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Mucositis as a biological process: a new hypothesis for the development of chemotherapy-induced stomatotoxicity

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Abstract

Mucositis induced by antineoplastic drugs is an important, dose-limiting and costly side effect of cancer therapy. The ulcerative lesions which result are frequent systemic portals of entry for microorganisms which inhabit the mouth and consequently are often sources of systemic infection in the myelosuppressed patient. A number of clinical observations and the inconsistency of responses to a broad range of treatment modalities suggests a physiological complexity to mucositis which has not previously been comprehensively considered. We now propose a hypothesis as to the mechanism by which mucositis develops and resolves, which is based on four phases: an initial inflammatory/vascular phase; an epithelial phase; an ulcerative/bacteriological phase; and a healing phase. The role of cytokines as initiators and ampliers of the process is discussed, as is the potential influence of genetic factors in establishing risk and modifying the course of stomatotoxicity.

1. Introduction

Mucositis induced by antineoplastic drugs is an important, dose-limiting and costly side effect of cancer therapy. The ulcerative lesions produced by stomatotoxic chemotherapy are painful, restrict oral intake and, importantly, act as sites of secondary infection and portals of entry for the endogenous oral flora [1]. The overall frequency of mucositis varies and is influenced by the patient's diagnosis, age, level of oral health and the type, dose and frequency of drug administration [2]. Some degree of mucositis occurs in approximately 40% of patients who receive cancer chemotherapy [2]. About one-half of those individuals develop lesions of such severity as to require modification of their cancer treatment and/or parenteral analgesia. The condition's incidence is consistently higher among patients undergoing conditioning therapy for bone marrow transplant, continuous infusion therapy for breast and colon cancer and therapy for tumours of the head and neck. Among patients in high risk protocols, severe mucositis occurs with a frequency in excess of 60% [3–5].

As a consequence, it is not unusual for mucositis to necessitate a de-escalation of a planned dosing regimen. Because of the concomitant neutropenia which often occurs secondary to chemotherapy-induced myelosuppression, mucositis is a significant risk factor for systemic infection. Patients with mucositis and neutropenia have a relative risk of septicemia that is greater than four times that of individuals without mucositis [6].

In addition to its impact on quality of life and morbidity and mortality, mucositis also has a significant economic cost. For example, in patients undergoing autologous bone marrow transplant for haematological malignancies, the length of hospital stay among patients with mucositis is 5 days longer than patients without the condition [7]. At an average day rate of $4,500 for this patient population, this results in additional charges of $22,500 per patient.

A number of clinical observations suggest a physiological complexity in the development of mucositis. There is great variability in the stomatotoxicity of treatment regimens [8]. Patient age effects risk: younger patients develop mucositis more frequently than older patients receiving the same form of treatment for similar malignancies [2].

Once lesions develop, they heal more quickly in the younger population. Patient diagnosis affects risk as patients with haematological malignancies are more likely to develop lesions than are patients with solid

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tumours [2]. Concomitant radiation significantly enhances the stomatotoxic potential of chemotherapy. Patients who receive total body irradiation as part of a conditioning regimen for BMT develop mucositis of an intensity and frequency that exceeds patients who receive only chemotherapy [4,5]. The status of the patient's oral health is a well-established modifier [9,10]. Patients in good dental health who maintain scrupulous oral hygiene during cancer treatment tend to have fewer episodes of mucositis than do patients with poor oral health and maintenance. Finally, is the observation that patients of the same age, having the same tumour, receiving the same dose and form of chemotherapy and with equivalent oral status do not develop mucositis at the same frequency.

The development of effective treatment or the prevention and elimination of mucositis has been elusive. More than 50 published studies exist which document clinical investigations aimed at the palliation, prevention or reduction of stomatotoxicity. The range of medications that have been used for a mucositis indication is extensive and includes topical antimicrobials [11,12], marrow-stimulating cytokines [13–16], vitamins [17], inflammatory modifiers [18–21], palliative rinses [22], amino acid supplements [23], cryotherapy [24,25] and laser treatment [26]. While a lack of a standardised assessment scale confounds interpretation of outcomes [8,27–29], the analysis of treatment modalities suggests an inconsistency of response that is often hard to reconcile relative to the mechanism by which mucositis occurs. Simiarly, results of animal studies in which different cytokines and antimicrobials have been tested have also, at times, been puzzling.

Analyses of mucositis has been largely based on observational data. While there have been suggestions as to the mechansims whereby mucositis develops, for the most part, the pathophysiology of the condition is undefined. Although different potential therapeutic agents sometimes modified outcome, they did so in a way that was not always reproducible or consistent [30,31]. We now propose a hypothesis as to the mechanisms by which mucositis develops and heals which is based on animal and clinical data, but is to some degree still speculative.

