Cancer Chemother Pharmacol (2001) 47 (Suppl): S29–S34

ORIGINAL ARTICLE

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Co-medication with hydrolytic enzymes in radiation therapy of uterine cervix: evidence of the reduction of acute side effects

Abstract *Purpose*: The use of additional therapy with an oral enzyme preparation containing trypsin, chymotrypsin and papain has been suggested for the reduction of toxicity due to radiation therapy. This study was conducted to test the efficacy and tolerability of this enzyme combination in preventing or reducing the acute side effects of radiation therapy in patients with locally advanced cervical cancer. *Methods*: A prospective, randomised, open, clinical trial was carried out on 120 patients (aged 24–85 years) with locally advanced, biopsy-proven carcinomas of the uterine cervix (stages IIa, IIb or IIIb). Patients received 50 Gy of external radiation therapy over a period of 5 weeks, followed by intracavitary brachytherapy (20–30 Gy). Patients assigned to the test group (60 patients) received additional treatment with enzymes. Patients were evaluated at weekly intervals for acute radiation therapy-related side effects, according to the RTOG/EORTC grading criteria, and then after the end of radiation therapy for another 8 weeks. Occurrence of adverse events, if any, was also recorded. *Results*: The study revealed that the maximum extent of acute radiation side effects was reduced in the enzyme group: skin reactions (mean: 0.97 vs 1.68 in the control group, $P < 0.001$), vaginal mucosal reactions (0.55 vs 0.85, $P = 0.10$), genitourinary symptoms (0.93 vs 1.38, $P < 0.001$) and gastrointestinal reactions (1.12 vs 1.30, $P = 0.12$). The sum-scores during treatment, expressed as area under the curve, were significantly less in the enzyme treated patients. In the follow-up visits all observed side effects of radiation therapy were of lower intensity in the enzyme group than in the control group. *Conclusions*: In patients with locally advanced cancer of the uterine cervix, oral enzyme therapy was found to be effective in significantly reducing radiation therapy-related side effects such as genitourinary symptoms, subcutaneous changes and reactions of the vaginal mucosa.

Key words Cervix cancer · Radiation therapy · Oral enzyme therapy · Supportive care · Acute side effects

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Introduction

Cancer of the uterine cervix is the second most common form of malignancy in women. On average, cancers of the uterine cervix account for 11.6% of all female cancers, with 437,000 new cases being reported per year worldwide: 9,000 in Japan, 39,000 in Europe and 16,000 in North America. This disease is responsible for approximately 7,000 deaths in the US alone [1]. In India cervical cancers comprise about 50% of the cancer cases among women [2–4].

Radiation therapy with or without chemotherapy is the standard treatment for locally advanced cancer of the uterine cervix (FIGO stages II & III). Radiation therapy has been reported to be very effective in the treatment of cervical carcinomas. Approximate cure rates include 80% for stage I, 60% for stage II, 30% for stage III and 10% for stage IV [5]. However, severe acute side effects can necessitate interruption or cessation of radiation therapy. Treatment gaps with consequent prolongation of overall treatment time may result in a decrease in local control and survival rates [6].

Chemotherapy with cytotoxic drugs has a definite role in cervical carcinomas but the severity of side effects is a limiting factor. Some of the drugs are known to cause myelosuppression, pulmonary fibrosis, thrombocytopenia and neuropathy as well as unspecific toxicity.

Numerous drugs have been tested in an attempt to reduce acute and delayed radio-chemotherapy-associated toxicity, but none have shown a consistent and

significant beneficial effect. Thus the present clinical supportive management of acute treatment toxicity, which includes changes in the diet, optimum local hygiene, anti-diarrhoeal drugs and urinary antiseptics, is based purely on symptoms and has not proved to reduce directly the intensity or duration of radiation-and chemotherapy-induced mucositis.

