The Management of Mucositis in 2005

a report by
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DOI: 10.17925/EOH.2005.0.0.1a

Introduction

Mucositis is defined as the damage that occurs to the tissues of the alimentary canal following chemotherapy and/or radiotherapy. For many years, the literature concentrated on the damage done to the oral mucosa, namely the erythema, mouth ulcers and pain. However, other more distal parts of the alimentary canal are affected, particularly the oesophagus and small intestine, but also the colon and rectum. In each area, pain is a manifestation, and in distal damage diarrhea, abdominal bloating and rectal bleeding can also occur. High dose chemotherapy, prior to stem cell or bone marrow transplantation and head and neck radiotherapy, have the highest frequency of severe mucositis for the number of patients treated (50% to 90%). However, the enormous numbers of patients receiving multi-cycle standard dose chemotherapy mean that standard dose chemotherapy actually causes the bulk of the problem even though the frequencies are much lower (10% to 30%). Up until very recently, treatment of mucositis was merely palliative, with the use of analgesics, mouth washes and treatment reductions or delays. In 2004, the US Food and Drug Administration (FDA) approved the first agent (Palifermin) for the reduction of mucositis in transplant patients with haematological malignancies. However, there is still no licensing of any agents for use in solid tumours and multi-cycle chemotherapy or radiotherapy.

Measuring Mucositis

There are many scales available for assessing oral mucositis, and only a few for the assessment of the rest of the alimentary canal. The discrepancy is partly to do with the inaccessibility of the distal parts of the gastrointestinal tract and partly to do with the greater incidence of oral compared with more distal mucositis. The scales range from those that are easy to use in the clinic on a daily basis, such as the World Health Organization (WHO) and National Cancer Institute Common Toxicity Criteria (NCI/CTC) scores, and those that are suited more to intensive research where highly trained investigators are performing the assessments. The FDA has recognised the utility of the WHO score in registration trials for oral anti-mucotoxics, and the NCI/CTC are used for the rest of the gastrointestinal tract (see Table 1).

Epidemiology and Impact on Healthcare System

Measuring the exact incidence and severity of alimentary mucositis is very difficult. These particular toxicities are often only reported as a secondary endpoint in clinical trials, and this can lead to underpowering to detect the true incidence. Well designed, prospective trials, particularly of the newer anti-cancer agents, are required to determine the total burden of this problem. However, in its recent review of the literature, the Mucositis Study Group of Multinational Association of Supportive Care in Cancer (MASCC) did report the incidence of grade 3 or 4 mucositis for various common regimens. The incidences of grade 1 to 2 mucositis were not felt to be reliably reported. While the incidence of gastrointestinal (GI) mucositis was generally lower than that of oral mucositis (OM) there were exceptions, such as Irinotecan, where GI mucositis is much more common than OM. Risks of grade 3 to 4 mucositis ranged from <10% with the anthracyclines to >15% with 5-Fluorouracil (5-FU). 5-FU and Irinotecan combined had GI mucositis rates >30%. If total body irradiation was used with high dose chemotherapy, the rates of OM exceeded 60%.

While these rates for standard dose chemotherapy may seem low, the implications for healthcare costs are enormous. In the presence of Grade 3 to 4 mucositis, 35% of patients will have a dose delay, 60% will have a dose reduction and 30% will have the treatment stopped all together. More than 50% will also need feeding tubes and/or admission to hospital. The incidence of fever is approximately 60%. Opioid analgesic requirements also rise, and the costs per cycle rise by approximately US$5,500.

Risk Factors

It would be a great advantage to be able to accurately predict those at the highest risk of developing any form of mucositis. The risk factors, as currently understood,
can be divided into treatment- or patient-related. The former are the type and dose of chemotherapy, the location of radiotherapy (increased if alimentary canal is in the treatment field) and particularly the combined use of chemotherapy and radiotherapy. The latter are much harder to define. It was previously believed that children were at a higher risk than adults. However, this is not borne out in the incidences reported in clinical trials. The risks for the elderly are unknown because they have not been specifically studied. There is a possibility that gender has an impact, and there is an increased risk in the obese compared with those of normal weight. However, this last risk may be due to inadvertently using larger doses of chemotherapy in the obese due to body surface area dose calculations.

Overall, risk prediction is currently unsatisfactory. There is, however, work being done on genetic risk prediction, and this is an exciting area of research.

Pathogenesis of Mucositis

It is now understood that following the insult of chemotherapy or radiotherapy, the development of overt mucositis is the result of a complex interplay between all levels of the epithelium and sub-epithelial tissues. Generation of reactive oxygen species (ROS) seems to be a key event, leading to direct damage of cells, tissues and blood vessels. The direct cell damage, however, is not sufficient to lead to the severity of mucosal damage that is later seen. Rather, ROS also lead to stimulation of various transcription factors, such as nuclear factor (NF)-kappa B, and activation of pro-inflammatory cytokines tumour necrosis factor (TNF)-alpha, interleukin (IL)-1beta and IL-6. There is also activation of the cyclo-oxygenase-2 pathway, and consequent angiogenesis, as well as activation of the ceramide pathway and macrophages. Following on from this, there develops a feedback loop leading to amplification of the response, probably mediated by the pro-inflammatory cytokines. It is important to note that all this occurs within hours of the insult, and thus days before any overt damage is visible.

