AP&T Alimentary Pharmacology and Therapeutics

Randomised clinical trial: preventive treatment with topical rectal beclomethasone dipropionate reduces post-radiation risk of bleeding in patients irradiated for prostate cancer

L. Fuccio*, A. Guido†, L. Laterza*, L. H. Eusebi*, L. Busutti†, F. Bunkheila†, E. Barbieri† & F. Bazzoli*

*Department of Clinical Medicine, S.Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy.
†Division of Radiation Oncology, S.Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy.

Correspondence to:
Dr L. Fuccio, Department of Clinical Medicine, S.Orsola-Malpighi Hospital, University of Bologna, Via Massarenti 9, 40138, Bologna, Italy.
E-mail: lorenzofuccio@gmail.com

Publication data
Submitted 18 March 2011
First decision 10 April 2011
Resubmitted 30 June 2011
Accepted 30 June 2011
EV Pub Online 25 July 2011

SUMMARY

Background
Radiotherapy is an established treatment modality for prostate cancer; however, up to a third of patients develops a radiation-induced proctopathy.

Aim
To assess the effect of topical beclomethasone dipropionate (BDP) in the prevention of radiation-induced proctopathy in patients undergoing radiotherapy for prostate cancer through a double-blind, placebo-controlled, randomised trial.

Methods
Patients were randomised either to BDP or to placebo (PL). Patients received daily a 3 mg BDP enema or identical-looking PL during radiotherapy and, subsequently, two 3 mg BDP suppositories or PL for 4 more weeks. Clinical and endoscopic evaluations before, 3 and 12 months after the end of radiotherapy were assessed with the RTOG/EORTC toxicity scales, the modified Simple Clinical Colitis Activity Index (SCCAI), the modified Inflammatory Bowel disease Quality of Life Index (IBDQ) and the Vienna Rectoscopy Score (VRS).

Results
From June 2007 to October 2008, 120 patients were randomised to the BDP (n = 60) and PL (n = 60) arms and were followed up for 12 months. The overall assessment of rectal side effects did not show significant differences between the two groups of treatment. However, when only rectal bleeding was considered, a significantly reduced risk was observed in patients on BDP (OR 0.38; 95% CI 0.17–0.86; P = 0.02; NNT = 5). Patients on BDP had also significantly lower VRS scores (P = 0.028) and significantly higher IBDQ scores (P = 0.034).

Conclusions
Preventive treatment with topical rectal BDP during radiotherapy for prostate cancer significantly reduces the risk of rectal bleeding and radiation-induced mucosal changes and improves patient's quality of life, but does not influence other radiation-induced symptoms.

Aliment Pharmacol Ther 2011; **34**: 628–637

© 2011 Blackwell Publishing Ltd
doi:10.1111/j.1365-2036.2011.04780.x

INTRODUCTION

Prostate cancer is the fifth most common cancer in the world and the second most common in men.[1] Radiotherapy is an established treatment modality; however, up to a third of patients develops a radiation-induced proctopathy, characterised by several symptoms (i.e., diarrhoea, urgency and bleeding) and mucosal changes (i.e. angiectasia and ulcer), which can present with variable grades of severity and substantially reduce patient's quality of life.[2] As up-to-date medical therapies have shown disappointing results, management of radiation-induced disease still remains challenging.[3] After radiotherapy, an inflammatory process rapidly develops and usually completely withdraws. However, in some cases, for yet unknown reasons, it evolves into a more severe inflammation with subsequent blood vessels damage, ischaemia and finally to fibrosis.[4] Therefore, reducing or abolishing the initial inflammatory process could be a reasonable strategy for the prevention of radiation-induced rectal alterations.

Glucocorticosteroids are the most effective anti-inflammatory agents available for several inflammatory diseases, but their prolonged use is limited by the development of severe side effects. Therefore, nonsystemic glucocorticosteroids, such as beclomethasone dipropionate (BDP), with a different pharmacokinetic profile, have been proposed.[5] Based on these characteristics, nonsystemic steroids could be considered efficient agents for the prevention of radiation-induced proctopathy as well.

We investigated in a double-blind, placebo-controlled, randomised trial, whether topical rectal beclomethasone dipropionate treatment can prevent the development of radiation-induced proctopathy in patients who underwent radiotherapy for prostate cancer.

METHODS

This was a single centre randomised study conducted at S.Orsola-Malpighi University Hospital, Bologna, Italy. The protocol was approved by local ethics committee and written informed consent was obtained from all patients. The trial has been registered in a publicly accessible registry (EudraCT registration number: 2006-005697-46).