Infectious complications are the most frequent cause of death in cancer patients after chemotherapy. The choice of appropriate anti-bacterial therapy is limited by frequent complications such as renal insufficiency and age of the patient. The efficacy and safety of monotherapy with broad-spectrum beta-lactam antibiotics or beta-lactam antibiotic/beta-lactamase inhibitor combinations such as ticarcillin/clavulanate, remain to be confirmed in gynaecological oncology patients [7].

Radiation therapy-related complications include severe small bowel, rectosigmoid and bladder injuries. Patients suffering from severe acute side effects may be at higher risk of developing late post-radiation therapy complications which could include ureteral stricture, vesicovaginal fistula, rectovaginal fistula, sigmoid stricture, small bowel obstruction, proctitis and large rectal ulcers. The late side effects can, however, be further aggravated in patients with inflammatory reactions in the pelvic organs [6, 8–12].

In earlier clinical studies [13–15] a beneficial effect of an additional oral therapy with a combination of trypsin, chymotrypsin and papain (Wobe-Mugos E, Mucos Pharma, Geretsried, Germany) in the management of radiation- or chemotherapy-induced side effects was shown. We, therefore, set up an open prospective randomised trial to investigate the effects of such medication in the setting of radiation therapy treatment of cervical cancers in India.

Patients and methods

The study was conducted between October 1996 and September 1997, at the Nargis Dutt Memorial Regional Cancer Hospital at Barshi, Maharashtra in India. The study protocol was reviewed and duly approved by the Institutional Ethics Committee of the cancer centre.

Patient characteristics and eligibility

All patients with locally advanced, biopsy-confirmed carcinomas of the uterine cervix at stages IIa, IIb or IIIb, and fulfilling the inclusion criteria were eligible to be enrolled in the study. At the start of the study baseline laboratory investigations were conducted. All patients with a previous history of radiation therapy, chemotherapy or surgery, and those with WHO performance index below 70% or with uncontrolled systemic diseases were excluded from the study. The age range in the patients was 24–85 years.

Study design

This study was designed as a prospective, open, randomised, phase III clinical trial. A total of 120 patients was enrolled in the study after giving their written informed consent. Patients were randomised into two groups, the study group and the control group, each consisting of 60 patients. Randomisation was carried out by a computer-generated randomisation list. Patients in both arms received 50–60 Gy of external beam radiation in 25–30 fractions over a period of 5 weeks, followed by intra-cavitary brachytherapy at a dose of 20–30 Gy using a BARC applicator. The enzyme group patients additionally received the test drug. Any use of anti-inflammatories, topical anaesthetics or mucoprotectants for radiation toxicity and concomitant medication e.g. anti-emetics and anti-diarrhoeal drugs was recorded.

Study drug administration

One enteric coated tablet of the test drug Wobe-Mugos E contains 100 mg papain, 40 mg trypsin, and 40 mg chymotrypsin. The patients in the study group received three tablets four times a day, beginning 7 days before start of radiation therapy. Enzyme therapy was continued for 9 weeks thereafter. Control-group patients did not receive any study medication. Patients' compliance with treatment was verified by maintaining a "pill count" of the medication returned by the patients.

Evaluation

All patients were monitored weekly for 5 weeks. Patients were followed-up at intervals of 6 weeks, and 3 months, after completion of radiation therapy. During each visit patients were evaluated for clinical signs and symptoms of radiation toxicity. Vaginal mucosal reactions, skin reactions, and changes in the gastrointestinal and urinogenitary system were graded according to the RTOG/EORTC criteria, by a single observer (score 0 to 4) [16].

Statistical evaluation

The primary efficacy variables were defined as the maximum extent of observed side effects during the planned period of treatment (week 1 to week 5), evaluated according to RTOG/EORTC criteria. The Wilcoxon rank-sum test (two-sided) was used to test for treatment differences. In order to account for multiple tests of significance ($n = 4$), the crude P values were adjusted according to the step-down method of Bonferroni-Holm. The secondary variables were evaluated descriptively. For assessment of homogeneity of the treatment groups with respect to certain characteristics, the Wilcoxon rank-sum test was used to test formally for differences in distribution of continuous variables, whereas for categorical variables Fisher's exact test was used. Statistical analysis was performed by SAS programmes (SAS Institute, Cary, N.C., USA).