After several days, ulcers do develop, but not uniformly over the mucosa – the reason for this is not clear. Also unknown is why some people suffer from mucositis limited to one area of the alimentary canal, whereas others develop generalised damage. Bacterial colonisation is possible during the ulcerative phase, and can lead to systemic infection. Eventually, signalling from the extracellular matrix leads to increased epithelial proliferation and healing. However, even when the mucosa again appears normal, it is possible to measure residual angiogenesis, and the patient remains at risk of further mucositis with on-going anti-cancer therapy.

Guidelines for Prevention and Treatment of Mucositis

The Mucositis Study Group of MASCC/International Society for Oral Oncology (ISOO) reviewed the literature relating to mucositis from 1966 to 2002 in its initial guidelines. One of the major findings was that while many different agents had been tried, the quality and size of the published studies was such that, often, no recommendation for treatment could be made. However, one great benefit that did come out of the process was the forging of cross-discipline and international collaborations that have led to faster advances in understanding the patho-biology of mucositis, the ability to develop prospective clinical trials to look at the burden of illness and the more rational targeting of treatment. A summary of the guidelines that were possible is shown in Table 2.

Future Directions

Since the publication of the MASCC/ISOO mucositis guidelines, the FDA has approved the use of Palifermin1 for the reduction of oral mucositis in patients with haematological malignancies undergoing high dose chemotherapy and total body irradiation (TBI) with autologous stem cell transplant. Palifermin is a keratinocyte growth factor. It acts by stimulation of epithelial cell proliferation, leading to enhanced epithelial cell survival, maintenance of intracellular junctions, desmosomal attachments, and epithelial barrier integrity. It is a member of the fibroblast growth factor family, and several other members of this family are in various stages of development for the treatment of mucositis.

There is a theoretical risk with all the targeted growth factors that they may cause tumour protection, but there is currently no clinical evidence to support this.

Summary

For the first time, there are now agents available that can alleviate this distressing side-effect of anti-cancer therapy. This will have the effect of improving quality of life for patients with cancer, reducing costs and possibly improving patient survival by reducing treatment reductions and delays. However, there is much more work to be undertaken to completely solve this problem.

Table 1: The WHO Score for Oral Mucositis

<table>
<thead>
<tr>
<th>Source</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO</td>
<td>No Changes</td>
<td>Soreness with erythema</td>
<td>Erythema, ulcers, can eat solids</td>
<td>Ulcers, liquid diet only</td>
<td>Alimentation not possible</td>
</tr>
</tbody>
</table>

Table 2: Summary of MASCC/ISOO Mucositis Guidelines

Oral Mucositis – Foundations of Care
1. The panel suggests that oral care protocols that include patient education be used to attempt to reduce the severity of mucositis from chemotherapy or radiation therapy.
2. The panel recommends patient-controlled analgesia with morphine as the treatment of choice for oral mucositis pain in patients undergoing haematopoietic stem cell transplantation.

Radiation Therapy – Prevention
3. To reduce mucosal injury, the panel recommends the use of midline radiation blocks and three-dimensional radiation treatment.
5. The panel recommends that chlorhexidine not be used to prevent oral mucositis in patients with solid tumours of the head and neck who are undergoing radiotherapy.

Standard-dose Chemotherapy – Prevention
6. The panel recommends that patients receiving bolus 5-fluorouracil (5-FU) chemotherapy undergo 30 minutes of oral cryotherapy to prevent oral mucositis.
7. The panel suggests that 20 to 30 minutes of oral cryotherapy be used to attempt to decrease mucositis in patients treated with bolus doses of edatrexate.
8. The panel recommends that acyclovir and its analogues not be used routinely to prevent mucositis.

Standard-dose Chemotherapy – Treatment
9. The panel recommends that chlorhexidine not be used to treat established oral mucositis.

High-dose Chemotherapy with or without Total Body Irradiation plus Haematopoietic Cell Transplantation (HSCT) – Prevention
10. The panel does not recommend the use of pentoxifylline to prevent mucositis in patients undergoing HSCT.
11. The panel suggests that, for centres able to support the necessary technology and training, low level laser therapy be used to attempt to reduce the incidence of oral mucositis and its associated pain in patients receiving high-dose chemotherapy or chemoradiotherapy before HSCT.

Gastrointestinal Mucositis

Radiation Therapy – Prevention
1. The panel suggests that 500mg sulphasalazine orally twice-daily be used to help reduce the incidence and severity of radiation-induced enteropathy in patients receiving external beam radiotherapy to the pelvis.
2. The panel recommends that oral sucralfate not be used.
3. The panel recommends that 5-amino salicylic acid and its related compounds mesalazine and olsalazine not be used to prevent GI mucositis.

Radiation Therapy – Treatment
4. The panel suggests that sucralfate enemas be used to help manage chronic radiation-induced proctitis in patients who have rectal bleeding.

Standard-dose and High-dose Chemotherapy – Prevention
5. The panel recommends either ranitidine or omeprazole for the prevention of epigastric pain following treatment with cyclophosphamide, methotrexate, and S-FU or treatment with S-FU with or without folinic acid chemotherapy.

Standard-dose and High-dose Chemotherapy – Treatment
6. When loperamide fails to control diarrhoea induced by standard-dose or high-dose chemotherapy associated with HSCT, the panel recommends octreotide at a dose of at least 100µg subcutaneously twice-daily.

Combined Chemotherapy and Radiation Therapy – Prevention
7. The panel suggests that amifostine be used to reduce oesophagitis induced by concomitant chemotherapy and radiotherapy in patients with non-small cell lung cancer.