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Tropisetron Compared With a Metoclopramide-based Regimen in the Prevention of Chemotherapy-induced Nausea and Vomiting

H. Anderson, N. Thatcher, A. Howell, K. Logan, T. Sage and K.M. de Bruijn

This randomised, open, parallel group study compared the antiemetic efficacy and tolerability of tropisetron with metoclopramide plus lorazepam in 102 patients receiving a first course of non-cisplatin-containing chemotherapy. Control of acute vomiting by tropisetron was significantly superior to that of the metoclopramide regimen, with total control (no vomiting) in 45% of 51 patients in the tropisetron group compared with 22% of 51 patients in the metoclopramide group ($P = 0.013$); total and partial control (< 5 vomits) occurred in 67 and 47% of patients, respectively ($P = 0.044$). The incidences of acute nausea and of delayed nausea and emesis were similar in the two treatment groups. Both tropisetron and metoclopramide were well tolerated; no adverse effects were attributed to tropisetron administration with the exception of headache. One patient in the metoclopramide group reported confusion and tremor thought to be related to the antiemetic therapy. Tropisetron is an effective and well-tolerated agent in the prevention of chemotherapy-induced vomiting. The control of acute nausea was similar in the two treatment groups, but tropisetron was superior to a metoclopramide-based regimen in the control of acute vomiting.

Key words: tropisetron, metoclopramide, lorazepam, chemotherapy-induced emesis, comparative study
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INTRODUCTION

NAUSEA AND vomiting are among the most frequent and distressing adverse effects of cancer chemotherapy. Failure to control chemotherapy-induced emesis has a detrimental effect upon patients' quality of life, increasing the likelihood of non-compliance with, or refusal of anticancer treatment [1]. Antiemetic regimens, including high doses of metoclopramide and corticosteroids, can control chemotherapy-induced emesis, but their effectiveness may be offset by poor tolerability [2, 3].

The 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonists are a new class of antiemetic agents, of which tropisetron (ICS 205-930, Navoban®; Sandoz Pharma Ltd, Basle, Switzerland) is a member. Early non-comparative clinical studies have shown tropisetron to be effective and well tolerated in patients receiving

highly emetogenic cancer chemotherapy [4, 5]. A 5-mg intravenous dose of tropisetron administered before chemotherapy can prevent both nausea and vomiting for 24 h in up to two-thirds of patients receiving high-dose cisplatin treatment [6]. Increasing the dose of tropisetron (up to a maximum of 40 mg) provided no additional benefit [7].

In view of the demonstrated efficacy of tropisetron in the prevention of cisplatin-induced nausea and vomiting, this open randomised, parallel group study was undertaken to investigate the antiemetic efficacy and tolerability of tropisetron in patients receiving non-cisplatin chemotherapy. Tropisetron 5 mg once daily was compared with a regimen of metoclopramide plus lorazepam that was standard antiemetic treatment during chemotherapy of this type at the time of the study. Antiemetic treatment was continued for 4 days after chemotherapy to allow assessment of the effects of the two regimens on both acute and delayed nausea and vomiting.

PATIENTS AND METHODS

A total of 102 patients, 31 males and 71 females, aged between 18 and 80 years, with a histologically confirmed diagnosis of ovarian, breast, lung cancer or soft tissue sarcoma and due to receive three consecutive courses of chemotherapy were included in the study. Exclusion criteria comprised: previous cancer chemotherapy; brain involvement or leptomeningeal disease; medical conditions likely to interfere with the evaluation of the study drug (e.g. abdominal surgery within the previous month) or which constituted risk to the patient (e.g. cardiac insufficiency, uncontrolled infection, hypersensitivity or drug allergy); liver enzyme or renal function tests of more than twice the normal value; alcoholism or drug abuse; use of drugs, other than the study medication, likely to influence emesis or diarrhoea; inability to cooperate with medical or nursing staff; childbearing potential without adequate contraception or lactation; and HIV positivity. The study was carried out in accordance with the guidelines laid down in the Tokyo and Venice amendments of the Declaration of Helsinki.

The demographic and baseline characteristics of the two treatment groups are presented in Table 1. There were no statistically significant differences between the groups with respect to sex, age, height and weight. At the time of study entry, 63 patients (62%) had at least one disease other than cancer. Coexisting disorders included lung disease (14 patients), hypertension (13 patients), cardiac disease (3 patients), migraine (3 patients), diabetes mellitus (2 patients) and peptic ulcer (1 patient).