Results

The two groups were comparable with regard to patient demographic and clinical baseline data including tumour staging, WHO performance index and haematological parameters (Table 1). Both groups received comparable cumulative doses of external radiation therapy. Control-arm patients received 50 ± 0 Gy (mean ± SD) over a total period of 35 ± 1 days while enzyme-treated patients received an average dose of 50 ± 3.5 Gy over 35 ± 6 days. The enzyme-group patients additionally received enzymes over a period of 69 ± 15 days with treatment starting 8 ± 1 days before radiation therapy. Two patients, both belonging to the enzyme group, dropped out of the study, one due to hepatitis and the

other due to brain metastasis. Both events were reported to be unrelated to the study medication.

There were significantly fewer urogenital symptoms (evaluated as maximum extent) in the enzyme-treated group (Table 2). The treatment effect was observed from 1 week after start of radiation therapy until the last follow-up visit (Fig. 1A). During the course of radiation therapy, only 10% of the patients in the enzyme group, but 38.3% of the patients in the control group, showed increased severity and frequency of micturition with dysuria, pelvic pain and frequent frank haematuria (Table 3). In both groups most of the patients showed a slight increase in frequency of micturition and dysuria which did not require any clinical intervention. Out of the 60 enzyme-treated patients, ten did not show any change over the baseline values compared with only one patient in the control group.

Radiation damage to the gastrointestinal system was characterised by diarrhoea and increased frequency of stools. Although the maximum extent was reduced in enzyme-treated patients (mean: 1.12; vs 1.30 in the control group), this difference was not statistically significant ($P = 0.12$). However, from the fourth week up to the last follow-up visit, the enzyme-treated patients showed a decreased, albeit not significantly reduced, extent of side effects compared with patients in the control arm (Fig. 1B). In the control arm, a higher number of patients (31.6%) was observed to have diarrhoea requiring treatment with parasympatholytic drugs, and abdominal pain requiring analgesics. Only 11.7% of the enzyme-treated patients showed similar symptoms. In both groups most of the patients showed only a slight increase in the frequency of stools, change in the quality of bowel habits and rectal discomfort. However, none of the symptoms was severe enough to require clinical intervention. Six patients (three per group) showed bloody stools, perforations and fistulae.

Effects of enzyme treatment were also observed in the extent of side effects recorded for vaginal mucositis among both groups, beginning 3 weeks after start of radiation therapy and continuing up to the last follow-up visit (Fig. 1C). The maximum extent was reduced in enzyme-treated patients (mean: 0.55; vs 0.85 in the control group), although the difference was not statistically significant ($P = 0.10$, adjusted for multiple testing). During the course of radiation treatment patients initially exhibited patchy vaginal mucositis which gradually progressed to confluent fibrous mucositis. Most of the patients in the enzyme group (51.6%) did not show any change in their condition with respect to the baseline status. An equal number of patients in both the groups (41.6%) experienced mild pain which, however, did not require the use of any medication. In the control group, 16.6% patients exhibited patchy mucositis with serosanguineous discharge. Patients also experienced moderate pain requiring the use of analgesics. Only 6.6% of the enzyme-group patients showed similar signs and symptoms. None of the enzyme-treated patients exhibited confluent fibrous mucositis or had severe pain. However, two of the control-arm patients had confluent mucositis with severe pain requiring the use of narcotic anaesthetics.

