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A Double-blind Comparison Study of Tropisetron and Placebo in the Prevention of Radiation-induced Diarrhoea

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RADIATION TO fields which encompass intestinal mucosa produces diarrhoea as a major symptom. The occurrence and severity of diarrhoea varies between patients and with the fraction size, duration of treatment and total dose of radiation [1]. During recent years, prevention of diarrhoea has focused on many different measures such as careful treatment planning, prophylactic use of pharmacological substances (loperamide, acetysallicylate, sucralfate) and diet. However, no effective prophylaxis or treatment has yet emerged [2–4].

The known side-effect of 5-HT_3 receptor antagonists, i.e. constipation, might be helpful in the prevention of radiation-induced diarrhoea. Although tropisetron is one of the first selective antagonists of the 5-HT_3 receptor, clinical experience of its use in radiotherapy to control diarrhoea is sparse, particularly regarding long-term administration [5,6]. The purpose of this study was to assess the prophylactic value of tropisetron in the prevention and treatment of radiation-induced diarrhoea in a group of patients receiving pelvic radiotherapy.

From October 1988 to April 1990, 33 patients between the ages of 38 and 79 years, with histologically confirmed tumours of prostate (10 patients), urinary bladder (13 patients) and cervix (10 patients), were recruited into the study. The trial was designed as a prospective, randomised, double-blind study. Informed consent was obtained from all patients, who were randomised to receive either 6 weeks of treatment with tropisetron (25 mg daily), 3 weeks of treatment with a placebo followed by 3 weeks of treatment with tropisetron (25 mg), or 6 weeks of treatment with placebo. The treatment with drug or placebo commenced the same day as the radiotherapy.

The patients were scheduled to receive 2 Gy per fraction radiotherapy to the pelvic area (target volume) for at least 4 days per week for between 5 and 6.5 consecutive weeks. Patients were given standard dietary advice and were seen by a doctor at least once weekly. The patients were requested to complete a daily card stating the number of bowel actions, the severity of abdominal pain associated with the diarrhoea and the consistency of the stools. Acute gastrointestinal symptoms were managed according to normal practice. 9 patients withdrew from the study: 4 with adverse events, 4 because of insufficient efficacy and 1 patient because of protocol violations. All 33 patients were included in the evaluation of efficacy and tolerance.

Overall, no between-treatment differences in the number of bowel actions was found during the study. The severity of abdominal pain was low for all three treatment groups throughout the study and there was no discernible difference in the percentage of patients experiencing watery/liquid stools and blood/mucus in stools during the study. None of the patients suffered any weight loss during the course of radiation treatment. 18 patients (54.5%) reported a total of 38 adverse events during the study; 5 who received tropisetron throughout the study, 9 patients who were randomised to the placebo/tropisetron group and 4 patients in the placebo group. The adverse events were mostly gastrointestinal symptoms such as constipation, nausea, abdominal pain and flatulence. Constipation occurred in 1 patient in the placebo group, in 4 patients in the placebo/tropisetron group and in 1 patient who received tropisetron throughout the study.

The absence of an anti-diarrhoeal effect for tropisetron was probably not due to a low dose. We used 25 mg daily, while in chemotherapy studies the effective antiemetic dose has been shown to be 5 mg daily [7]. It seems more probable that neuroendocrine mechanisms operating via 5-HT_3 receptors are not involved in the pathogenesis of radiation-induced diarrhoea or that other mechanisms dominate, such as loss of resorptive intestinal mucosal surface after radiotherapy [8,9].

This study only concerned the prophylaxis of radiation-induced diarrhoea occuring during treatment in patients where diet was not strictly regulated. This is however, the clinical situation in which diarrhoea is most frequently troublesome. We conclude that this schedule of tropisetron is not of value in the prevention of radiation-induced diarrhoea, despite the fact that 18% of our patients experienced constipation.

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