Patients were assigned to one of three groups on the basis of their cancer type (ovarian cancer, breast cancer or soft tissue sarcoma, lung cancer). Five different chemotherapy regimens were used, as shown in Table 2. Enrolment of patients with breast cancer or soft tissue sarcoma was stopped early (when only 7 patients had been recruited) because the practice of treating these tumours with doxorubicin monotherapy had been abandoned.

Within each diagnosis group, patients were randomly assigned to receive tropisetron (n = 51) or a metoclopramide-based regimen (n = 51). Tropisetron treatment comprised a 5-mg dose given as an intravenous infusion over 15 min immediately before chemotherapy on day 1, followed by oral administration at a dosage of 5 mg once daily for the 3 days after chemotherapy (days 2 to 4). The metoclopramide-based regimen differed according to cancer diagnosis. Immediately before the start of chemotherapy, patients with ovarian cancer received lorazepam 2–4 mg plus metoclopramide 100 mg as an intravenous infusion over 1 h, patients in the breast cancer/soft tissue sarcoma group received metoclopramide 20 mg intravenously, and patients with lung cancer received lorazepam 2–4 mg plus metoclopramide 20–40 mg intravenously (as a slow intravenous bolus). After the start of chemotherapy, patients were given oral metoclopramide 20 mg (20–40 mg for those with lung cancer) every 4–6 h for the remainder of day 1 and then 20 mg three times daily on days 2–4. Thus, patients received a total metoclopramide dose of 2–5 mg/kg on day 1 and then 20–40 mg three times daily of days 2–4.

Concomitant medication was taken by 84 patients (82%) during the first course of chemotherapy, 69 (87%) of the 79 patients who received a second course of chemotherapy and 48

Table 1. Demographic and baseline characteristics of the antiemetic treatment groups

	Tropisetron	Metoclopramide*
Patients entered (n)	51	51
Male (n)	15 (29%)	16 (31%)
Female (n)	36 (71%)	35 (69%)
Mean age (years)	55.9	54.3
Mean weight (kg)	61.9	63.9
Mean height (cm)	162.9	164.9
Coexisting disease at entry (n)	29 (57%)	34 (67%)
Prior medication at entry (n)	32 (63%)	33 (65%)
Tumour type (n)		
Ovarian cancer	23 (45%)	25 (49%)
Small cell lung cancer	21 (41%)	19 (37%)
Non-small cell lung cancer	3 (6%)	4 (8%)
Breast carcinoma/soft tissue sarcoma	4 (8%)	3 (6%)

* ± lorazepam.

Table 2. Cancer chemotherapy regimens (given on day 1 unless otherwise indicated)

Diagnosis	Chemotherapy
Ovarian cancer (n = 48)*	Carboplatin 300 or 150 mg/m² + cyclophosphamide 600 or 300 mg/m² alternating with ifosfamide 5 or 2.5 g/m² + doxorubicin 50 or 25 mg/m²
Breast cancer or soft tissue sarcoma (n = 7)	Doxorubicin 75 mg/m²
Lung cancer	
Small cell (n = 40)	Carboplatin 300 mg/m² + ifosfamide 5 g/m² + etoposide 120 mg/m² on days 1 and 2 and 240 mg/m² on day 3
Non-small cell (n = 7)	Carboplatin 400 mg/m² + ifosfamide 5 g/m² + mitomycin C 6 mg/m²

* In chemotherapy course one, 33 patients (16 tropisetron, 17 metoclopramide) received the high-dose regimen and 15 (7 tropisetron, 8 metoclopramide) the low-dose regimen.

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(77%) of the 62 patients who received a third course. Although the concomitant use of drugs which were likely to influence emesis or diarrhoea was disallowed in the study protocol, 8–28% of patients in each course of chemotherapy took benzodiazepines as hypnotics and 24–50% received opioid analgesics. These drugs were being taken prior to the study, and their use was continued during the study. Use of concomitant medication was similar in the two antiemetic treatment groups.

The occurrence of nausea and vomiting was recorded during five consecutive 24-h periods (days 1–5) after the start of chemotherapy. After discharge from hospital, the patients recorded their symptoms on diary cards. Control of nausea and vomiting were defined as follows:

Vomiting	Total control—no vomits Partial control—one to four vomits No control—five or more vomits
Retches	These were counted as vomits
Nausea	Total control—no episodes of nausea Partial control—one to four episodes of nausea No control—five or more episodes of nausea

An episode of nausea was defined as any period of 1 h in which nausea occurred.

