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Short Report

Pentoxifylline to Treat Radiation Proctitis: A Small and Inconclusive Randomised Trial

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ABSTRACT:
This prospective randomised controlled study of 40 patients could not show a statistically significant advantage with 6 months of pentoxifylline compared with standard measures for late radiation-induced rectal bleeding. However, a modest benefit cannot be excluded and larger randomised placebo-controlled trials with longer durations of pentoxifylline treatment may be justified. Venkitaraman, R. *et al*. (2008). *Clinical Oncology* 20, 288–292

Key words: Pentoxifylline, radiotherapy, rectal bleeding

Introduction

Proctitis is a common late side-effect of pelvic radiotherapy [1]. The incidence of rectal bleeding in prostate cancer patients is clearly related to the radiotherapy technique and to the dose delivered [2–6]. A variety of pharmacological approaches have been used to treat radiation proctitis, including topical/oral steroids, rectal sucralfate suspension, oral amino-salicylic acid derivatives, metronidazole, topical intrarectal formalin, hyperbaric oxygen and cautery with an endoscopic Nd:YAG laser [1,6–16]. Randomised studies have shown significant benefits with sucralfate suspension enema for treating late radiation proctitis [10,14,17].

Pentoxifylline (Trental®, Aventis Pharma, New Jersey, USA), a methyl xanthine derivative, has been shown to increase erythrocyte and leukocyte deformability, inhibit neutrophil adhesion and activation, reduce blood viscosity, stimulate prostacyclin release causing decreased platelet aggregation and thrombus formation, increase fibrinolytic activity, improve tissue oxygenation, act as a free radical scavenger and inhibit the production of tumour necrosis factor and interleukin-6 in *in vitro* studies [18–21]. It is generally well tolerated with minimal side-effects [22,23]. It has been shown to prevent or correct pathological changes due to vascular impairment in various conditions, such as peripheral vascular disease, proliferative diabetes, cerebrovascular insufficiency, and to improve survival of compromised surgical flaps and pedicle grafts [24].

Radiation proctitis is thought to be an ischaemic phenomenon from capillary injury [25]. The enhancement of microvascular blood flow by pentoxifylline may promote the healing of soft tissue injury in the rectum and bladder after radiation and delay the progression of telangiectasia [23,26]. Pentoxifylline has been used either as a single agent or in combination with tocopherol for treating radiotherapy-related pelvic insufficiency fractures, osteoradionecrosis and soft tissue fibrosis, pain and necrosis, with promising results [22,24,27–38]. Three published randomised studies comparing pentoxifylline with conservative treatment have shown significant benefits for treating late normal tissue damage after radiotherapy for breast and head and neck cancers, whereas one placebo-controlled randomised study has shown no benefit with pentoxifylline for treating chronic arm oedema and fibrosis after radiotherapy for breast cancer [34,38–40].

We initiated a prospective randomised controlled trial to test the hypothesis that pentoxifylline can reduce the frequency of rectal bleeding after pelvic radiotherapy.

Materials and Methods

Inclusion Criteria

Patients from the Royal Marsden Hospital who received radical radiotherapy for prostate cancer during the period 1983–2000 were enrolled during the study period 1994–2002 after written informed consent. The study was approved by the Research Ethics Committee of the Royal Marsden Hospital NHS Trust. Patients at inclusion had symptomatic late morbidity with at least one episode of rectal bleeding more than 6 months since pelvic radiotherapy. Eligible patients had no evidence of disease progression at the primary tumour site or rectum, had normal serum fibrinogen levels, were not on anti-coagulants or

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anti-platelet medications and had a life expectancy of more than 6 months.

All patients received standard treatment for late radiation-induced bleeding, including blood transfusion, analgesics, anti-inflammatory agents, dietary modification, local steroids applications or sucralfate enemas. Sigmoidoscopic visualisation and cautery of bleeding points were carried out as clinically indicated. Patients were randomised to either the control group managed with standard therapies or the study group of standard therapies plus oral pentoxifylline 400 mg three times daily for 6 months. The study was non-blind and the patients in the control group did not receive placebo. The randomisation was carried out in-house using Randomised Computed Blocks software.