Mucositis is a complex biological process which occurs in four phases (Fig. 1):

1. inflammatory/vascular phase;
2. epithelial phase;
3. ulcerative/bacteriological phase;
4. healing phase.

Each phase is interdependent and is the consequence of a series of actions mediated by cytokines, the direct effect of the chemotherapeutic drug on the epithelium, the oral bacterial flora and the status of the patient's bone marrow. As demonstrated by observations in models of graft versus host disease, injury to host tissues elicited by radiation and/or chemotherapy is capable of causing the release of cytokines from the epithelium and connective tissues [32,33]. Chemotherapy, in particular, affects the release of both interleukin-1 (IL-1) and tumour necrosis factor-alpha from the epithelium [34]. Ionising radiation, at doses which in themselves are not directly damaging to tissue, also causes the release of these cytokines from the epithelium and connective tissues [35]. Tumour necrosis factor is capable of causing tissue damage [36] and may be an accelerating and initiating event in the mucositis process. IL-1 incites an inflammatory response resulting in increased subepithelial vascularity [37] with a potential consequent increase in the local levels of cytotoxic agent.

It is likely that this response is relatively acute. Early sequential histological data obtained from mice treated with bleomycin or 5-fluorouracil (5-*FU*) demonstrate more cellularity of the subepithelial tissue, vascular dilitation, and leukocyte margination only 24 h after drug administration [38]. The inflammatory/vascular response is probably not as specific to certain classes of chemotherapeutic agents as is the epithelial phase of therapy. In addition, the concomitant use of radiation and chemotherapy is likely to amplify and prolong the release of cytokines and thereby exacerbate tissue response.

The epithelial phase is probably the best documented. Dividing cells of the oral mucosal epithelium are nonspecifically affected by many antineoplastic agents [39]. It is apparent that not all cancer chemotherapeutic drugs are equally active in this role; those drugs which affect DNA synthesis (the S phase of the cell cycle) seem to be the most efficient.

Thus, antimetabolites, such as methotrexate, 5-FU and cytarabine, which are cell a cycle, phase specific agents affecting the S phase, are more stomatotoxic than are drugs which are cycle phase non-specific drugs. Support for the hypothesis that epithelial basal cell damage leads to mucositis comes from clinical and experimental observations. Children, who typically have a higher proliferating fraction of basal cells are three times more likely to develop mucositis than are elderly adults in whom the basal cell proliferative rate has slowed [40]. The administration of epidermal growth factor to animals prior to the administration of 5-FU markedly increases the incidence of mucositis, most likely by increasing the rate of basal cell proliferation and thereby sensitising the cells to the stomatotoxic effects of chemotherapy [41]. Finally, temporarily taking basal cells out of cycle with transforming growth factor-β3 appears to be stomatoprotective [42,43], as does modification of apoptotic cell death [44].

The epithelial phase may be the most profound in terms of the production of ulcerative lesions. Reduced epithelial renewal results in atrophy and typically begins

