How can we nutritionally support someone who develops mucositis following cancer chemotherapy?

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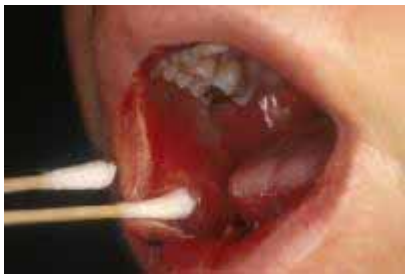
Introduction

The impact of cancer on our community is significant. In real terms, 1 in 4 women and 1 in 3 men will be diagnosed with cancer before the age of 75 years[1]. A large number of these people will be offered chemotherapy and/or radiotherapy as treatment modalities.

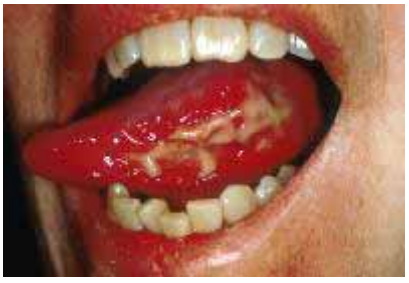
Between 10 – 40% of people receiving chemotherapy will develop, as a treatment side-effect, a condition known as mucositis[2]. Mucositis is more correctly known as mucosal barrier injury, and occurs throughout the gastrointestinal system. In its milder form, mucositis presents as erythema (reddening) of the mucous membranes. In the most severe form, mucositis presents as deep ulcerating erosions within the mucous membranes, and the lesions are often bleeding and can become infected.

1. Erythematous oral mucositis lesion on the buccal mucosa.

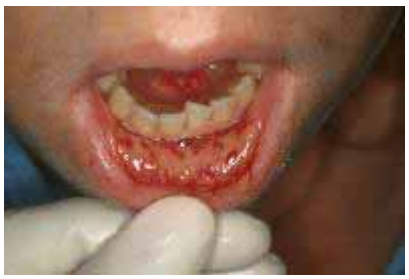


2. Ulcerative oral mucositis lesion on the buccal mucosa.

3. Ulcerative oral mucositis lesion on the lateral and ventral surfaces of the tongue.



4. Ulcerative oral mucositis lesions on the labial mucosa and the floor of the mouth.



(Images courtesy of Woo SB and Treister NS, 2006, Chemotherapy-Induced Oral Mucositis, http://www.emedicine.com/derm/topic682.htm)

The potential costs related to mucositis are enormous. People may require hospitalization for the management of symptoms; future doses of chemotherapy may have to be reduced or omitted; quality of life may be diminished; and malnutrition often results.

This report will present a detailed discussion of chemotherapy-related mucosal barrier injury. As such, the pathophysiology and current medical management will be outlined. However, the primary focus of this document will be the nutritional management of mucositis.

DISCUSSION

In order to fully appreciate the nutritional implications of mucosal barrier injury, it is necessary to provided some background information on the pathobiology, assessment and management of the condition

From the oral cavity to the anus, the gastrointestinal (GI) system is lined with mucous membrane. The rapidly dividing epithelial cells that make up the GI mucous membrane are particularly vulnerable to the cytotoxic effects of chemotherapy.

Despite much effort to identify exact causes, by the very nature of their complexity, the factors contributing to the development of chemotherapy- induced mucosal barrier injury remain uncertain. Animal studies suggest that the primary mechanism of mucositis is apoptosis of epithelial stem cells[3] – the primitive cells from which all other cell types differentiate. Epithelial stem cells are located at the base of the mucous membrane.

When required, stem cells mature into an epithelial cell and migrate forward, to replace cells that have been shed from the luminal surface of the membrane.

