

# Management of Oral Mucositis in Oncology

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## Introduction

Oral mucositis (OM) is caused by the direct toxic effect of chemotherapy and radiation therapy on the oral epithelium, which in turn may lead to injury and disruption of the oral mucosal barrier in cancer patients.<sup>1</sup> Factors contributing to disruption of the oral barrier and the onset of OM include the type of agents used, use of oral preventive measures

and the individual patient's response.<sup>1,2</sup>

OM is a debilitating condition in cancer patients which may result in the delay of subsequent chemotherapy and radiotherapy treatment cycles. It may also negatively impact patient quality of life and has implications for recovery and ultimately survival.<sup>3</sup> The total cost for

hospitalisation has been reported to be US\$43,000 more in OM patients with ulceration compared to those without OM due to increased length of hospital stay and cost of analgesic agents.<sup>3</sup>

OM is a major cause of severe pain and debilitating symptoms such as ulceration and also infection. Sources of infection include pre-existing periodontal disease, which may progress following cancer treatment.<sup>3</sup> The pain and ulceration associated with OM often has a knock-on effect on the patient's ability to swallow and eat, which in turn may affect their recovery time.<sup>4</sup> The pain of OM also disrupts sleep patterns and affects the patient's mood. In a recent survey of 24 patients who



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had developed OM, it was evident that the physical symptoms have a negative impact on physical well-being and patient quality of life.<sup>5</sup> The patients, who were being treated for a range of cancers (including breast, lung, colorectal and head and neck) experienced severe pain (rated 6-10 [10=most severe pain]) due to ulceration, which disrupted their sleep patterns and ability to eat.<sup>5</sup> They also commented that they had difficulties swallowing and were obliged to restrict their diet to particular foods. This survey also highlighted that OM symptoms may often lead to shame and embarrassment even in front of their family.<sup>5</sup> The patients in the survey often did not associate the onset of OM symptoms with their cancer treatment<sup>5</sup> and this underlines the need to counsel all patients about OM prior to initiation of chemotherapy or radiotherapy and to give advice on preventive measures.<sup>6</sup>

Current management options for OM place an emphasis on the prevention of oral disease with the aim of reducing intraoral bacterial counts and prevent superinfection of mucosal ulcers.<sup>6</sup> A number of studies have evaluated different agents or strategies to prevent or treat OM associated with high-dose chemotherapy and also radiotherapy.<sup>6,7</sup>

Caphosol® (EUSA Pharma, Oxford, United Kingdom) which is a super saturated calcium phosphate rinse has been shown to be effective and safe in both the prevention and treatment of OM symptoms in patients receiving cancer treatment.<sup>6,8,9,10,11</sup> In a prospective, randomised study of 95 patients undergoing hematopoietic stem cell transplantation (following a range of conditioning regimens) Caphosol (+ fluoride rinsing) significantly reduced the duration and severity of OM symptoms compared to the group who received a standard regimen of fluoride rinsing alone.<sup>6</sup> Patients in the Caphosol group experienced OM pain for a mean of 2.86 days ( $\pm 0.61$ ) compared to a mean of 7.67 days ( $\pm 0.82$ ) in the control group ( $P < 0.0001$ ).<sup>6</sup> Patients in the Caphosol group also required significantly less morphine compared to the patients who received the standard prevention regimen alone.<sup>6</sup>

In a study in a similar group of 23 patients (compared to a

historical control group) use of Caphosol administered four times daily (from the day before the start of chemotherapy) was associated with significant reduction in the incidence of OM, duration of OM symptoms and duration of analgesic treatment ( $P < 0.001$ ).<sup>11</sup> Patients in the Caphosol group required concomitant antibiotic treatment for between 0 and 7 days compared to between 7 and 20 days in the control group ( $P = 0.02$ ).<sup>11</sup>

Caphosol has also been shown to improve patient quality of life and reduce the cost of treatment in a range of cancer patients.<sup>8,9,10</sup> In an open-label registry analysis of 218 patients receiving chemo- and/or radiation therapy Caphosol was used between 4-10 times daily to prevent OM symptoms in high-risk patients.<sup>8,9</sup> In this analysis only 2% of the patients experienced Grade 4 (severe) OM symptoms and in 49% of patients OM symptoms were reported as  $\leq$  Grade 1 (mild).<sup>8</sup> Importantly only 7% of patients experienced interruption of their cancer treatment.<sup>9</sup> The majority of patients (79%) in this study were either 'satisfied' or 'very satisfied' with Caphosol treatment.<sup>8</sup>