Clinical Assessments

Baseline assessments included a detailed history, a physical examination including a digital rectal examination, complete blood counts, coagulation profile and an examination of stool and urine samples. Hypofibrinogenaemia is a known side-effect of pentoxifylline and all patients in the study group had plasma fibrinogen levels measured every 4 weeks [20]. All patients had sigmoidoscopy/colonoscopy to visualise any rectal ulcers or stricture at baseline and later on in the study if the bleeding was not controlled with conservative measures. The frequency and severity of the rectal bleeding episodes were recorded by each patient using a 'daily patient symptom diary'. Baseline data of the daily rectal bleeding episodes were recorded for 4 weeks before randomisation and study data were collected for 6 months after randomisation. Patients were seen fortnightly during the study period and formally assessed using a late morbidity checklist. Patients with disease progression at the primary site or requiring any systemic treatment for relapse were removed from the study.

Statistical Methods

The primary end point measured was cessation of rectal bleeding for a minimum continuous period of 1 week during the study and complete success of treatment was defined as continuous cessation of bleeding until the end of the study period. A recurrence of bleeding or surgical intervention for rectal bleeding during the study period was considered as treatment failure. The secondary outcome measures analysed were time to cessation of bleeding and duration of freedom from bleeding.

The sample size was determined from the main end point, i.e. the cessation of rectal bleeding for 1 week. We had planned to accrue 80 patients over a period of 4 years, for the study to have an 80% power of detecting a reduction in the incidence of patients with recurrent symptoms from 60% with standard conservative management to 30% with the addition of pentoxifylline at a 5% statistical significance. The statistical analysis was conducted with SPSS 13.0 statistical software. The significance of differences for variables was assessed by Wilcoxon's signed-rank test and difference with $P < 0.05$ was considered significant. For each 2-week block for the first 3 months and 4-week blocks for the final 3 months, the proportion of patients with rectal bleeding was compared with the baseline data for the respective study groups.

Results

The analysis was undertaken after a total of 50 patients had been randomised, in view of the slow recruitment rate and to assess whether the trial should be discontinued as futile. Ten patients were excluded because of inadequate baseline morbidity and follow-up information, and data from 40 patients were analysed. The median time from radiotherapy to trial entry was 733 days (range 231—4070). The median radiotherapy dose delivered to the isocentre was 64 Gy (range 54—74). Twenty patients were randomised to each group and both groups were well balanced with regard to patient and disease characteristics.

Sixteen patients in the pentoxifylline group and 12 in the control group had cessation of rectal bleeding for a week or more ($P = 0.17$). The median time to cessation of bleeding was 22 days (range 1—119 days) in the study group and 95 days (range 13—172) in the control group ($P = 0.12$). However, at least one episode of recurrent bleeding occurred in 14 of the 16 patients in the study group and in all the 12 patients who had cessation of bleeding in the control group. The median duration of freedom from bleeding was 12 days (range 8—290) in the study group and 11 days (range 7—133) in the control group. There was an overall trend to a reduction of rectal bleeding episodes with time in both groups of the study, as judged by the proportion of days in which one or more rectal bleeding episode was reported (Table 1). There was a suggestion of a reduction in the proportion of days on which bleeding occurred compared with baseline in the pentoxifylline group from week 3 onward. Both the control group and the pentoxifylline group seemed to have improved by week 17 (Fig. 1). More severe bleeding (two or more daily bleeding episodes) only reduced in the pentoxifylline group after 4 months of treatment.

Table 1 — Proportion of days of rectal bleeding episodes per month in the patients analysed ($n = 40$)

Months in study	Proportion of days with one or more rectal bleeding episode		Proportion of days with two or more rectal bleeding episodes	
	Pentoxifylline	Control	Pentoxifylline	Control
Baseline	0.38	0.54	0.06	0.10
1	0.30	0.49	0.05	0.12
2	0.31	0.51	0.10	0.14
3	0.30	0.52	0.06	0.15
4	0.29	0.50	0.02	0.15
5	0.22	0.40	0.03	0.10
6	0.20	0.39	0.02	0.12