OECD

Organization for Economic Co-operation and Development, an international organization helping governments solve the economic, social and governance challenges of a globalized economy.

Oncogenes

Mutated genes that are the cause of a cancer. The normal gene is called the proto-oncogene. These genes are usually involved in the regulation of cell growth or survival or the intermediate steps in those processes.

Opportunistic infection

Infections with bacteria, viruses, fungi, or protozoa to which individuals with a normal immune system are not usually susceptible. That is, infections that are caused by microbes that are not very infectious, but that can be so when the normal immune system is not functioning properly.

Opsonins

A process by which bacteria are altered by the attachment of antibody so that they are more readily and more efficiently engulfed by phagocytes.

Opsonization

Coating of bacteria or cells with complement (mainly C3b) or immunoglobulins. Opsonization serves as an identification for attachment by phagocytic cells, which possess receptors for C3b or antibody.

Oral Mucositis and Immunotoxicology

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Synonyms
Mucositis, stomatitis, ulcerative mucositis, ulcerative stomatitis, radiation mucositis, oral ulcer.

Definition
Oral mucositis is a frequent toxicological complication of high-dose chemotherapy as well as head and neck radiotherapy. This insidious condition manifests as inflammation of the moist mucosal lining the mouth and back of the throat and ranges from redness to severe ulceration over vast portions of the region. Symptoms of oral mucositis vary from local pain and discomfort to the inability to chew and/or swallow food or fluids, or to communicate.

Characteristics
Oral mucositis induced from either chemotherapy or radiotherapy is characterized by painful and often incapacitating ulcerative lesions of the oropharyngeal mucosa (1). Chemotherapy-induced mucositis often presents as lesions involving the buccal and tongue mucosa, the soft palate, and the floor of the mouth. In contrast to this broad area of injury associated with chemotherapy, patients being treated for head and neck cancers with ionizing radiation manifest mucositis on those oral mu-
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Cosal sites that lie in the direct path of radiation beam. The targeted oropharyngeal mucosa is lined by mucus membranes with a high mitotic index and is exceptionally sensitive to the antiproliferative effects of chemotherapy and radiotherapy.

At the tissue and cellular level, oral mucositis manifests initially as hypoplasia and destruction of superficial epithelial cells along with a lack of cell renewal. The subsequent erythematous areas proceed to desquamation and eventually ulcers covered by an exudate. From the host defense perspective, cancer treatment and resultant oral ulcers serve to weaken the defense system of the lining of the mouth leading to marked local infections. In addition, the potential for systemic infection due to opportunistic and acquired oral flora has been documented in cancer patients. This further complicates the already challenging health status of immunosuppressed patients where morbidity and mortality due to infection is of prime concern. While not considered life-threatening to the extent that chemotherapy-induced myelosuppression has historically been, oral mucositis is often identified by cancer patients as the single worst side effect of therapy. Symptoms may be so severe that they may limit a patient's ability to tolerate their chemotherapy or radiotherapy, resulting in delayed or shortened treatment and limited efficacy (2).

More recent research has broadened our understanding to suggest a more complex pathology with multifaceted interactions between connective tissue, endothelium and epithelium, myelosuppression and the oral microenvironment. A conceptual model for oral mucositis outlining the probable pathophysiology was published by Sonis in 1998 (3). In this model, mucositis as broken down into four phases (also see Figure 1):

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

**Inflammatory/Vascular Phase**

In this early phase, chemotherapy or radiotherapy directly or indirectly induce events leading to local inflammatory events, including reactive oxygen-induced cell damage, NF-kB/early response gene activation, and proinflammatory cytokine induction, all of which serve as a foundation for local tissue damage and initiate the events leading to development of mucositis.

**Epithelial Phase**

Dividing cells of the epithelium begin to atrophy and cell renewal is diminished in the face of any continued antiproliferative cancer therapy. Inflammatory events serve to augment the negative effects of tissue destruction.
Ulcerative/Bacteriological Phase
This is generally considered to be the most symptomatic phase with ulcerative erosions of the mucosa and an altered opportunistic microbial microenvironment.

Healing Phase
This involves renewal of the epithelial cell population, re-establishment of microbial homeostasis and local immune function.

While oral mucositis is biologically complex and progresses as a continuum of these phases, the depiction outlined by Sonis in 1998 allows a focus on the characteristic and likely primary events of the disorder as it progresses from initiation to healing. Research conducted over the last 5 years (4,5) has served to add support for the model put forth by Sonis and elucidates in greater detail the cellular and subcellular events associated with oral mucositis. Considering the involvement of reactive oxygen species (ROS) in mediating other manifestations of chemotherapy or radiation toxicity, it seems likely that ROS play a role in the initiation and progression of mucosal injury (5).

Preclinical Relevance
Oral mucositis remains under extensive laboratory investigation. Animal models of mucositis have been developed in a variety of species using radiation alone or both chemotherapy and radiation protocols. Possessing a cheek pouch accessible to treatment and observation, the hamster has provided much of the currently available preclinical information, though rodents have also been used with some success. Critical understanding into the roles of mucosal immune dysregulation and wound healing are imperative areas of preclinical research that will improve prospects for effective prophylactic or treatment strategies.

Relevance to Humans
Myelosuppression was previously the major dose-limiting toxicity associated with cancer therapies. With therapeutic advances in the 1980s relative to infection prevention and reduced myelosuppression via growth factors such as granulocyte colony stimulating factor (G-CSF), thrombopoietin and erythropoietin, non-hematologic toxicities have now become significant dose-limiting concerns. Of these non-hematologic toxicities, oral mucositis has emerged as one of the most problematic toxicities associated with current therapeutic regimens with direct impacts on cure rates and long-term survival (2). Considering the frequency of oral mucositis, which is determined by the type of cancer therapy (e.g. approximately 40% in patients treated with systemic chemotherapy to nearly 100% of patients treated for head and neck cancer), this unmet clinical need remains an active area of clinical investigation.

Regulatory Environment
A plethora of approaches have undergone clinical assessment around the world with no single approach showing any consistent benefit. Currently no medication is approved by the Food and Drug Administration (FDA) to prevent or treat oral mucositis. While clinical trials investigating a variety of novel approaches continue, most patients and clinics manage symptoms with morphine or other narcotic analgesics, with mouth rinses, changes in diet, and cold liquids.

The FDA recognizes that oral mucositis is a serious illness that needs to be addressed expeditiously and as such has granted Fast Track designation to some candidate therapeutics in clinical development. Fast Track designation is intended to expedite the regulatory review and approval process for a product and claim that addresses a significant unmet medical need.

References