Patients who vomited five or more times within the first 24 h after chemotherapy were given alternative antiemetic therapy and withdrawn from the study on the grounds of treatment failure. Antiemetic treatment was also considered to have failed in patients who experienced persistent vomiting (two or more vomits on three consecutive days) after day 1 and were withdrawn from the study.

At the time of entry into the trial, body temperature, blood pressure and heart rate were measured, an ECG recorded, and routine haematological and biochemical laboratory tests performed. For each course of chemotherapy, vital signs were measured, before initiating antiemetic treatment, at 4-h intervals for 12 h after administration of the study drugs, and then every 12 h for as long as the patient remained in hospital. Laboratory tests were repeated between each course of chemotherapy. The nature and intensity of any adverse events occurring during antiemetic treatment were recorded.

Statistical methods

Results for the various types of malignancy and for the different forms of chemotherapy have been pooled for statistical analysis. Variation between chemotherapy groups was taken into account in the statistical methods used for antiemetic treatment group comparisons and results presented as two-sided P values based on the average response across all chemotherapy regimens. For efficacy data, the Breslow–Day test was used to verify the homogeneity of the odds ratio over the five regimens. Demographic characteristics of the treatment groups were compared using the Mantel–Haenszel test (sex) and the van Elteren test (age, height and weight). Rates of control of nausea and vomiting during the first course of chemotherapy were compared using the Mantel–Haenszel test or Fisher's exact test.

RESULTS

All of the 102 patients recruited were included in the efficacy evaluation for the first course of chemotherapy. 38 and 41 patients in the tropisetron and metoclopramide groups, respectively, were given the antiemetic study drug during a second course of chemotherapy and 26 and 36, respectively, during a third. Thus, 40 patients discontinued between the start and end of the study. The reasons for discontinuation of these 40 patients were: failure of antiemetic treatment according to the criteria of the protocol in 20 patients in the tropisetron group (10 failed course one, 10 course two) and 11 in the metoclopramide group (7 failed course one, 4 course two). Of the patients with failure of antiemetic control after the second course of chemotherapy, 8 of 10 on tropisetron had ovarian cancer and 1 of 4 on metoclopramide had ovarian cancer. In addition, 4 patients on metoclopramide discontinued due to: confusion (1), a request to withdraw from study (1), a myocardial infarction which precluded further chemotherapy (1) and chemotherapy given at another hospital (1). 5 patients in the tropisetron group were withdrawn because of cessation of chemotherapy due to a low creatinine clearance (2), progressive cancer (2), and 1 patient requested withdrawal because of severe nausea without emesis.

Acute nausea and vomiting

Control of vomiting and nausea in the two antiemetic treatment groups during the first 24 h of chemotherapy course one is shown in Figure 1. Total control of vomiting was achieved in 23 (45%) patients in the tropisetron group compared with 11 (22%)

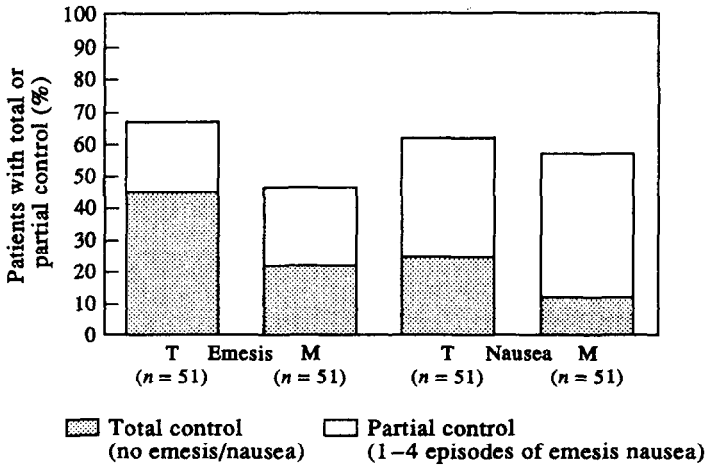

Figure 1. Control of nausea and vomiting in the first 24 h of chemotherapy course one in patients treated with tropisetron (T) or metoclopramide (M).