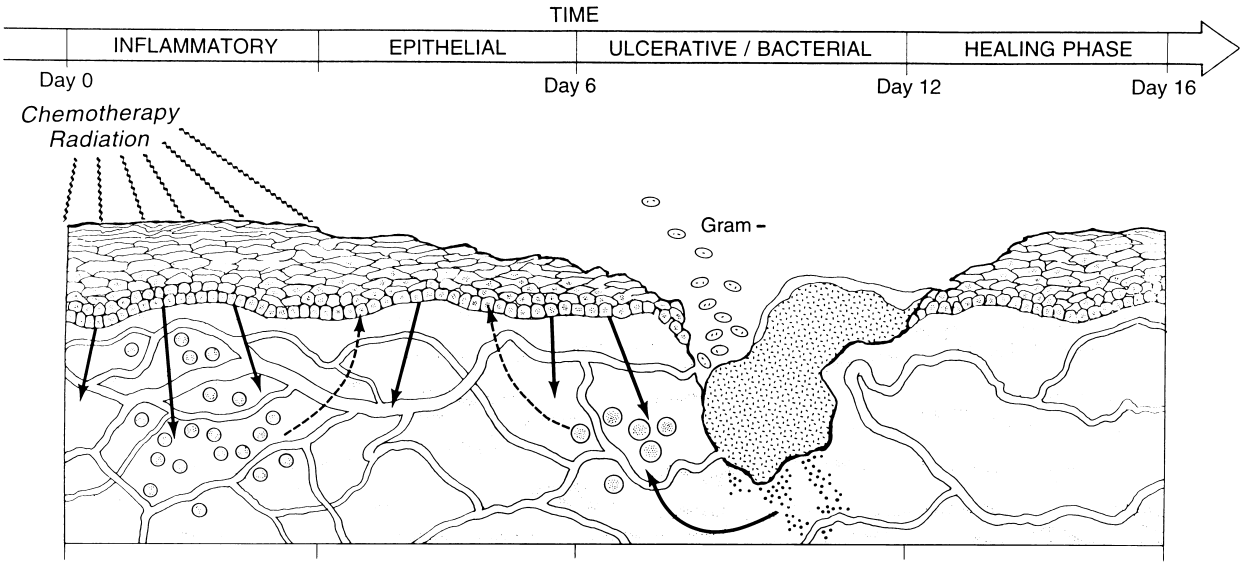

Fig. 1. The four phases of mucositis. The times indicated may vary slightly. Phase 1. Inflammatory/vascular phase. Shortly after the administration of radiation or chemotherapy cytokines are released from the epithelial tissue. These include tumour necrosis factor-α, interleukin-1 and perhaps, interleukin-6. Ionising radiation also incites cytokine release from the adjacent connective tissue. It is likely that these cytokines cause local tissue damage as the initiating event in the development of mucositis. Increased vascularity caused by IL-1 may result in additional concentrations of cytotoxic drug in the mucosa. Increased submucosal cellularity is evident at this stage. Phase 2. Epithelial phase. Both radiation and chemotherapy, especially with drugs effecting the S phase of the cell cycle, impact on the dividing cells of the oral basal epithelium, resulting in reduced epithelial renewal, atrophy and ulceration. The latter is most likely exacerbated by functional trauma and amplified by a flood of locally produced cytokines. Phase 3. Ulcerative/bacterial phase. The ulcerative phase is the most symptomatic and perhaps the most complex. Localised areas of full-thickness erosions occur which often become covered by a fibrinous pseudomembrane. Secondary bacterial colonisation of the lesion occurs with a mixed flora, including many gram negative organisms, providing a source of endotoxin (lipopolysaccharides) which further stimulate cytokine release from connective tissue borne around the cells. These cytokines, plus nitric oxide, serve to intensify the patient's condition. Importantly, from the standpoint of overall morbidity, the ulcerative phase generally occurs at the time of the patient's maximum neutropenia. Phase 4. Healing. The healing phase consists of a renewal of epithelial proliferation and differentiation, normalisation of the peripheral white blood cell count and re-establishment of the local microbial flora.

about 4–5 days after drug administration. It is initially synchonous with the inflammatory/vascular phase (G. Shklar, personal communication). It is probable that the marked erythema noted in many chemotherapy recipients [45] represents a combination of increased vascularity and reduced epithelial thickness. In addition, a flood of locally produced cytokines may amplify tissue destruction. Once the tissue becomes atrophic and its renewal is inhibited, functional trauma leads to ulceration.

The ulcerative phase is the most symptomatic and perhaps the most biologically complex phase of mucositis, as it presents the opportunity for both intrinsic and extrinsic factors to interact. Additionally, it is the time at which mucositis has the greatest potential impact on the patient's well-being. By the time ulceration is clinically apparent, typically about 1 week after the administration of the drug, early evidence of neutropenia is notable.

The severity of neutropenia progresses to a nadir, usually 14 days after the initiation of therapy and about 3 or 4 days after peak mucositis [46,47]. Bacterial colonisation of mucosal ulceration is a common finding leading to local secondary infection and, as previously noted, a microbiological resevoir for a systemic influx of organisms. Importantly, the oral flora of neutropenic patients differs from that of the healthy population in that it is rich in gram negative organisms, in addition to typical alpha-haemolytic streptococci [48].

The result is a flow of endotoxin (lipopolysaccharides) into submucosal tissue where it is likely to interact with tissue-borne mononuclear cells to cause the release of additional IL-1 and TNF and the production of nitric oxide [49], all of which may play an amplifying role in the patient's local mucosal injury.

It is important to note that it is quite possible that a role exists for transcription factors which modify the genetic expression of cytokines and enzymes which are critical in producing tissue damage [50]. Such factors, such as NF-kappa B, increase the rate of gene transcription and thereby the rate of messenger RNA and protein production [51].

While environmental modification of transcription factor expression has been described, the impact of chemotherapy has yet to be investigated. In addition, it seems possible that genetic influences on inflammatory response might offer at least a partial explanation for the variance in patient response to antineoplastic therapy.

The final phase of mucositis is that which is related to healing, and includes elements related to cell proliferation

and differentiation, normalisation of peripheral blood white cells and control of the local bacterial flora. The rapidity with which this phase proceeds affects the duration of the condition, but probably not peak intensity. Any factor which negatively impacts on wound healing will undoubtedly affect this phase.

The hypothetical mechanism proposed here for mucositis development and healing attempts to correlate a variety of clinical and laboratory findings into a comprehensive picture of the condition. It seems likely that additional detail will result as more research is done in this area. Importantly, this model offers a variety of therapeutic opportunities which could be directed at any of the four phases of the condition. With the increased use of aggressive chemotherapeutic regimens, the importance of mucositis as a limiting toxicity is escalating, making its control an important priority in clinical oncology.

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