Apoptosis is an active process of self-destruction that cells undergo in response to certain conditions. It is known as programmed cell death, or cell suicide[4]. Apoptosis is a protective mechanism. It ensures that cells with old, damaged or faulty DNA are destroyed, thereby minimizing the chance of ongoing abnormal cell proliferation. Chemotherapy is believed to induce cellular DNA damage by the production of reactive oxygen species (free radicals), or through a complex interaction of enzymes and cytokines[5]. It is in this way that tumour cells, along with some normal cells (collateral damage!) are destroyed.

Mucosal barrier injury is described as having five phases:

1. initiation
2. up-regulation with generation of messengers
3. signaling and amplification
4. ulceration with inflammation, and
5. healing[6,7].

Initiation

Cells, tissues and blood vessels are directly damaged by oxidative stress, and this is believed to be the initiating event leading to mucositis. The generation of reactive oxygen species subsequently stimulates the production of a number of biological chemicals, the effects of which characterize the acute response of the tissues to the initial injury[8].

Up-regulation with generation of messengers

Is characterized by the simultaneous occurrence of a number of events involving all tissues at all levels:

- the death of basal epithelial cells;
- the release of a number of transcription factors – these are thought to drive the evolution of mucositis. Nuclear Factor-kappa B (NF-κB) is of particular interest;
- activated NF-κB up-regulates many genes, most significantly those that are responsible for the production of proinflammatory cytokines: Tumour Necrosis Factor-α (TNF-α), Interleukin-1β (IL-1β), and Interleukin-6 (IL-6). These chemicals promote tissue injury and apoptosis; and

- other equally tissue-damaging biological pathways are activated (cyclooxygenase-2 and ceramide pathways for example)[9].

Signaling and amplification

The cyclooxygenase-2 and ceramide pathways, mentioned above, (amongst others) can also exert an indirectly injurious effect on the tissues of the gastrointestinal tract, by further promoting the production of the proinflammatory cytokines TNF-α, IL-1 β, and IL-6. The result of this phase is that the mucous membranes are now biologically changed, even though they may still appear normal[10].

Ulceration

In this phase, the mucosa demonstrates a significant level of inflammation, and colonization by gram-negative, gram-positive and anaerobic bacteria occurs. This, in itself, can further complicate the tissue damage because bacterial fragments can promote the production of the proinflammatory cytokines mentioned earlier[11]. Ultimately, there is full-thickness loss of integrity of the mucous membranes; the tissues become oedematous, friable, and bleed easily; the risk of bacteraemia and sepsis is increased; and the person experiences considerable pain.

Healing

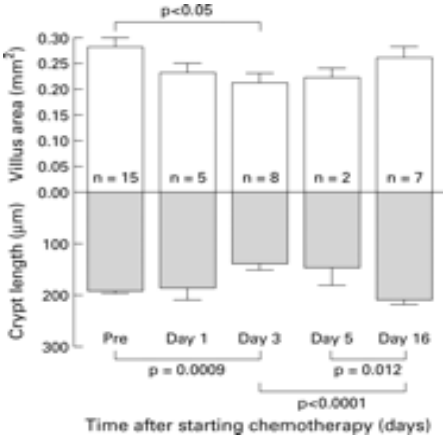
A signal from the extracellular matrix initiates the healing process in oral mucositis. Epithelial proliferation, differentiation and migration occurs at the wound margins, leading to repair of mucosal integrity. Once integrity is regained, recolonisation by microbial normal flora occurs. After this phase, the mucous membrane appears normal – but it has been permanently altered[12]; the person is more likely to experience mucositis with subsequent treatments, and in future the condition is likely to be more severe[13].

Oral mucositis is often considered separately to alimentary mucositis, although the pathological processes leading to mucosal barrier injury are likely to be the same in both areas. Indeed, with chemotherapy treatment, if oral mucositis occurs the patient is often troubled by symptoms of alimentary mucositis as well. Mucosal barrier injury confined to only the mouth, or individual parts of the gastrointestinal tract (oesophagus, stomach, small intestine, large intestine, rectum for example) is generally seen only when treatment is localized to that specific area, as happens with radiotherapy.