Table 3. Patients with total, and total and partial control of vomiting and nausea in the first 24 h of the second and third courses of chemotherapy

	Course 2		Course 3	
	T (n = 38)	M (n = 40)*	T (n = 26)	M (n = 36)
Vomiting				
Total control	4 (11%)	5 (13%)	8 (31%)	5 (14%)
Total + partial	17 (45%)	13 (33%)	18 (69%)	18 (50%)
Nausea				
Total control	4 (11%)	5 (13%)	7 (27%)	10 (28%)
Total + partial	16 (42%)	21 (53%)	16 (62%)	25 (69%)

T, tropisetron; M, metoclopramide ± lorazepam. * Data missing for 1 patient.

Table 4. Adverse events reported more than once in a treatment group (including events identified from patient diary data)

Event	Number (%) of courses	
	Tropisetron (n = 115)	Metoclopramide* (n = 128)
Headache	28 (24%)	12 (9%)
Constipation	10 (9%)	5 (4%)
Depression	4 (3%)	2 (2%)
Fatigue/somnolence	5 (4%)	4 (3%)
Confusion	1 (1%)	4 (3%)
Myocardial infarction	—	2 (2%)
Convulsions/tremor	—	4 (3%)
Migraine	2 (2%)	—

* ± lorazepam.

in the metoclopramide group (P = 0.013). Total or partial control of vomiting occurred in 34 (67%) tropisetron-treated patients and 24 (47%) patients in the metoclopramide group (P = 0.044). 13 (25%) tropisetron recipients and 6 (12%) metoclopramide patients were free from nausea during this period, with total or partial control of nausea in 32 (63%) patients and 29 (57%) patients, respectively. There were no statistically significant differences between the two antiemetic treatments with respect to total, or partial control of nausea. Rates of total control of acute vomiting in course one among patients with ovarian cancer and those with small cell lung cancer were comparable to those seen in the overall study population.

Compared with the first course of chemotherapy, control rates for acute vomiting and nausea were similar or slightly lower during courses two and three in both treatment groups (Table 3). Results for the two antiemetic treatment groups were similar, although no statistical comparison was made because of the selection introduced by withdrawal of patients with inadequate control of emesis in the first course of chemotherapy.

Delayed nausea and vomiting

As shown in Figure 2, the occurrence of both nausea and vomiting declined progressively on successive days after the start of chemotherapy course one. The percentage of patients with total or partial control of vomiting or of nausea on all 5 days of treatment did not differ between tropisetron and metoclopramide.

Safety evaluation

Only 1 patient, in the metoclopramide group, experienced adverse events that were directly attributed to antiemetic therapy; the symptoms involved were confusion and tremor. Overall 32 (63%) patients in the tropisetron group and 27 (53%) of patients in the metoclopramide group experienced adverse events during the study period, but no patient stopped taking study medication as a result.

The events most frequently reported during all three study courses of chemotherapy are summarised in Table 4. Headache was reported after 28 of 115 (24%) courses of tropisetron compared with 12 of 128 (9%) courses of metoclopramide (P = 0.003), and was severe on three and two occasions, respectively.

2 patients in the metoclopramide group died after completing all three courses of chemotherapy, 1 after 26 days and the other after 8 weeks. Both had small cell lung cancer and their deaths were related to tumour progression. 3 patients experienced non-fatal serious adverse events. The renal function of 1 tropisetron recipient deteriorated during the first course of chemotherapy; this was considered to be the result of chemotherapy and preexisting prostate disease. 2 patients in the metoclopramide