Selection criteria

Patients with histological proof of prostate cancer without distant metastases, undergoing a course of external beam radiation therapy, were considered eligible for this study.

Patients with a known allergy to beclomethasone dipropionate, a history of inflammatory bowel disease, active malignant intraluminal gastrointestinal tumours or active inflammatory process (i.e. diverticulitis, inflammatory bowel disease), a previous history of pelvic radiotherapy or previous colorectal surgery were considered ineligible.

Patient data collection

The following data were collected upon patient enrolment: demographic data, vital signs (weight, blood pressure and pulse rate), medical history and concomitant therapies (i.e. aggregation inhibitors, anticoagulants and hormone therapy), cancer stage, cancer-related surgery (prostatectomy with or without lymphadenomectomy), type of radiotherapy (adjuvant or radical) and radiotherapy technique (4 or 5 fields).

Randomisation and intervention

The operations office of the Contract Research Organization (OPIS srl, Desio, MB, Italy) served as randomisation centre for this study. Patients were randomly assigned, according to a computer-generated list with an allocation ratio of 1:1, to receive either beclomethasone dipropionate or placebo. The list was generated according to a randomised block design (block-size = 4). The random allocation sequence was generated by the Contract Research Organization before the baseline evaluation. Concealment of allocation sequence was guaranteed by the central randomisation. Double-blind method was used to ensure blinding of treatment assignment.

Patients were treated with a 3 mg BDP enema (Topster enema, Sofar s.p.a., Trezzano Rosa, MI, Italy) or identical-looking placebo the evening before each radiation session, for the entire duration of radiotherapy. In particular, patients were invited to perform the enema at bedtime and retain it overnight. Immediately after the end of radiotherapy, patients stopped the enema formulation and received two 3 mg beclomethasone dipropionate suppositories (Topster suppository), one in the morning and one in the evening, or identical placebo, for 4 more weeks. Patients were responsible for self-administration and were asked to retain the enema and the suppository for as long as possible. Compliance was assessed by asking patients to return any unused enema or suppository at the completion of the whole treatment.

Radiotherapeutic treatment

All patients received three-dimensional conformal radiotherapy and were treated on linear accelerators with minimum energy of 6 MV, using four- or five-field

© 2011 Blackwell Publishing Ltd

techniques. Patients were treated in the supine position and immobilised at the pelvis. Patients were asked to empty the rectum before the planning computed tomography scan to enhance the reliability of the rectal dose-volume histogram. Dosing schedules followed the institutional protocols. All patients received external-beam radiation, with a total dose ranging from 66 to 74 Gy, given in 33–37 fractions over 6–7 weeks using daily fractionation of 2 Gy, 5 days/week. The radiation dose was prescribed to the isocentre. The mean rectum dose and the rectum volume were obtained from the dose-volume histograms. The rectum was contoured from the anal verge to the rectosigmoid junction. In addition, for each patient, the percentage of rectum volume receiving at least 50Gy (V50), 60Gy (V60) and 70Gy (V70) were calculated, as well as the dose taken by 1/3, 2/3 and 3/3 of the rectum volume.

Outcomes and follow-up

Primary aim of our study was the evaluation of the efficacy of topical beclomethasone dipropionate compared with placebo for the prevention of radiation-induced proctopathy in patients submitted to radiotherapy for prostate cancer. Secondary aims were the evaluation of the impact of topical BDP on patient's quality of life and the evaluation of risk factors associated with the development of radiation-induced proctopathy.

Radiation-induced proctopathy was defined as a syndrome characterised by the presence of symptoms such as rectal bleeding, changes in defaecatory frequency and/or continence, with or without rectal endoscopic signs (e.g. angiectasia, ulcer) that occur as a result of radiotherapy for prostate cancer. Therefore, the development of radiation-induced proctopathy was evaluated by both clinical and endoscopic assessments. For the clinical assessment, several questionnaires have been applied: a modified Simple Clinical Colitis Activity Index (SCCAI)[6] and the Radiation Therapy Oncology Group acute and late toxicity scales (RTOG/EORTC).[7] Patient's quality of life was evaluated according to the modified Inflammatory Bowel Disease Quality of Life Index (IBDQ).[8] Specifically, SCCAI evaluated day and night stool frequency, urgency and the presence of blood in the stool; extra-intestinal manifestations and general well-being, normally evaluated by the SCCAI, were not considered by our modified scoring system because extra-intestinal manifestations were beyond the aims of our study and general well-being was more deeply investigated by the modified IBDQ. Traces of blood in stools had to be present at least once a week to be considered in the score. The SCCAI ranged from 0 (no symptoms) to 11. The RTOG/EORTC toxicity scales evaluated stool frequency, bleeding, abdominal pain, severe complications and the need for medical, endoscopic or surgical interventions. The RTOG/EORTC toxicity scales ranged from score 0 (no symptoms) to score 4. The IBDQ includes 32 questions grouped into four categories: bowel function, systemic symptoms, emotional function and social function; response options are presented as seven-point Lickert scales, ranging from 32 (worst quality of life) to 224 (best).[8]