Alimentary (or gastrointestinal – GI) mucositis does vary in its manifestation somewhat depending on where it occurs, because of the physiological and functional differences between the sections. For example, the oesophagus has a slightly different structure, and a considerably different function to the small intestine. Regardless of these differences, however, the implications of the condition remain the same – the increased financial costs (in terms of extra hospitalization and treatment required) and personal costs (in terms of quality of life, and treatment delays) are significant.

Keefe et al (2000) investigated mucosal damage in the small intestine of people who had received chemotherapy – seeking to determine the time course for pathological changes. Participants underwent endoscopic examination and duodenal biopsy prior to commencement of treatment, and then once more at 1, 3, 5 or 16 days following chemotherapy. The biopsy samples were assessed for apoptosis, villus area, crypt length, and mitotic index – all parameters indicative of the level of mucosal damage. The results were as follows:

- there was a dramatic increase (seven-fold) in apoptosis at day 1 after chemotherapy, with a gradual decline to twofold by day 5 – compared with pretreatment values;
- villus area and crypt length had decreased at day 3 after chemotherapy, but returned to pretreatment dimensions by day 16;



Changes in villus area and crypt length before (Pre) and after chemotherapy for cancer. Data are given as means (SEM).

(Figure courtesy of Keefe et al, 2000, Chemotherapy for cancer causes apoptosis that precedes hypoplasia in crypts of the small intestine in humans, www.gutjnl.com)

- enterocyte size, and mitotic count (suggestive of cellular replication activity) were also reduced by day 3 following treatment, but had returned to normal by day 16[14].

The last two parameters in particular, suggest a decrease in mucosal integrity and an increase in intestinal epithelial permeability, lasting for approximately two weeks following

chemotherapy. This information has relevance when considering appropriately supportive nutritional strategies.

Mucositis assessment and management

The severity of the mucosal barrier injury is influenced by:

- the type of chemotherapy drugs used (5-fluorouracil – 5-FU, Methotrexate, doxorubicin, irinotecan, and taxanes are examples of drugs with which mucositis is *most likely* to occur)
- the use of two or more drugs known to cause mucositis in a treatment protocol
- the number of treatment cycles undertaken
- concurrent treatment with radiotherapy, and
- the nutritional status of the patient prior to treatment commencement.

Several agencies, including the World Health Organisation (WHO) and the National Cancer Institute (NCI), have developed toxicity scales for the measurement of mucositis. They are four- or five-point surveys that rate the overall condition of the mouth based on visual examination of the mucosa, severity of patient pain, and changes in functional capacity (for example the ability to eat)[15]. Accurate assessment and reporting of mucositis is important, as treatment options are often dictated by the 'grade' of severity.

World Health Organisation (WHO) oral mucositis scale[16]

Grade 0	No changes
Grade 1	Soreness/erythema
Grade 2	Soreness/erythema + ulceration + can eat solid foods
Grade 3	Soreness/erythema + ulceration + can use a liquid diet only
Grade 4	Soreness/erythema + ulceration + oral alimentation is not possible

Medical Treatment of Mucositis

Mucositis is a self-limiting condition. Even without supportive interventions, the damage to the mucous membranes will eventually resolve. There are currently no effective prevention strategies, although cryotherapy (sucking of ice-chips during short-term infusions of 5-FU) can lead to a reduction in the severity of the lesions, by up to 50%[17,18].

The treatment goals, therefore, when dealing with chemotherapy-induced mucositis are:

1. Minimise the potential complications associated with mucositis (infection, haemorrhage, malnutrition for example); and
2. Provide symptomatic relief of pain, anorexia and diarrhoea.

Nutritional support in Mucositis

Current conventional medical nutrition advice will be outlined initially, followed by a discussion of naturopathic nutritional strategies.