In a study of 21 patients who received Caphosol from the initiation of intensity modulated radiation therapy (IMRT) for head and neck cancer were retrospectively matched with a group of patients receiving other supportive regimens.<sup>10</sup> A smaller proportion of the Caphosol treated patients experienced severe OM (Grade 3-4) compared to the control group (38% vs 71% respectively).<sup>10</sup> The reduction in severe OM was accompanied by a decreased need for PEG tube placement (33% vs 57%) and hospitalisation (0% vs 19%).<sup>10</sup> Per patient OM related costs for the Caphosol-treated patients were reduced by US\$1,700 based on one cost model and US\$6,900 for a second cost model.<sup>10</sup>

This article focuses on the practical aspects of OM management with Caphosol across a range of cancer types and at different stages of disease. The emphasis of the article is on those factors that may help to maximise both the prevention and treatment of OM with Caphosol, together with 'real-life' case material.

## Practical Aspects of Oral Mucositis Management in Cancer Patients

**Dr Christof Scheid, Clinical Director of Stem Cell Transplantation Programme, Department I of Internal Medicine, University of Cologne.**

### *What is the Incidence of OM in your Patients?*

Our patients fall into two main categories. Firstly those receiving autologous stem cell transplants such as patients with myeloma or lymphoma. The multiple myeloma patients receive treatment with high-dose melphalan and up to 50% of them will experience OM. Lymphoma patients are mostly treated with the BEAM high-dose chemotherapy regimen and virtually 100% of these patients will develop OM.

The second group of patients are those receiving allogeneic stem cell transplants and they are treated with a wide range of regimens. OM is a particular problem in patients with acute lymphoblastic leukaemia who receive total body irradiation (TBI) together with etoposide and who develop very severe OM in virtually 100% of cases.

In our patients the type and toxicity of treatment regimen drives the risk of developing OM and severity of symptoms.

### *How Important do you Think it is to Prevent/Treat OM in your Patients?*

It is extremely important to prevent OM as it can have important medical consequences for recovery and also ultimately for survival in some cancer patients.

Ten years ago we would have been concerned about nausea and vomiting as the main side effect of chemotherapy. However, since the advent of more effective antiemetic drugs this is no longer the case. OM is now one of the main complications of cancer treatment in haematological patients.

From a medical perspective OM results in the patient not being able to eat which in turn leads to gut atrophy and impairs the gut barrier. This increases the risk of systemic infection from the gut. Drugs like morphine do not fully control the pain associated with OM but can result in

further complications such as nausea and constipation. It becomes a vicious circle.

### *What Effect does OM have in your Patients?*

If the patients cannot eat and have pain, they are more likely to be confined to their hospital bed, which in turn may put the patient at higher risk of developing pulmonary infection. In some patients this may result in them being admitted to the intensive care unit and acquiring further serious complications.

OM also often affects the patient's quality of life and mood and depression becomes an issue. Some patients also find the symptoms of OM embarrassing in a social context as they cannot speak properly.

### *Who is Responsible for Managing OM in your Patients?*

The clinicians have a strategic role and are responsible for planning the cancer treatment protocols. However, it is the nursing team who are the key people in the prevention of OM. Mouth rinses are usually not seen as part of the medical 'high-tech' treatment, but rather associated with the general supportive measures provided by the nursing team. As a consequence if the nursing team is not convinced about their value, the patients will not be motivated to use them on a regular basis.

### *When did you First Start using Caphosol for the Management of OM and Why?*

We were first rather enthusiastic about keratinocyte growth factor that was supposed to stimulate keratinocytes and mucosal cells and prevent OM. However, it was a very expensive treatment and it also had to be given by intravenous injection. Unfortunately it did not live up to expectations in terms of efficacy and it also caused toxicity such as skin reactions and taste disturbance.

