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An introduction to mucositis

Mucositis is a burdensome adverse reaction to chemotherapy (CTX) and radiotherapy (RTX) that significantly impairs the quality of life. Damage to the mucosa leads to anorexia and cachexia, preventing the full dose of CTX from being used or delaying the scheduled RTX, jeopardising the treatment.

Definition and pathophysiology

The high rate of proliferation and short duration of the cell cycle, which are the results of the high capacity for growth and regeneration of oral and gastrointestinal mucous membrane epithelia, are the reasons for the tremendous non-specific destructive effect of adverse reaction to chemotherapy/radiotherapy (CTX/RTX). Synergistic damage of mucous membrane function, differentiation and regeneration caused by CTX + RTX are symptoms of this direct toxicity. Functional breakdown primarily of serous and mucus glands, resulting in a reduction or complete breakdown of the physiological protective barrier, provide ideal conditions for microorganisms in an adhesive, saliva. Consequently, breakdown of the barrier to infection leads to thrush and a serious danger of sepsis as depicted in Figure 1 [1, 2]. Mucositis contributes to the morbidity and mortality of cancer patients. Few options for alleviating the symptoms of mucositis are available to date.



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and staff education, appropriate use of oral rinses, ice chips, palifermin, appropriate use of analgesics, proton-pump inhibitors, anti-diarrhoeal agents and the avoidance of agents without proven evidence [3].

Therapeutic options

Traditional approaches

Since virtually no evidence-based studies are available for the prophylaxis of mucositis, no recommendations besides general oral hygiene are possible. Treatment strategies lack evidence-

based studies as well.

Mucositis mouthwashes are often (multi-component) mixtures of pharmaceuticals based on historical clinical tradition lacking proof of efficacy, or even worse, compatibility. The wide variety of formulations should be considered doubtful even if they possess euphonic names such as 'magic mouthwash'. Allopurinol mouthwash did not have any of the desired effect in humans that was seen in animal models [4, 5].

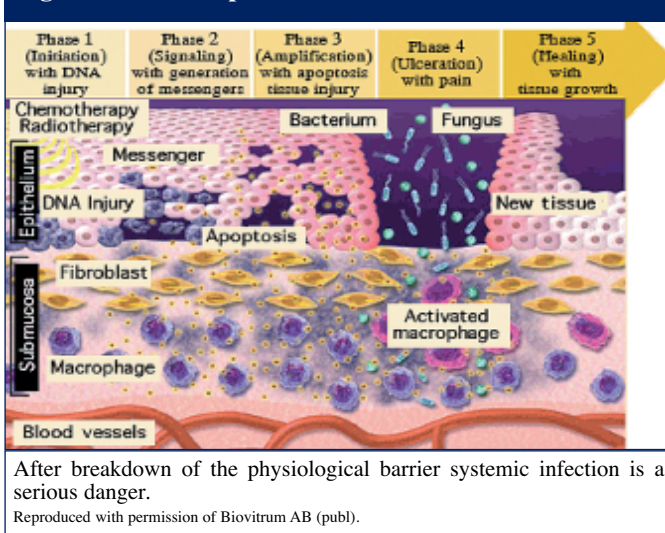
Uridine 10% adhesive paste seems to be a real antidote to palmar-plantar erythrodysesthesia (PPE) and 5FU-related mucositis. It was developed by the Pharmaceutical Department of the University of Essen, Germany; see EJOP 2009; 3(2):22-3. Calcium folinate 4% adhesive paste against mucositis after high-dose methotrexate has also been developed in Essen and seems to work as a local antidote. Clinical trial data do not exist, but positive clinical experience allows this paste to be recommended. The formula is:

R
 Calcium folinate 0.6 g
 Paraffin 10.1 g
 Carbopol 974 P 4.3 g or alternatively:

Calcium folinate 0.6 g
 Paraffin q.s.
 Hypromellose adhesive paste 40% (*Neues Rezeptur Formularium* 7.8) ad 15.0 g
 Flavouring can be added as required.

Many popular global, non-specific prophylaxis and therapeutic remedies show few or only subjective effects. Sage tea and chamomile extract both reduce inflammation with subjective benefit. According to Fidler et al, chamomile did not show any benefit for 5FU-induced mucositis and dysphagia [6]. Dexpantenol remedy, myrrh tincture, suspensions of sucralfate or diluted Betaisodona (Betadine), chlorhexidine, locally used

Figure 1: The five phases of mucositis



Guidelines

Guidelines for supportive measures have been published by the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (MASCC/ISOO). They are available in English, German and Greek on www.mascc.org. They contain a list of substances and procedures that are **not recommended**: no sucralfate for prevention (RTX), no antimicrobial rinses (RTX), no chlorhexidine (CTX + RTX), no acyclovir (or analogues) for prevention, no pentoxifylline with autologous haematopoietic stem cell transplantation. **Positive recommendations** are good oral hygiene and basic oral care; patient, caregiver

antibiotics and anaesthetics such as Lidocaine and Tetracain or H₂O₂ 1-3% are examples of lots of suspensions used without measurable usefulness.

Contradictory opinions have been reported for glutamine suspension 50%. In animals, a glutamine-enriched diet has been shown to reduce chemotherapy-induced enterotoxicity [7]; however, no significant positive effects in mucositis have been reported for supplementation of oral and parenteral glutamine in humans [8-10].