Conventional medical nutritional recommendations

For all grades of mucositis, dietary interventions are aimed at

- Increasing nutrient intake, and
- Minimising mucosal discomfort.

To that end, specific suggestions include

- Increasing protein and caloric intake (using nutritional supplements if necessary – Sustagen® or Ensure® products for example), or
- Increasing intake of foods like eggs, custards, milkshakes, pasta
- Increasing fluid intake
- Avoiding foods that are either too hot, or too cold (risk of thermal injury to vulnerable mucosa)
- Avoiding dry, coarse or hard foods (risk of abrasive mucosal injury)
- Avoid foods that are spicy, salty, acidic (increases mucosal discomfort)
- Avoid citrus fruits and tomatoes, alcohol and tobacco (potentially irritating to oral mucosa), and
- Modify food texture (mince or puree) to facilitate swallowing[19, 20].

For Grade 1 and 2 mucositis with mild to moderate oral discomfort, patients may choose to restrict their oral intake for a day or two until the level of discomfort improves. In the well-nourished patient, this is usually not a problem – as long as fluid intake is maintained[21].

For severe mucosal injury (Grade 3 and/or 4), the patient may require hospitalisation with enforced fasting until the ulcerative and inflammatory lesions resolve. In this situation the patient often reports pain to the extent that even swallowing their own saliva is impossible. With this degree of functional impairment, the patient is usually supported with opioid

analgesic infusions and intravenous hydration, and enteral or parenteral nutrition (ie. feeding via a nasogastric tube, or intravenously with total parenteral nutrition – TPN)[22].

Naturopathic nutritional strategies

As described in the literature, many chemotherapeutic drugs cause the gastrointestinal mucosa to develop inflammatory and ulcerative changes. As a consequence of this, there is an increase in the permeability of the mucosal lining. It would seem reasonable, therefore, to assume that many of the interventions accepted as being beneficial for the treatment of other inflammatory bowel conditions would also confer some benefit for mucositis.

In the setting of chemotherapy-induced mucositis the nutritional considerations are:

- The presence of varying degrees of inflammation
- The potential for ulcerative mucosal changes
- Impaired mechanical and/or chemical digestion
- Potential for malabsorption of nutrients due to reduced digestive enzyme production
- Increased need for nutrients required for tissue repair; recognizing that
- The nutritional challenges for patients with mucositis should fundamentally resolve within a couple of weeks of the completion of treatment.

In people who find achieving an adequate nutritional intake challenging (up to grade 3 mucositis), it is important to provide nutrient-rich foods – in small amounts often. Nutrient-poor foods and liquids should be avoided:

- Highly refined or processed foods that have had much of the nutrient value removed – white flours, white sugar, sweets
- Low calorie foods and drinks – diet cordials, low-fat products
- Foods with artificial additives
- Alcohol.

Nutrient-rich foods that can be consumed regularly (up to 6 times per day) include:

- ✓ Soups with meat stocks, root vegetables and legumes
- ✓ Well-cooked grains and cereals – rice, oats, barley (with added fruits and vegetables
- ✓ Fruits and vegetables (freshly cooked or raw) – avocadoes are good

- ✓ Well-cooked, low-fat meats – fish, chicken
- ✓ Nut/seed spreads can be added to foods
- ✓ Eggs.

The anti-inflammatory effects of an alkaline-forming diet have been well documented for a wide range of diseases where gut inflammation is believed to be a contributing factor. Soft, easily consumed foods belonging to the alkaline category may be quite soothing to the inflamed mucous membranes, in that they encourage the body to maintain the pH at a more alkaline level[23]: watermelon, cantaloupe, mango, asparagus, avocado, apple, ripe bananas, pumpkin, egg yolks, and tofu for example.