Therefore we were keen to find something to prevent OM as it is such an important issue for our patients. We tested a range of mouth washes and rinses. Caphosol was the last product in a long line we tested and we had very negative expectations. When we tasted it we thought it was very

<b>Case 1 - Acute Lymphoblastic Leukaemia Patient with Severe Oral Mucositis (OM)</b>	
<b>Age Range</b>	30-35 years
<b>Diagnosis</b>	Relapsed acute lymphoblastic leukaemia in second remission
<b>Oncology Treatment Regimen</b>	Total body irradiation 12 Gy and high-dose etoposide followed by allogeneic stem cell transplantation from a matched, unrelated donor
<b>Clinical Presentation</b>	After completing the full course of the intensive multi-cycle chemotherapy the patient relapsed and achieved a second remission after salvage chemotherapy. She was admitted for allogeneic stem cell transplantation with full intensity conditioning. As the combination of TBI with etoposide and methotrexate as immunosuppression is known to cause very severe OM we advised the patient to use the newly introduced Caphosol very regularly as prophylaxis. In contrast to all our previous experience the patient never stopped eating and required only partial parenteral nutrition (PN). She stopped PN on day +12 and was discharged on day +25, almost a week earlier than all the previous patients on the same protocol but without Caphosol.
<b>OM Symptom Grading</b>	Grade 3 (1-5 scale)
<b>Pain Grading</b>	Grade 3 (1-5 scale)
<b>OM Treatment</b>	Caphosol 4 times daily, morphine continuous infusion until day +15, partial (50%) parenteral nutrition until day +12
<b>Patient Assessment</b>	<ul style="list-style-type: none"> <li>• Possible to use even with severe mucositis</li> <li>• No bad taste</li> <li>• Oral food intake possible despite OM</li> <li>• Much less morphine and PN than expected from the information obtained prior to transplantation</li> </ul>

**Table 1.** Case 1 - Acute Lymphoblastic Leukaemia Patient with Severe Oral Mucositis

neutral and also easy to use. In our patients we saw a dramatic reduction in OM symptoms both in our BEAM and TBI patients and we were very impressed by their positive reaction. The efficacy of Caphosol is very good and many patients can eat throughout their treatment – they are now much less dependent on parenteral nutrition or morphine and they are discharged earlier from hospital.

It is important to convince the nursing team about the value of Caphosol in preventing OM in order to

maximise compliance.

### **How do your Patients Describe their Experience with Caphosol?**

They comment on the salty taste and they find that acceptable. However, they do not have anything to compare it with as we use Caphosol prior to conditioning to prevent OM. The most striking result for me is to see the patients sitting at the table having lunch while receiving high-dose chemotherapy (see Table 1).

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### ***What is the Incidence of OM in your Patients?***

Our practice includes a wide range of cancer patients including breast, lung, colorectal, urological, gynaecological and haematological cancers. We treat patients at all stages from neo-adjuvant through to those with metastatic disease. I would estimate that between 40-50% of patients will experience OM symptoms at some time during their cancer treatment.

The development of OM is not only linked to the toxicity of a drug regimen (pharmacology, pharmacokinetics) but it also depends on the biology (pharmacodynamics) of the individual patient. A patient may still develop OM on a less toxic regimen. Diet and lifestyle also have an impact on the risk of developing OM. Therefore it is important to counsel all patients about OM prior to the start of their cancer treatment.

### ***How Important do you Think it is to Prevent/Treat OM in your Patients?***

It is crucial to prevent OM as it can have important medical consequences for the outcome of cancer treatment and it also affects the patient's quality of life.

Neo-adjuvant patients tend to be younger and we take a relatively aggressive approach to their treatment at this stage as our intention is to achieve a 'cure'. We are keen to keep their treatment on schedule and to maintain dose intensity. In the adjuvant group it is important to maximise the effect of chemotherapy or radiotherapy following surgery.

Therefore it is very important to prevent OM in these patients to maintain the momentum of treatment and maximise outcome.

In patients with metastatic disease it is important to

maintain their quality of life, which perhaps is a more important factor at this stage than delivering treatment on time. In these patients OM can have a devastating effect on their well-being and mood. If they are in pain and cannot eat they become miserable.