New developments

Recombinant keratinocyte growth factor (rHuKGF) stimulates epithelial cells that physiologically play an important role after damage. Palifermin (Kepivance) claims to induce cell proliferation and increase epithelial thickness, upregulate cytoprotective mechanisms, reduce DNA damage, upregulate levels of detoxifying enzymes and therefore protect against oxidative stress. So it claims to reduce proinflammatory cytokines, reduce apoptosis (in oral mucous membranes) and accelerate re-epithelisation of tissue leading in short to fewer ulcerated areas and less pain. Kepivance was approved in 2005 for patients with haematological tumours, myeloablative CTX (which bears a high risk of oral mucositis) and patients who are targeted for autologous stem cell transplantation only. Application of 60 µg/kg/d as IV bolus must take place three days prior to and three days after myeloablative CTX (not during CTX). In total, six doses have to be given, the last injection 24-48 hours before further CTX. Subcutaneous application will not be tolerated. In a clinical trial, administration of palifermin within 24 hours of chemotherapy resulted in increased severity and duration of oral mucositis. The safety and efficacy of palifermin have not been established in patients with non-haematological malignancies. KGF receptors are present on epithelial cells in many tissues including the tongue, buccal mucosa, oesophagus, stomach, intestine, salivary gland, lung, liver, pancreas, kidney, bladder, mammary gland and skin. One case of aggravation of PPE after BEAM (carmustine 300 mg/m² day 1, etoposide bd 100 mg/m² days 2-5, cytarabine bd 100 mg/m² days 2-5, melphalan 140 mg/m² day 6) has been reported, raising the question whether palfermin might have contributed to the severity of this side effect on the skin, usually seen after cytosine arabinoside [11].

Traumeel S, a mixture of homeopathic extracts from plants and minerals, is used in Germany for the treatment of traumatic, inflammatory and degenerative processes. The manufacturer is developing a new formulation for use as protection against mucositis [12].

Benzydamine is one option supported by an evidence base that inhibits the development of mucositis and might be given prophylactically [13]. Dr Dirk Keiner, from the Pharmacy Department of the Head and Neck Clinic in Suhl, Germany, has developed a benzydamine-containing but alcohol-free, palatable mouth gel adhesive to mucosa. Fast effectiveness against bacteria lowers the risks of ulceration and infection, local anaesthesia and high affinity to membranes explain the advantages for the patients. The gel contains benzydamine HCl, sodium hydrogen carbonate, saccharine sodium, polysorbate, polyvidone, glycerol and hydroxyethyl cellulose and is

able to cover lesions and protect against painful stimulation [14]. Several mucoadhesive products (Gelclair, MuGuard), or the hypersaturated CaPO₄ solution in Caphosol are coming onto the market. These medical products form a barrier in order to reduce pain. Whether or not these film-forming solutions will reduce the duration and severity of mucositis in clinical practice remains to be seen.

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References

1. Sonis ST. The pathophysiology of mucositis. *Nat Rev Cancer*. 2004; 4(4):277-84.
2. Sonis ST, Elting LS, Keefe D, et al. Perspectives on cancer therapy-induced mucosal injury, pathogenesis, measurement, epidemiology and consequences for patients. *Cancer*. 2004;100(10):1995-2025.
3. Keefe DM, Schubert MM, Elting LS, et al. Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer*. 2007;109(5):820-31.
4. Loprinzi CL, Cianflone SG, Dose AM, et al. A controlled evaluation of an allopurinol mouthwash as prophylaxis against 5-fluorouracil-induced stomatitis. *Cancer*. 1990;65(8):1879-82.
5. Fox RM, Woods RL, Tattersall MH, et al. Allopurinol modulation of fluorouracil toxicity. *Cancer Chemother Pharmacol*. 1981;5(3):151-5.
6. Fidler P, et al. Prospective evaluation of a chamomile mouthwash for prevention of 5-FU induced oral mucositis. *Cancer*. 1996;77(3):522-5.
7. Anderson PM, et al. Oral glutamine reduces the duration and severity of stomatitis after cytotoxic cancer chemotherapy. *Cancer* 1998;83(7):1433-9.
8. Jebb SA, et al. 5-fluorouracil and folinic acid-induced mucositis: no effect of oral glutamine supplementation. *Br J Cancer*. 1994;70(4):732-5.
9. van Zaanen HC, et al. Parenteral glutamine dipeptide supplementation does not ameliorate chemotherapy-induced toxicity. *Cancer*. 1994;74(10): 2879-84.
10. Okuno et al. Phase III controlled evaluation of glutamine for decreasing stomatitis in patients receiving fluorouracil-based chemotherapy. *Am J Clin Oncol*. 1999;22(3):258-61.
11. Keijzer A, Huijgens PC, van de Loosdrecht AA. *Br J Haematol*. 2007;136(6):856-60.
12. Oberbaum M, Yniv I, Ben-Gal Y, et al. Randomisierte, kontrollierte klinische Studie zum Nachweis der Wirksamkeit von Traumeel S bei der Behandlung von chemotherapieinduzierter Stomatitis bei Kindern nach Stammzelltransplantation. *Biol Med*. 2002;31:25-31.
13. Schubert MM, Newton RE. The use of benzydamine HCl for the management of cancer therapy-induced mucositis: preliminary report of a multicenter study. *Int J Tissue React*. 1987;9(2):99-103.
14. Keiner D, Möller C, Pöhlmann R. Benzydamin-Empfehlungen und Erfahrungen bei oraler Mukositis. *Arzneimitteltherapie*. 2008;26(2):62-7.