Due to the increased intestinal permeability caused by the inflammation and/or ulceration of the membranes, a diet that adheres to food choices that carry a low antigenic load would seem appropriate – to minimise the risk of food intolerances developing: skinless chicken, white fish, rice/oat milk, tofu, most fruit and vegetables, legumes, rice, quinoa. In this instance it is recommended that wheat products, gluten-containing foods, and dairy products be avoided.

Maintaining an adequate fluid intake is essential. Waste products and toxins cannot be eliminated from the body if there is inadequate intra- and extracellular water in which to transport them. Striving to consume at least two liters of water per day is advised. Other suitable fluid options are: herb teas (especially green tea), freshly juiced fruit and vegetables, home-made fruit juice ice-blocks, and nut milks (preferably organic).

Specific nutrients for the support of chemotherapy-damaged gastrointestinal mucosa:

Glutamine

Intestinal cells use the amino acid glutamine as their primary fuel source, metabolising nearly all dietary glutamine, and absorbing large amounts from the circulation. Animal and human studies have demonstrated that glutamine supplementation can reduce the mucosal injury associated with methotrexate, and a glutamine deficiency may contribute to mucosal damage[24].

The specific functions that glutamine has in the small intestine include

- Increasing height of the villi
- Stimulates proliferation of intestinal mucosal cells
- Promotes mucosal integrity
- Prevents increased gut permeability
- Prevents bacterial migration beyond the epithelial surface[25].

Investigating the possible benefit conferred by glutamine in chemotherapy-induced mucositis, Anderson et al (1998) conducted a randomized, double blind, crossover placebo controlled study (with patients serving as their own controls) over 4 courses of chemotherapy. Glutamine was administered as a swish-and-swallow solution for at least 14 days – beginning on the day of chemotherapy – at a dose of $2g/M^2$ twice daily. For two courses of chemotherapy patients received glutamine, then for the next 2 cycles they crossed over to the placebo arm. Patients were asked to report onset, duration and severity of mouth pain following chemotherapy, and the paired data results were analysed. Based on the data, there is sufficient evidence to suggest that both the duration and severity of the oral mucositis following chemotherapy were significantly reduced[26].

The administration of glutamine in high doses has been recommended (up to 20g/day or more), and it is a well tolerated supplement without signs of toxicity. Commencing supplementation on the day of chemotherapy, and continuing the treatment for at least 2 weeks is advised to ensure that reasonable glutamine stores are achieved[27,28].

Pre- and Probiotics

Any disruption to the mucosal lining of the gut will result in an imbalance in the microbial populations. Beneficial bacterial strains (normal flora) are reduced, and pathogenic organisms flourish. Recolonisation of the gut with commensal organisms is vital to restore balance.

Commensal organisms provide the following benefits:

- Decrease pH of intestinal lumen
- Produce short-chain fatty acids that enterocytes use for fuel
- Increased production of secretory immunoglobulin A (sIgA) – essential for health of intestinal mucosa
- Increased production of anti-inflammatory cytokines

- Prevention of migration of pathogenic organisms through the epithelium[29] into the systemic circulation.

Different strains of probiotic bacteria have different functions. *Lactobacillus plantarum* is a potent inhibitor of pathogenic organism overgrowth. To this end, it assists the rebalancing of intestinal commensal populations. It promotes repair of damaged gut mucosa[30], and is also the predominating strain of the Lactobacillus species found in the oral and intestinal mucosa[31] – it would appear reasonable, therefore, to supplement this organism when repair of oral and intestinal mucosal function is required.

It is suggested that probiotic supplementation should commence some time prior to the start of chemotherapy, and continue for several months beyond the completion of treatment[32].

Support of intestinal recolonisation with supplemented beneficial bacteria is recommended to ensure optimal outcomes. This is achieved by the addition of prebiotic nutrients, with the aim of providing the probiotic organisms with a ready source of fuel for their metabolic function. Soluble dietary fibres (inulin, pectin and oligofructose for example) selectively promote the growth of certain bacteria[33], and promote intestinal health by adding bulk to the intestinal contents. This increases bowel transit time, and promotes excretion of waste products and toxins which may contribute to mucosal inflammation.