Follicular and faint erythema appeared as early evidence of radiation damage to the skin. With accumulating doses of radiation, the skin showed bright erythema with patchy to confluent moist desquamation, moderate oedema and occasionally frank ulceration. There was a statistically significant improvement in

Table 1 Patients' data (*WBC* white blood cell count)

	Control group	Enzyme group	*P* value
Age in years (mean ± SD)	49.3 ± 13.9	49.9 ± 10.5	0.84
Performance status (WHO)			
1	54	51	0.58
2	6	9	
Stage of disease			
IB	2	0	
IIB	16	19	0.46
IIIB	42	41	
Haematological parameters/mean ± SD			
Haemoglobin (g/dl)	10.3 ± 1.7	10.0 ± 1.3	0.30
WBC ($\times 10^3/mm^3$)	7.3 ± 2.6	6.6 ± 2.4	0.07
Platelets ($\times 10^3/mm^3$)	120 ± 35	111 ± 27	0.29

Table 2 Mean maximum extent of radiation therapy-related acute side effects (RTOG/EORTC grading)

Side effect	Group	*n*	Mean	Standard deviation	Mean difference	95% CI	*P* value[a]
Urogenital	Control	60	1.38	0.56	0.45	0.20–0.70	< 0.001
	Enzyme	60	0.93	0.52			
Gastrointestinal	Control	60	1.30	0.81	0.18	−0.078–0.44	0.12
	Enzyme	60	1.12	0.64			
Vaginal mucosa	Control	60	0.85	0.82	0.30	0.040–0.56	0.10
	Enzyme	60	0.55	0.62			
Skin	Control	60	1.68	0.87	0.72	0.41–1.02	< 0.001
	Enzyme	60	0.97	0.82			
Haematological	Control	60	2.15	0.61	0.45	0.20–0.70	0.0016
	Enzyme	60	1.70	0.77			

[a] Adjusted for multiple testing ($n = 4$) by the step-down method of Bonferroni-Holm

