Reducing the misery of oral mucositis

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“It felt as if my mouth was full of razor blades”

This description from a cancer patient captures the sort of pain experienced by patients undergoing intensive chemotherapy and radiotherapy if they develop severe oral mucositis (OM).

OM is a particularly unpleasant side effect of chemotherapy and radiotherapy arising from damage to the delicate lining of the mouth and throat. The extent and frequency of mucositis is related to the type of therapy, but for patients undergoing bone marrow transplantation with haematopoietic stem-cell support (HSCT) or irradiation of the head and neck, OM occurs in 70 to 100% of patients (Bellm et al., 2000; Sonis et al., 2001; Rubenstein et al., 2004).

Symptoms range from mild erythema to intensely painful ulcerative lesions (figure 1). While mild cases of mucositis may cause difficulty in eating and drinking, severe cases can compromise all oral intake, prevent conversation, impact upon mood, cause sleep disturbances and leave a patient susceptible to infection. It is no wonder that prevention of OM is the most debilitating effect of their treatment (Rose-Ped et al., 2002).

The absence of effective options for preventing OM has meant that nurses generally focus on symptom relief, especially pain management (Stone et al., 2005). The cornerstone of pain treatment for OM is opioid-based regimens and morphine administered through a patient-controlled system is emerging as the method of choice (Coda et al., 1997; Rubenstein et al., 2004). While this undoubtedly helps relieve the pain, it also brings a myriad of other problems in its wake. Patients on morphine may experience confusion, sedation, constipation and respiratory depression.

As well as the human misery, OM also has a financial impact on health services since it is associated with increased duration of hospitalisation, increased opioid use, and the use of antibacterial, antiviral and antifungal agents (Elting et al., 2003; Oster et al., 2005).

New understanding of the pathobiology of mucositis has given us a new agent for preventing OM

Due to significant advances in understanding the biology underlying oral and gastrointestinal mucosal injury we can now elucidate the steps involved in the pathogenesis of OM. Although there is a continuous progression of events, 5 stages in the development of OM can be described: initiation, primary damage response, signal amplification, ulceration, and healing. (Sonis et al., 2000; 2004).

Understanding this 5-phase model has allowed a different approach to managing OM by allowing scientists to identify the biological agent that can help to prevent or minimise oral mucosal damage, not just to treat symptoms or promote healing. (Donnelly et al., 2003). This biologically active agent is keratinocyte growth factor, which acts to increase epithelial thickness and upregulate cytoprotective mechanisms. By giving this agent before and after the chemotherapy, the mucosa is increased in thickness and more resilient to damage.

Not only does OM impact negatively on quality of life, but there are obvious medical consequences of these symptoms: people who cannot eat are susceptible to dehydration and weight loss and often require parenteral feeding. As the integrity of the oral mucosa breaks down patients are susceptible to bacterial, viral or fungal infections, which may be localised or, in the neutropenic patient, systemic infection leading to sepsis may develop (Elting et al., 2003; Sonis et al., 2004). However, the symptom that seems to most problematic is pain. Pain has obvious impact on quality of life and importantly has been cited as the reason for treatment delays, which can compromise outcome (Kwong et al., 1997; Cox et al., 1992).

This situation presents a challenge to nurses caring for susceptible patients since the majority of widely used interventions for preventing OM are not very effective. A recent Cochrane review (Worthington et al., 2006) assessed information from 71 trials including 5217 patients and involving 29 different interventions for prevention of OM. (This review did not include palifermin, a keratinocyte stimulating factor (see below)). Evidence of any benefit could only be demonstrated for around one third (10) of the agents in use. Mostly, the evidence was weak and only four interventions could be reliably demonstrated to have benefit: amifostine, antibiotic pastilles or paste, hydrolytic enzymes and ice chips. In one case (ice chips) the benefit was only demonstrable in relation to one type of chemotherapy (bolus 5-FU).

Palifermin (Kepivance® Amgen) is a recombinant form of human keratinocyte growth factor (KGF) that stimulates the proliferation, differentiation, migration, and survival of epithelial cells lining the mouth and throat. Palifermin is thought, based on animal studies, to lead to faster replacement of cells killed by cancer treatment, to speed up the healing of mucosal ulceration and protect against mucosal damage at the cellular level, possibly by reducing levels of inflammatory cytokines (Blijlevens, 2006). It is believed that it helps to maintain the integrity of the mucosa throughout the vulnerable period during and following conditioning treatment for HSCT. It is the first FDA-approved therapy for the prophylaxis against OM in patients with haematological malignancies requiring HSCT (haematopoietic stem cell support) (Stiff et al., 2006) - a vulnerable group for suffering OM. Studies are currently underway to investigate the efficacy and safety of palifermin in the solid tumour setting.