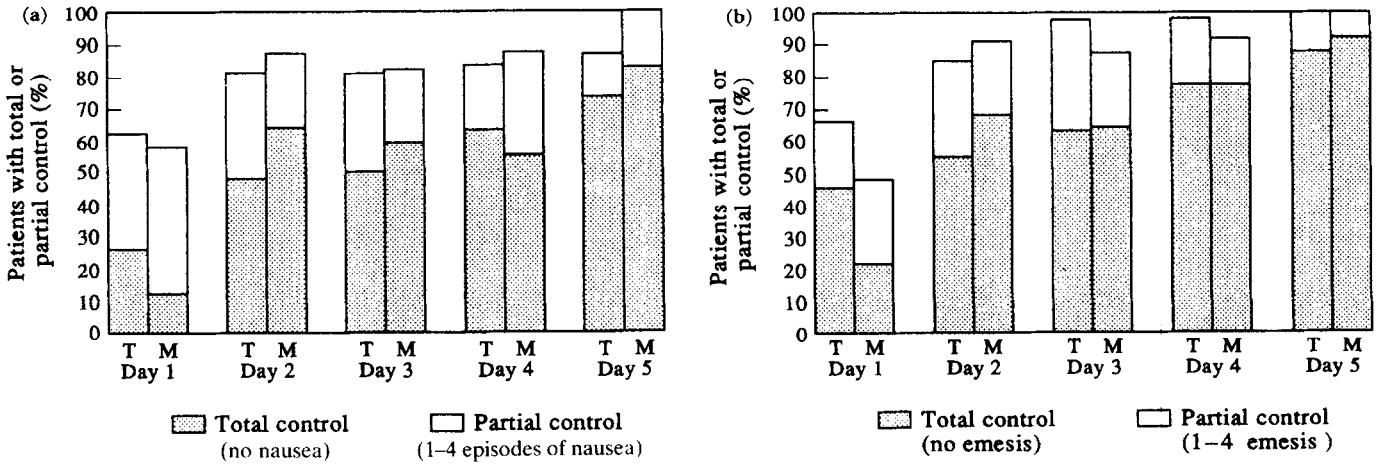

Figure 2. Control of (a) nausea and (b) vomiting on days 1–5 of the first course of chemotherapy in patients treated with tropisetron (T) or metoclopramide (M).

group had an acute myocardial infarction. In 1 patient this occurred 1 day after starting treatment and in the other it took place 23 days after the last dose of metoclopramide; in neither case was antiemetic therapy implicated.

Abnormalities of laboratory variables, vital signs and ECG were similar in the two antiemetic treatment groups and were ascribed to the underlying cancer or the effects of chemotherapy, rather than to administration of tropisetron or metoclopramide. In particular, there were no increases in plasma concentrations of liver enzymes attributable to antiemetic treatment.

DISCUSSION

The results from this controlled clinical trial show that a single 5-mg dose of tropisetron is more effective than a regimen consisting of metoclopramide (2–5 mg/kg) plus lorazepam (2–4 mg) in controlling acute vomiting following cancer chemotherapy. The two antiemetic regimens exhibited similar efficacy against delayed vomiting, and acute and delayed nausea. In the first course, tropisetron 5 mg prevented vomiting during the first 24 h after chemotherapy in 45% of patients, with 67% of patients vomiting fewer than five times. Among the patients treated with metoclopramide (usually with additional lorazepam before chemotherapy), 22% experienced no vomiting and 47% vomited fewer than five times during the same period. Analysis of results by treatment subgroup gave similar results for tropisetron and metoclopramide.

There was total or partial control of nausea (< 5 episodes) on day 1 of the first course of chemotherapy in a greater proportion of the tropisetron group than the metoclopramide group (63 versus 57%), but the difference between the treatment groups was not statistically significant. However, the relatively small numbers of patients included in the study may have contributed to the failure to produce a significant result.

During the second and third courses of chemotherapy, there was no apparent difference between the antiemetic effects of the study treatments. Acute nausea and vomiting were less well controlled in the later courses, especially during course two when the ovarian cancer patients received ifosfamide plus doxorubicin instead of carboplatin plus cyclophosphasmide. Ifosfamide appears to be highly emetogenic.

The emetic effects of both carboplatin and cyclophosphamide are characterised by a delayed onset (6–12 h after administration) and may persist for several days in some patients [7–10]. In this study, most chemotherapy was administered on the first day of the course and, therefore, nausea and vomiting occurring after the first 24 h are at least partially a reflection of delayed effects. The incidence of vomiting and nausea on day 2 of the first course was similar in the two antiemetic treatment groups, with total or partial control in approximately 75–80% of patients. The presence of persistent symptoms, especially nausea, in a small number of patients emphasises the importance of continuing antiemetic treatment for several days after chemotherapy.

Both antiemetic treatments used in this study were well tolerated, with no patient discontinuing antiemetic treatment because of adverse effects. As with other 5-HT_3 antagonists tropisetron was associated with headache; however, the majority of symptoms reported were related to either the underlying cancer or chemotherapy. Extrapyramidal reactions are often associated with metoclopramide treatment [11] but were not observed during this study, probably because of the use of concurrent lorazepam.