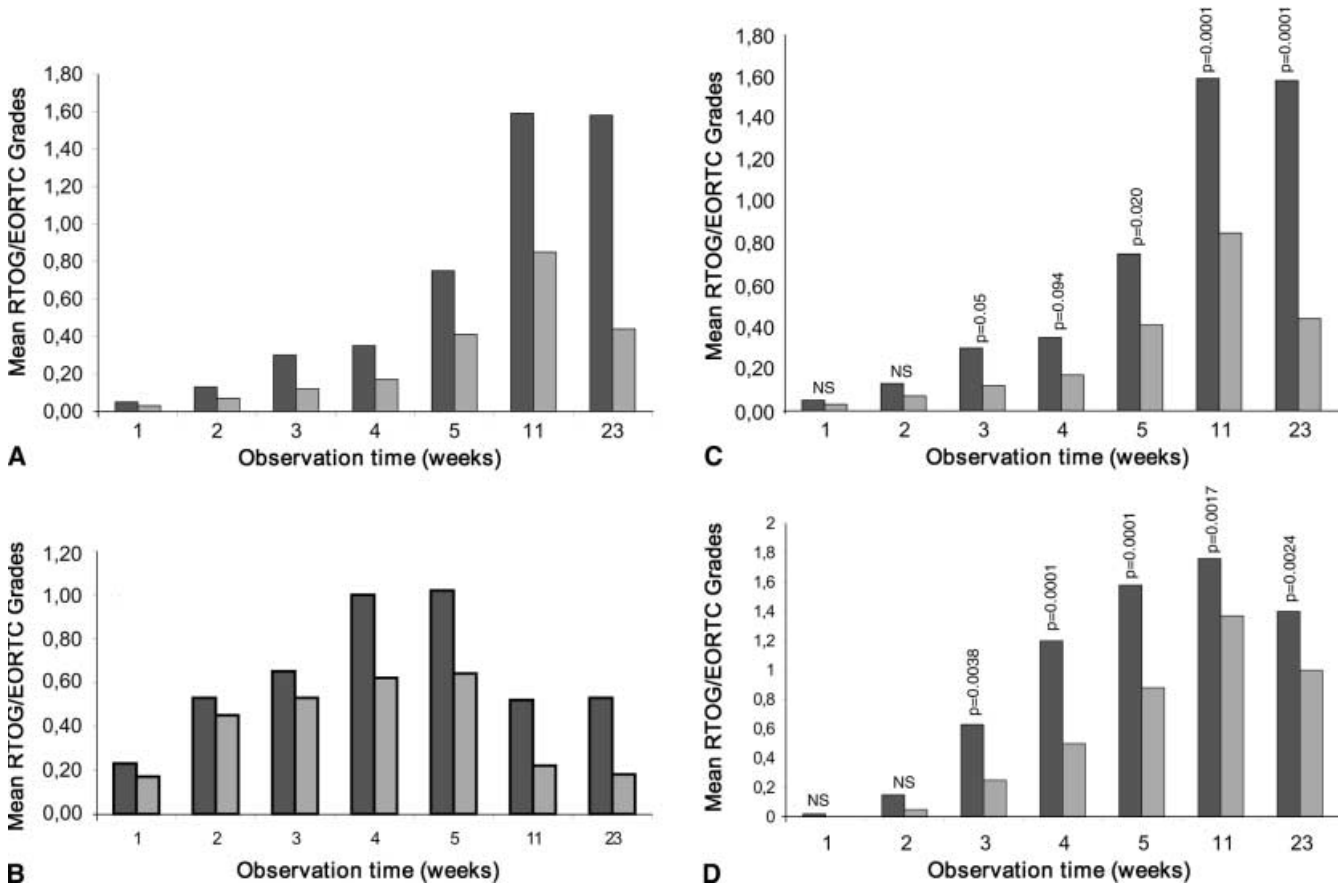

Fig. 1 Mean scores for **A** urinogenitary symptoms, **B** gastrointestinal symptoms, **C** vaginal mucosal reactions, **D** skin reactions (EORTC/RTOG, grade 0–4) for the 5 weeks of radiation therapy, and at follow up (6 weeks and 3 months after end of radiation therapy). Patients receiving test drug (*light bars*), and controls (*dark bars*)

favour of the enzyme-treated group with respect to the maximum extent of these side effects (0.97 vs 1.68, $P < 0.001$). The extent was less in the enzyme group than in the control group from the second week of radiation therapy (Fig. 1D). Most of the enzyme-treated patients (78.3%) did not show any skin reaction worse than faint erythema, while in 40.0% of the control group, moderate to bright erythema or patchy moist desquamation were seen. In this group the condition further deteriorated with 15.0% of patients showing confluent moist desquamation and pitting oedema. Only 5.0% of the enzyme-treated patients showed similar symptoms. None of the enzyme-treated patients showed ulceration or skin necrosis whereas one patient in the control group showed frank skin ulceration.

Side effects observed were not discriminated between being radiation therapy-induced or possibly being related to the test drug. This was done because the typical side effects of oral enzyme therapy normally are gastrointestinal ones, occurring in about 3 to 4% of the patients, and stomach aches, diarrhoea, and flatulence are typical symptoms [17]. As gastrointestinal side effects are also typical for radiation therapy, one might rather expect an increased incidence in the test group, which

Table 3 Frequency distribution of the maximum extent of radiation therapy-related acute side effects (RTOG/EORTC grading)

	Group	Grade 0	Grade I	Grade II	Grade III	Grade IV
Urogenital	Control	1	36	22	1	0
	Enzyme	10	44	6	0	0
Gastrointestinal	Control	8	30	19	2	1
	Enzyme	6	44	7	3	0
Vaginal mucosa	Control	23	25	10	2	0
	Enzyme	31	25	4	0	0
Skin	Control	4	22	24	9	1
	Enzyme	18	29	10	3	0
Haematological	Control	0	6	40	13	1
	Enzyme	2	23	26	9	0

was not the case. To the contrary, gastrointestinal side effects observed were less in the enzyme group, although the difference was not statistically significant (Tables 2 and 3, Fig. 2). Thus we found no evidence of safety problems when administering oral enzymes to our patients, and conclude that this additional therapy can be regarded as being without difficulties in such patients receiving radiation therapy.