Dosing prior to induction chemotherapy is based on the principle of employing proactive measures to protect against OM and shift clinical practice away from the sometimes unsatisfactory situation of only being able to treat the symptoms of established OM.
In a study of 212 patients with haematological malignancies, who were undergoing autologous HSCT (Spielberger et al., 2004), people who received palifermin showed a lower incidence of WHO Grade 3 and 4 mucositis and more patients had only Grade 1 or 2 symptoms. (Table 1 shows the WHO grading system). While 60% of people in the placebo group experienced Grade 4 mucositis, only 20% of those receiving palifermin had grade 4 symptoms (p<0.001). Palifermin also reduced the duration of WHO Grade 3/4 mucositis from a median of 9 days in the placebo group to 3 days in the palifermin group; a reduction of 67% (p<0.001).

<table>
<thead>
<tr>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
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</thead>
<tbody>
<tr>
<td>None</td>
<td>Soreness ± erythema</td>
<td>Erythema, ulcers, and patient can swallow solid food</td>
<td>Ulcers with extensive erythema and patient cannot swallow solid food</td>
<td>Mucositis to the extent that alimentation is not possible</td>
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Figure 2: Oral mucositis incidence (All WHO Grades).
Results from a randomised, double-blind placebo-controlled phase 3 study, n=212 (Spielberger et al., 2004).

According to prescribing information, pre- and post-dosing administration is indicated. Palifermin is therefore given for three consecutive doses before the start of the conditioning regimen and again for three consecutive doses after radiotherapy and chemotherapy. Palifermin should not be administered within 24 hours before, during infusion of, or within 24 hours after administration of cytotoxic chemotherapy.

This dosing regimen does require careful planning of treatment schedules, and may require liaison between departments including the weekend staff. However simple charts are available that assist in treatment planning and also calculating the correct dosage.

Published data show that palifermin is generally well tolerated. In the Spielberger study the most frequently reported adverse reactions in the palifermin-treated patients were rash, pruritus, erythema, mouth and tongue thickening or discolouration, and taste alterations. Most of these adverse events were consistent with the pharmacological action of palifermin on skin and oral epithelium. All were mild to moderate in severity, transient in nature, and not a cause for discontinuation of the study drug.

A recent update from the Mucositis Study Section of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (MASCC/ISOO) now lists palifermin as one of the three preventative treatments recommended for patients undergoing HSCT (MASCC Clinical Practice Guidelines Update 2005). The other treatments recommended are ice-chips for high dose melphalan and low-level laser therapy, which, as the guidelines state, requires expensive equipment and specialist training, so is not an option for many clinics.

**Nurses’ perception of benefits of palifermin for patients**
At a pan-European Nurses Advisory Board, nurses who have experience with palifermin were asked to share their thoughts and opinions about its effects through discussion around specific questions. The nurses reported that in their opinion:
- Patients receiving palifermin experienced a decrease in both incidence and severity of OM.
- Most patients experienced less pain and lower infection rates compared with patients who had other treatments for OM.
- There was a noticeable decrease in the duration of hospitalization of patients, a decreased use of opioids, and a decreased use of antibiotics.
- Generally, patients receiving palifermin had less difficulty in eating, swallowing and communicating which profoundly influenced their mood, and improved their approach to treatment.
- Patients reported feeling less sleepy since they were taking fewer painkillers, and more inclined to have conversations, both of which made them feel better overall.
- Patients reported less feelings of isolation.

Nurses also reported that their patients experienced similar side effects to those reported in the Spielberger study (Spielberger et al., 2004) (rash, tongue thickening associated with a white coating and altered taste perceptions). Nurse participants stressed the importance of educating patients about possible side effects and reassuring them that they would resolve a few days after treatment with palifermin was ceased and did not need treatment.

It was also important that medical and all nursing staff were educated and did not confuse these side effects with other pathological conditions (e.g. confusing the rash with an allergic reaction or the white tongue with candidal infection) which could lead to inappropriate treatments or discontinuation of palifermin prematurely.

Patients who had experienced OM in previous treatment cycles were especially appreciative of the effects of palifermin and reported a better quality of life than when they had treatment without the inclusion of palifermin. Subjectively, patients seemed to be faring better in the post-transplant period if they had received palifermin.

