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Relationship of Chemotherapy-induced Mucositis and Myelosuppression in Hamsters

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ULCERATIVE MUCOSITIS of the mouth is a common, painful and, at times, dose-limiting complication of cancer chemotherapy [1]. Not only do the lesions produce severe discomfort resulting in patient misery and reduced oral intake, but the loss of epithelial integrity predisposes to the systemic influx of the oral flora with the consequence of sepsis [2, 3]. Breakdown of the oral mucosa occurs initially as the result of the inhibition of basal epithelial regeneration by the chemotherapeutic agent and is often prolonged and exaggerated by the myelosuppressive effects of the drug.

That the relationship between the oral changes noted in response to chemotherapy and the degree of myelosuppression is not casual has been suggested by anecdotal data and clinical observations [4]. In an effort to understand better the relationship between myelosuppression and mucositis and, in particular to define the temporal relationship between these variables, we undertook a preliminary study using an animal model which closely mimics the human condition [5].

Sixteen 8-week-old Golden Syrian hamsters (Charles River Laboratories, Wilmington, Massachusetts) weighing between 100 g and 142 g were used. Animals were individually numbered using ear tags. Mucositis was produced using three intraperitoneal injections of 5-fluorouracil (60 mg/kg) administered on days 0, 5 and 10 and superficial irritation of the right cheek pouch on days 0, 1, 2 and 3. Animals were weighed daily. At the same time, the right cheek pouch was everted and photographed. Mucositis was scored blindly at the conclusion of the clinical protocol by a single individual using coded photographs of each cheek pouch. The severity of mucositis was determined using a standardised scale which ranged from 0 (no mucositis) to 4 (severe, diffuse ulcerations).

Using randomised prospective selection, four animals were killed on days 8, 12, 16 and 20. At that time, the animals' femurs were removed and sectioned; half was preserved in 10% formalin and the other was placed in Zenker's solution to which 0.5% glacial acetic acid was added immediately prior to use. Specimens were prepared for histological examination in routine fashion. Sections were stained with haematoxylin and eosin. Bone marrow cellularity was determined by two observers in blinded fashion by establishing the percentage of cells in the intrabecullar space. Ninety eight per cent of specimens so evaluated were of adequate size and fixation. The remaining 2% were not included for study.

As expected, a temporal relationship was noted between the development of ulcerative mucositis and the degree of myelosuppression. Breakdown of the oral mucosa preceded the maximum myelosuppression. Similarly, healing of the oral mucosa occurred before recovery of the marrow. By day 5 of the study, severe mucositis was a consistent finding. Three days later, the first time the animals were killed, only 70% of animals demonstrated severe mucositis, yet marrow cellularity was 41% compared with a baseline of 80%. While by day 12 a significant improvement in mucositis was noted (40% of animals had severe mucositis), marrow cellularity continued to drop to a nadir of 32.5%. 20% of hamsters demonstrated severe mucositis throughout the remainder of the experiment. Recovery of myelosuppression was seen by day 16 (79%) and appeared to plateau as it was 81% at day 20. Regression analysis confirmed the correlation between the clinical mucositis scores and level of myelosuppression ($r=-0.6$).

It seems probable that the differences in the mitotic activity of the two tissue compartments studied is the most likely explanation for our observations. The turnover time of the hamster oral mucosa is approximately 7 days, while that of the marrow is somewhat longer. This difference in mitotic frequency suggests that the mucosa is likely to be more acutely susceptible to the antimitotic impact of the 5-fluorouracil than are the cells of the marrow. The length of time that both groups of cells were inhibited was essentially the same. Since the oral mucosal cells were first effected, mucosal healing was completed before the marrow fully recovered.

While studies with more time points would help to further define the relationship between mucositis and myelosuppression, it seems clear that a temporal relationship between the two is real. Additional investigations may help to elucidate the mechanisms for this interaction.

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