THE EFFECT OF CYTOTOXIC CHEMOTHERAPY ON THE MUCOSA OF THE SMALL INTESTINE

by

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Abstract

This thesis investigated the effect of chemotherapy on the mucosa of the small intestine both in humans and in rats.

Introduction: Mucositis after chemotherapy for cancer is becoming increasingly important, both as a cause of patient morbidity and occasional mortality, and because the resulting toxicity potentially limits the dose, and therefore the chance of cancer cure. The reasons for mucositis becoming more predominant are two-fold; protection from bone marrow toxicity by colony stimulating factors has led to increased doses of drugs being given, and there is a drive to increase doses in order to increase cure rate. The aims of the project were to investigate the prevalence, duration and severity of mucositis in the gastrointestinal tract following chemotherapy.

Literature review: this covers the areas of mucositis, small intestinal morphology, apoptosis, nutrition and malignancy, intestinal sugar permeability, and the effects of chemotherapy on the small intestine. Most chemotherapeutic agents kill rapidly dividing cells, making the gastrointestinal tract particularly vulnerable. Cytotoxic agents kill cells at different levels of the crypt hierarchy, leading to crypt hypoplasia followed by regeneration. The exact mechanism of mucositis is not known, nor is it apparent if there are functional abnormalities of absorption, and how these correlate with symptoms such as bloating, abdominal pain and diarrhoea.

Research plan: the project is split into four areas:

1. Mucositis was studied after high dose chemotherapy and autologous blood stem cell transplantation in forty patients. Symptoms were recorded and mucositis assessed indirectly by an intestinal sugar permeability test. Oral mucositis occurred in 100% of patients, with 50% having grade 3 or 4 oral mucositis. Small intestinal symptoms (diarrhoea, vomiting) of grade 3 or 4 occurred in 41%, permeability peaking at an increase over baseline value of 6.8-fold at day 14. The conclusion from this study was that high dose chemotherapy causes a transient increase in intestinal permeability associated with small intestinal symptoms.

2. A second study was undertaken of small intestinal mucositis after both standard and high-dose chemotherapy, to further define the prevalence, duration and symptom severity at intervals of 3 days up to 14 days, and then at 28 days after chemotherapy. Symptoms were scored by questionnaire, and mucositis was assessed by an iso-osmolar sugar permeability test. Nutritional changes were small. Serum endotoxin and combined breath tests for bacterial overgrowth were unhelpful.

3. A third study assessed small intestinal mucosal histology following chemotherapy. Morphological changes began with a transient increase in crypt apoptosis at day 1 after chemotherapy, followed by a reduction in villus area, crypt length and mitotic index by day 3, the latter two rebounding to greater than baseline levels at day 16. Thus the new finding of this study was that mucositis is due to induction of early crypt apoptosis that precedes hypoplastic villous atrophy.

4. The effect of oral glutamine on ameliorating intestinal mucositis was assessed in the dark agouti (DA) rat given subcutaneous implants of isogeneic mammary adenocarcinoma and treated with methotrexate (MTX). Glutamine had no significant effect on tumour growth, nor did it ameliorate mucositis as assessed by apoptosis and villus area, crypt length and mitotic count. The conclusions were that this is a good model for further study of mucositis, and that glutamine does not protect against small intestinal mucositis.

Conclusions: The conclusion of this thesis is that small intestinal mucositis occurs symptomatically in a significant number of patients, and peaks 3-7 days after treatment. The principal mechanism is apoptosis of intestinal crypts that results in intestinal hypoplasia.