### ***What Effect does OM have in your Patients?***

Patients experience pain and discomfort, which affects not only their ability to eat but also the pleasure of eating, which we all take for granted. Often OM causes discomfort for the patient which is disproportionate to what is observed in the mouth – a small ulcer may cause significant pain. OM also affects the patient's mood and makes them depressed as they start to dread the next treatment cycle and recurrence of symptoms.

### ***Do your Patients Always Connect the Onset of OM with their Cancer Treatment?***

Sometimes there is a 'disconnect' between the timing of their cancer treatment and the onset of OM symptoms. Also two patients receiving the same treatment regimen will not react in the same way. Therefore it is important to counsel the patient before initiating treatment to assess their risk of OM. If they have risk factors (e.g. history of sore mouth, dental caries etc) they can be given advice on how to avoid OM and treatment initiated prior to chemotherapy or radiotherapy.

### ***Who is Responsible for Managing OM in your Patients?***

We use a team approach in the management of OM, which includes the nursing staff and pharmacists. The patient is also a member of the team. The lead clinician asks us all to extend our practice to the limits and we take responsibility to manage the situation if the patient presents with symptoms of OM. The nursing team are key to monitoring OM treatment compliance. A patient is only referred to a clinician if treatment for OM is not successful.

### ***When did you First Start using Caphosol for the Management of OM and Why?***

We were 'early adopters' of Caphosol. We had high expectations of the product prior to it being introduced in

<b>Case 2 – Ovarian Cancer Patient with Severe Oral Mucositis (OM)</b>	
<b>Age Range</b>	75-80 years
<b>Diagnosis</b>	Recurrent ovarian cancer
<b>Oncology Treatment Regimen</b>	Second line - 6 x cycles of docetaxel carboplatin
<b>Clinical Presentation</b>	The patient was admitted during second line chemotherapy with neutropenia; infection; diarrhoea; nausea; muscular aches; dysuria and a sore mouth. The sore mouth was due to mucosal erythema and ulcers and the patient was experiencing severe pain requiring mild to moderate analgesia.
<b>OM Symptom Grading</b>	Graded 3 by patient (1-5 scale)
<b>Pain Grading</b>	Graded 3 by patient (1-5 scale)
<b>OM Treatment</b>	Caphosol was initiated to treat OM symptoms. An average of four doses per day was administered for 5 days. The patient responded to treatment within two days, having severe OM for one day only after Caphosol was initiated. Morphine treatment was not required.
<b>Patient Assessment</b>	<ul style="list-style-type: none"> <li>• Easy to use</li> <li>• Pleasant to taste</li> <li>• Satisfied with response time</li> <li>• The patient requested a further supply for home - “just in case”</li> </ul>

**Table 2.** Case 2 - Ovarian Cancer Patient with Severe Oral Mucositis (OM)

the UK. We knew if it lived up to expectations it was going to be an important treatment for our patients. When we tried Caphosol we had a very positive experience and this has become self-perpetuating as patients respond well and they want to carry on with treatment for the next cycle. Also it is not ‘active’, it is easy to use and it can be used in patients who have an infection.

Most of our patients require less Caphosol for less time than with head and neck cancer patients. However, they respond well and are fully satisfied with the effect of the treatment.

If a patient develops OM at an early stage in their cancer treatment it is likely that they will develop it again if further treatment cycles are required. Therefore they

should be offered Caphosol prior to the next treatment cycle. If possible Caphosol should be used to prevent OM occurring rather than treating the symptoms when they have become established.

***Has there been a Particularly Dramatic Response to Caphosol in any of your Patients?***

We had a particularly dramatic response in a patient with recurrent ovarian cancer (Table 2). During treatment with a taxane + carboplatin-based regimen she presented with severe (Stage 3) OM. This patient responded to treatment with Caphosol after only two days.

We also had a very quick response in a surgical patient who had OM due to irritation from an endotracheal tube

(ET). She was prescribed Caphosol and the OM resolved after using only three doses.

### How do your Patients Describe their Experience with Caphosol?

The patients sometimes comment that it has a salty taste,

which they do not see as an issue. They also comment that it is easy to carry around and use – “it is just mixing the two constituent vials”. They also like the fact that it is a ‘natural’ product. Most importantly they tell me that it has a quick effect on their symptoms e.g. lack of pain, ability to eat etc. This is a consistent story (see Table 2).

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