A somewhat less immediately obvious reported benefit of using palifermin was that it improved nursing morale. Nurses felt that, by contrast to the previous situation, where they had great sympathy for patients with severe OM pain, but felt helpless as they had little to offer other than analgesia, they could now take a proactive approach and felt that they had something really positive to offer their patients. These feelings, along with seeing their patients experience decreased pain and distress, had a really beneficial effect on nurses’ morale.

1. These opinions were discussed at a European Palifermin Nurse Advisory Board which was convened to discuss the management of OM and the experiences of nurses during the first six months of palifermin use in clinical practice. The nurses contributing to this board were: Monica Fliedner, Switzerland; Brigitte Baguet, France; Joachim Blankart, Germany; Michelle Davies, UK; Elisabete Henriques, Portugal; Angela Janisch, Austria; Ann-Kristin Karlsson, Sweden; Angela Leather, UK; Ewa Mazur, Poland; Katalin Mihály, Hungary; Liesbet Peeters, Belgium; Agnes Radványiné, Hungary; Blanka Sedlackova, Czech Republic; Katrina Williams, Australia.
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References

Management of Febrile Neutropenia in Paediatric Patients

Experience from a shared Care System in Ireland.

Hilary Noonan, Staff Nurse

Fiona Brady, a colleague of mine, and I work in general paediatric wards in Limerick and Gaway, respectively. These wards provide shared care in conjunction with Our Lady’s Children’s Hospital (OLCH), located in Dublin. OLCH is the national referral and treatment centre for Childhood Cancers. The cancer unit at OLCH shares care with 16 paediatric units based at local hospitals throughout Ireland. Shared Care Centres provide general support for cancer patients. Their main focus of support is the medical and nursing management of chemotherapy-induced haematological toxicities. The most common dose-limiting haematological toxicity that shared care centres encounter as a result of chemotherapy is febrile neutropenia. Health care professionals should be aware of this, due to the seriousness of a febrile neutropenic episode, the resulting adverse events, and the need for prompt treatment of children presenting with the condition.

In May 2006 and I attended a TITAN study day (Training Initiative in Thrombocytopenia, Anaemia and Neutropenia). TITAN is a major new training initiative that is spearheaded by the European Oncology Nursing Society (EONS). TITAN encourages nurses to proactively apply their enhanced knowledge in the prevention, detection and management of these life-threatening conditions. As a result of this study day Fiona and I completed a dissemination project. We developed an education package from a shared care perspective. Our aim was to develop a concise, easily accessible and user-friendly education package on febrile neutropenia for nurses, doctors and other health care professionals.

The febrile neutropenia educational package we developed is based on OLCH guidelines and consists of a power point presentation, a pocket guide on febrile neutropenia and a checklist to be located at the patient’s bedside. All items were designed to aid health care professionals in providing consistent day-to-day management of febrile neutropenia in paediatric cancer patients. We carried out two educational sessions to train health care professionals to use these materials. A pre-training questionnaire was used to evaluate health care professionals prior knowledge of febrile neutropenia. A post-training evaluation was used to assess the effectiveness of the educational package and identify further educational needs.

Seventeen nurses, with a broad spectrum of experience, attended the two sessions. The post-training questionnaire showed our sessions were well received. We were shocked to learn that some nurses were unaware of the potential consequences of febrile neutropenia. They stated that they would now respond more actively to the symptoms of febrile neutropenia. The overall comments emphasised that this package was an excellent, easy to use tool and a much needed resource for staff.

Throughout this project we overcame many hurdles. For example, the cost of printing the pocket booklet by professional printers proved to be very expensive. Fortunately for us with the help of a friend we were able to print the booklet ourselves.

The principal outcome of our project was the production of a user-friendly educational package on febrile neutropenia primarily designed for health care professionals who care for paediatric cancer patients in shared care centres. Pending approval from OLCH, educational sessions in further shared care centres are planned. The impending publication of our pocket guide booklet and educational package aims to maintain and improve the standard of care for febrile neutropenic cancer patients.

I am delighted to inform you that our educational package won both the Irish and European TITAN dissemination competitions. As a result of TITAN we have been offered a great opportunity. We will be presenting our educational package at the EOCO conference in Barcelona in September. Amgen Ireland Ltd. and the Irish Association for Nurses in Oncology whilst supporting TITAN have also been very supportive to us in making our idea become a reality!