Essential Fatty Acids

These molecules play an integral role in the phospholipid bi-layer of cell membranes, and therefore have the ability to strongly influence many cellular functions. Cellular migration and proliferation are vital stages of the epithelial membrane repair process (known as epithelial restitution). It is thought that by supporting the composition of cell membrane, it is possible to promote the process of epithelial restitution – and the literature appears to support this theory[34].

Consumption of omega-3 fatty acid rich marine oils promotes the production of the potently anti-inflammatory prostaglandin-E, and has been shown to benefit mucosal injury produced by methotrexate[35].

Eicosapentanoic acid (EPA) and Docosahexanoic acid (DHA) favourably influence the

- rate of epithelial cell migration in the healing of damaged intestinal mucosa
- number of cells participating in the healing process
- activity of transporter and receptor proteins located in the cell membrane, to promote cellular activity[36].

The result of these functions is a more rapid and complete healing of injured mucosa, and a minimization of the risks associated with intestinal permeability.

Zinc

Zinc supplementation alone has been shown to reduce intestinal permeability, and improve Methotrexate-induced mucositis. When administered in combination with a whey-derived growth factor the effects were enhanced. It is suggested that supplementation of a pharmacologic dose of zinc may have clinical application in chemotherapy-induced mucostis[37].

Lactose intolerance

There is reasonable evidence to suggest that chemotherapy-induced gastrointestinal mucositis can induce a temporary state of lactose intolerance. This occurs because the enzyme lactase is produced by the cells at the ends of the villous projections in the small intestine. During the acute phase of mucosal barrier injury, the intestinal villi are reduced in size, or missing completely through ulceration of the mucous membrane. A study was conducted that evaluated patients undergoing chemotherapy for the development of lactose intolerance – this was assessed by lactose breath hydrogen testing (LBHT). The theory is that patients with lactase deficiency do not metabolise lactose in the small intestine – rather it is degraded in the large intestine by colonic bacteria. Hydrogen gas is produced as a bi-product of this process, and is excreted via the lungs where it can be measured. The results of this study showed that the majority of patients had greater LBHT readings following chemotherapy than compared to their pre-treatment levels, however only a small number of these patients actually developed symptoms commonly attributed to lactose intolerance (bloating, pain, diarrhoea). Based on this anomaly, the researchers concluded that dairy restriction in patients undergoing chemotherapy treatment is not warranted unless the distressing symptoms of lactose intolerance occur[38].

It is the opinion of this author that dairy avoidance in the setting of mucosal barrier injury is highly recommended. I believe there is little merit in consuming a food that is going to be

incompletely digested and absorbed, especially one that has been shown to have such adverse effects on gastrointestinal function. The permeability of the mucous membrane is increased, and the antigenic load presented to it from incompletely digested dairy foods has a high potential for causing problems in the future. It does not seem an unreasonable course of action to eliminate dairy completely from the diet for the duration of the chemotherapy treatment.

A prescription for the nutritional management of mucositis might look like:

Glutamine	20g/day in 4 divided doses, commencing 1 week before chemotherapy, and continuing until 14 days after completion
Probiotics	containing *Lactobacillus plantarum*, *acidophilus* and *casei* commencing as soon as possible prior to chemotherapy, and continuing for several months after completion
Prebiotics	containing a mixture of at least inulin and pectin
EFAs	4g/day in 2 divided doses, containing EPA and DHA
Zinc	40mg/day, separate from other supplements
Green tea	3 – 4 cups/day

In my alter-ego role as an oncology nurse, I have had enough feedback from people receiving cancer chemotherapy, to believe that there is a valuable (and grossly under-rated) role for specific dietary/nutritional strategies in the management of mucositis. All that remains to do is convince the medical establishment that it is worth serious consideration.

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