Discussion

Late stage II and stage III uterine cervix tumours involve the whole pelvis, and their treatment requires high-dose external and intra-cavitary irradiation. This increases the risk of complications to the neighbouring structures. Treatment complications mostly occur in rectum and bladder. Several clinical studies have reported the effect of high-dose radiation therapy and the associated complications, especially the incidence of early complications and a possible correlation to the subsequent onset of late radiation therapy side effects.

In a study on 220 patients with carcinoma of the uterine cervix treated by radiation therapy it was observed that patients with increased acute toxicity and diarrhoea during radiation therapy had significantly increased risk of late rectal injury, thus suggesting that early excessive damage of acute-responding components of the rectal wall might play an important role in the initiation of late injury [11]. Similar findings in another study on 209 patients receiving radiation therapy showed that severe late effects were associated with significant acute reactions [18].

Correlation of acute and late gastrointestinal and genitourinary morbidity based on the data obtained from 712 prostate cancer patients receiving at least 65 Gy conventional radiation therapy, showed acute gastrointestinal (GI) and genitourinary (GU) side effects in 246 and 201 patients respectively [10]. The acute and late GI morbidity was highly correlated. History of diabetes, treatment of pelvic nodes and age less than 60 years were significantly related to acute GI side effects. It was also found that acute GU side effects were significantly related to late Grade 2 or higher morbidity.

Earlier, an 8.2% incidence of late complications were reported to have developed in those patients who had experienced acute radiation therapy-related side effects, compared with a 3.0% incidence of late complications developing in patients without early complications [19]. Thus the risk of developing a late complication was greater by a factor of 2.7 in those patients developing an early radiation reaction ($P < 0.05$).

In curative radiation therapy of pelvic malignancies, the rectum is often the dose-limiting organ. Serous, mucoid and occasionally bloody diarrhoea are the symptoms. No proven effective prophylactic local or systemic therapies exist for radiation proctitis, nor is any causal medication known. Similarly, in the treatment of late radiation sequelae no clinically tested effective therapy exists. Topical anti-inflammatory, steroidal or non-steroidal therapeutics as well as sucralfate have been used with some degree of success. Treatment failures have been prescribed hyperbaric oxygen, with good clinical results in about 50% of the cases.

Thus an appropriate management of early radiation complications may play a pivotal role in the control of late radiation therapy-side effects. The present study, which examines the effect of an oral enzyme therapy on the reduction of early radiation complications, reveals a significant reduction in vaginal mucosal, gastrointestinal and urogenital changes, as well as a reduction in skin reactions. The maximum extent of radiation complications was seen after 4 to 5 weeks of radiation therapy. There did not appear to be any significant difference between both arms with regard to the time course. However they differed significantly in the severity of the side effects.

Radiation therapy side effects are more pronounced in the urogenital system due to its proximity to the site of the tumour. However, 90% of the enzyme-treated patients had either mild or no urogenital symptoms. The difference between the enzyme and study group was more pronounced after the third week. This observation holds significance since, on average, the radiation therapy-related acute side effects gradually become distinct during the second and third week of radiation therapy, constituting a peak towards the fifth week. Enzymes thus aid in controlling the complications that may arise during this crucial acute reaction phase of radiation treatment.

Similar results were obtained for gastrointestinal symptoms. From the fourth week, the enzyme-treated patients exhibited significantly less frequency of stools requiring no clinical intervention, whereas 5% of the patients of the control group progressed to Grade III and Grade IV.

Comparable observations have been recorded for the vaginal mucosal and skin reactions with patients exhibiting mild or no reactions from the third week to the last follow-up visit. The results of this prospective study reveal the significant benefit obtained through the management of radiation therapy-related complications in the treatment of cancer of the uterine cervix.

This open study indicates that oral enzyme therapy may effectively reduce the early complications, especially with regard to the genitourinary system. Concomitant enzyme therapy together with conventional radiation therapy may significantly reduce the risk of patients developing major urinary tract, gastrointestinal and rectal complications.

Acknowledgements The authors thank Dr. W. Schiess (Mucos Pharma, Geretsried) for his support in manuscript preparation.

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