effective (Jansman et al, 2001) although many have positive data.

Of the various mouth rinses, benzydamine, an anti-inflammatory mouthwash, is often given. There are data to support its use in the management of oral mucositis (Prada and Chiesa, 1987); however, its high alcohol content makes it painful to apply and can compromise compliance (Samanarayake et al, 1988). Additionally, other antibacterial or antiseptic mouthwashes are often used to control oral hygiene. Patients receive co-codamol, co-proxamol and often morphine to control the pain.

A NEW AND DIFFERENT APPROACH TO MANAGING MUCOSITIS?

Gelclair (Sinclair Pharmaceuticals, Godalming, UK) is a new concentrated oral gel for managing the painful symptoms of mucositis. It is a viscous gel containing the barrier-forming ingredients PVP (polyvinylpyrrolidone) and sodium hyaluronate. When Gelclair is used as an oral solution, these ingredients adhere to the mucosa to form a protective barrier.

Gelclair reduces the pain and discomfort in oral mucositis by preventing overstimulation of exposed and sensitized nerve endings within the mucosa. This can also allow patients to eat and drink more easily. It also has the potential to protect the oral mucosa from further painful damage as a result of mechanical stimulation.

Gelclair is used by diluting a sachet of gel with a small amount of water. The resulting solution is rinsed and gargled (where possible) within the mouth so that the protective barrier can reach the oropharyngeal mucosa.

GELCLAIR CONCENTRATED ORAL GEL

Gelclair may offer the following benefits for patients:

- As its action is exerted via a barrier and it is not pharmacologically active, it offers pain relief almost immediately
- The protective barrier formed by Gelclair enabled patients to eat and drink more easily in a clinical study (M Innocenti, G Moscatelli, S Lopez, unpublished data, 2001), and several more studies are under way. This benefit improves quality of life and may reduce the need for parenteral feeding and intravenous hydration
- Polypharmacy complications are minimized as the gel does not act pharmacologically
- As the gel does not contain alcohol, there is little or no stinging on application
- As it is presented as a concentrated gel, it may be diluted for use as an oral solution with most patients, but other more seriously affected patients may apply it undiluted with a syringe or sponge
- Gelclair is classified as a medical device, as its mode of action is through barrier formation. This means that Gelclair does not need to be given on prescription; it can be easily dispensed on an outpatient basis by the hospital pharmacy, or stocked by a hospice or GP surgery.

SUPPORTING DATA

Medium-sized studies have investigated the effect of Gelclair and others are continuing. One studied the effect of Gelclair on the quality of life of 30 patients with mucositis and other oral lesions of different causes (M Innocenti, G Moscatelli, S Lopez, unpublished data, 2001). Of these 21 had mucositis of the oropharynx and the remainder had painful oral lesions of other types, e.g. pain after oral surgery and diffuse aphthous ulcers. All subjects reported a substantial reduction in painful symptoms in the first 5–7 hours after starting Gelclair. On a numerical scale of 0–10 (where 0=no pain and 10=most pain), the mean pain value before administration was 8 and after Gelclair use was 1. This reduction in pain score was statistically significant ($P<0.005$).

The investigators also measured the effect of Gelclair on patients' pain and discomfort when eating and drinking over a 7–10-day period. The improvement in pain scores over this medium-term was also significant ($P<0.005$).

More UK trials are in progress to determine whether or not Gelclair may affect progression of mucositis, or the need to limit chemotherapeutic doses because of the problems caused by mucositis.

PROVEN AND POTENTIAL BENEFITS OF GELCLAIR

Gelclair may improve the quality of life of patients with this distressing and painful condition. By improving eating and drinking patterns and pain levels, the dose-limiting aspect of mucositis may be reduced. The protective barrier may also protect the oral mucosa from further damage resulting from mechanical stimulation such as speaking and chewing. These hypotheses are currently under investigation in UK trials. While awaiting these results, Gelclair offers simple relief for the painful symptoms of mucositis and helps to restore more normal eating and drinking patterns. HM

Conflict of interest: Dr Tom Smith was asked to write this article by Sinclair Pharmaceuticals.

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KEY POINTS

- Oral mucositis is a painful condition that is a common side-effect of chemotherapy, or radiotherapy to the head and neck.
- Patients with oral mucositis may find eating and drinking too painful, and will often need nutritional support.
- Oral mucositis is an expensive complication to manage.
- Various treatments are traditionally given to manage oral mucositis, but there is no 'gold-standard' therapy.
- Gelclair, a new concentrated oral gel, may provide an interesting new way of managing the pain associated with oral mucositis, and it may help patients to eat and drink more easily.