The reference antiemetic treatment, metoclopramide with additional lorazepam before chemotherapy, represented standard clinical practice in this hospital at the time of the initiation of the study. In the light of current knowledge, an antiemetic cocktail including a corticosteroid such as dexamethasone might have been chosen. Furthermore, the doses of metoclopramide given on day 1 (a total of approximately 2–5 mg/kg) were somewhat smaller than those utilised in many of the published studies of metoclopramide monotherapy (6–10 mg/kg in divided doses) in the prevention of nausea and vomiting after highly emetogenic chemotherapy [3, 12–14]. It is notable that the control of vomiting produced by the metoclopramide-based regimen in this study was comparable to that reported with high-dose metoclopramide therapy during cisplatin administration [3, 12–14].

When this study was designed, it was intended to stratify the patients according to type of cancer and chemotherapy received. In the event, this was not feasible because one treatment arm was abandoned as a result of a change in clinical practice, and because fewer patients than had been planned were enrolled. However, there was no statistically significant interaction between antiemetic outcome and cancer or type of chemotherapy (Breslow–Day test), and so pooling of all efficacy data for analysis is a valid procedure.

The disappointingly high rate of patient withdrawal from the study between chemotherapy courses one to three created further problems in analysing the results, because the numbers receiving study treatment during a second and third course were too small to allow meaningful comparison of the two antiemetic regimens. Therefore, only efficacy data from the first course of chemotherapy have been analysed statistically. Because of the overriding importance of providing patients with effective antiemetic treatment during chemotherapy, strict criteria were used to determine the conditions under which patients should be given rescue antiemetic therapy, and this probably contributed to the high withdrawal rate. The results illustrate the difficulties that can arise if a crossover design is used for antiemetic trials. A parallel-group design, such as that of the present study, allows the effects of antiemetic therapy to be observed over several consecutive courses of chemotherapy, and avoids the statistical problems associated with analysing a crossover study when the withdrawal rate is high [15].

In conclusion, tropisetron as a single agent given once daily is an alternative to combination therapy with metoclopramide and lorazepam in the prevention of nausea and vomiting after chemotherapy. In this study, tropisetron was well tolerated and more effective than the metoclopramide-based treatment in controlling acute vomiting, although the two treatments had comparable effects on delayed symptoms.

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Intrinsic Radiosensitivity of Adult and Cord Blood Lymphocytes as Determined by the Micronucleus Assay

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Predictive radiosensitivity testing necessitates rapid and reliable assays of radiosensitivity. We assessed the lymphocyte micronucleus assay as such an assay. We performed repeated experiments on lymphocytes from 10 healthy donors. Levels of radiation-induced micronuclei were measured following exposures of up to 4 Gy X-rays. When measuring the slope of the dose–response, we have found more variation between individuals than between repeated experiments on the same individual (F value 12.31, $P < 0.001$). There is also greater interindividual variation in the data following a single dose of X-rays of 2 Gy (F value 3.54, $P < 0.01$) and of 4 Gy (F value 7.55, $P < 0.005$). We performed the micronucleus assay on five different samples of cord blood lymphocytes (CBLs). Their radiosensitivities were compared with the mean radiosensitivity of the lymphocytes from the normal group of donors. Comparing the level of micronuclei induced by 2 Gy, only CBL1 ($P < 0.01$) and CBL2 ($P < 0.02$) were more radiosensitive than the mean of the adult lymphocytes. At 4 Gy, CBL1 ($P < 0.001$), CBL2 ($P < 0.05$), CBL3 ($P < 0.01$) and CBL5 ($P < 0.01$) were more radiosensitive than the mean radiosensitivity of the adult lymphocytes. This was also shown when the slope of the dose–response curves were measured. We conclude that the lymphocyte micronucleus assay shows more variability when applied to lymphocytes from different individuals than when repeatedly applied to lymphocytes from the same individual, a requirement for the determination of individual radiosensitivity.

Key words:radiosensitivity, micronucleus, normal tissue tolerance
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INTRODUCTION

IN PATIENTS undergoing radiotherapy, a range of severity of radiation-induced normal tissue damage is seen, from mild to life threatening. Turesson [1] estimates that only 20% of this variability can be accounted for by the dose received and the fractionation schedule. There appears to be a large component of patient responses due to genetic factors [1–3]. Schedules of radiotherapy are selected to achieve an acceptable incidence of normal tissue complications [4]. As there is a sigmoid dose response for tumour control by radiotherapy, and doses generally used are in the steepest part of that curve, it is possible that by altering the total dose by just a small amount, tumour control may be improved with minimal injury to normal tissues. Individualised modifications have been reported as successful for the treatment of some patients with radiosensitive, cancer prone genetic syndrome ataxia telangectasia (AT) [5]. This would be