The endoscopic assessment was performed with the flexible sigmoidoscopy. Endoscopic findings were described using the 'World Organisation of Digestive Endoscopy' terminology[9] and evaluated according to the Vienna Rectoscopy Score (VRS).[10] The VRS considered the presence and the severity of five parameters: mucosal congestion, telangiectasia, ulcer, stricture and necrosis. The VRS ranged from 0 (absence of rectal mucosal changes) to 5.

Clinical evaluation was performed before starting radiotherapy, 1 month after the end of treatment and every 3 months thereafter. Patients were endoscopically evaluated before randomisation as a part of the screening procedure, 3 and 12 months after the end of radiotherapy or if judged as necessary by the referring physician or by the investigators. During each visit, participants underwent symptom evaluation by the same trained physician interviewer (LL). During the whole study period, rectosigmoidoscopy was performed by the same endoscopist (LF), with expertise in radiation-induced lesions recognition and treatment, who was unaware of the responses to the questionnaires. Doubtful cases were discussed with a second investigator (FB). Patients who developed symptoms during the follow-up, such as diarrhoea, urgency and rectal bleeding, were invited to directly contact the investigators by phone call in order to evaluate whether to anticipate the scheduled control.

Haemorrhagic proctopathy was defined severe when endoscopic and/or hyperbaric oxygen treatments were needed due to the development of anaemia (Hb <13.5 g/dL) and drop of haemoglobin level of at least 1.5 g/dL.

Colonoscopy with retrograde ileoscopy was offered in case of persistent bleeding and/or anaemia despite treatments and to patients without clinically significant bleeding (i.e. not causing anaemia), lasting more than 3 months.

© 2011 Blackwell Publishing Ltd

Statistical considerations

Sample size estimation was based on the assumption that 45% of the patients on placebo would develop rectal bleeding during follow-up[4] and that preventive treatment with beclomethasone dipropionate would decrease the bleeding rate to 20%. A sample size of 54 patients per group would give the study power of 80%, with a two tailed alpha = 0.05. Therefore, the sample size population was fixed at 120 patients.

Analyses were conducted on the intent-to-treat (ITT) and Per Protocol (PP) basis. ITT analysis was defined as all patients who took at least one dose of study drug and had at least one assessment after randomisation. Per Protocol analysis was defined as ITT patients who completed the study without significant protocol violations. As the results conducted on the ITT and PP basis did not substantially differed, only the results according to ITT analysis were provided. The safety assessment was performed on randomised patients who took at least one dose of study drug.

The decision to analyse the individual components of the SCCAI and IBDQ questionnaires was taken before starting the study. The comparisons between treatments have been performed by the unpaired *t*-test or Wilcoxon's two sample test according to the normality or nonnormality of data distribution. Dichotomised data have been analysed using the chi-square test (χ^2) and the odds ratio was calculated. If the normality of data distribution for continuous or discrete variables was questionable, the rank transformation was performed and an appropriate nonparametric test was applied. A survival analysis was performed by the Kaplan–Meier method and log-rank test considering the time (months) from the end of radiotherapy to the first appearance of blood in the stools. The impact of beclomethasone dipropionate preventive treatment on radiation-induced proctopathy was also measured as the number needed to treat (NNT), computed as the inverse of the absolute risk reduction. The Vienna Rectoscopy Scores were separately analysed applying the Cochran-Mantel-Haenszel chi-quare test; however, scores >2 were grouped together since too few patients presented scores >2.

The odds ratios (ORs) and their corresponding 95% confidence intervals (95% CIs) of developing rectal bleeding associated with several risk factors (radiotherapy parameters, surgical procedures and concomitant treatments) were estimated using logistic regression models.

The statistical analyses were performed using the package SAS System version 9.2 (Cary, North Carolina, USA).

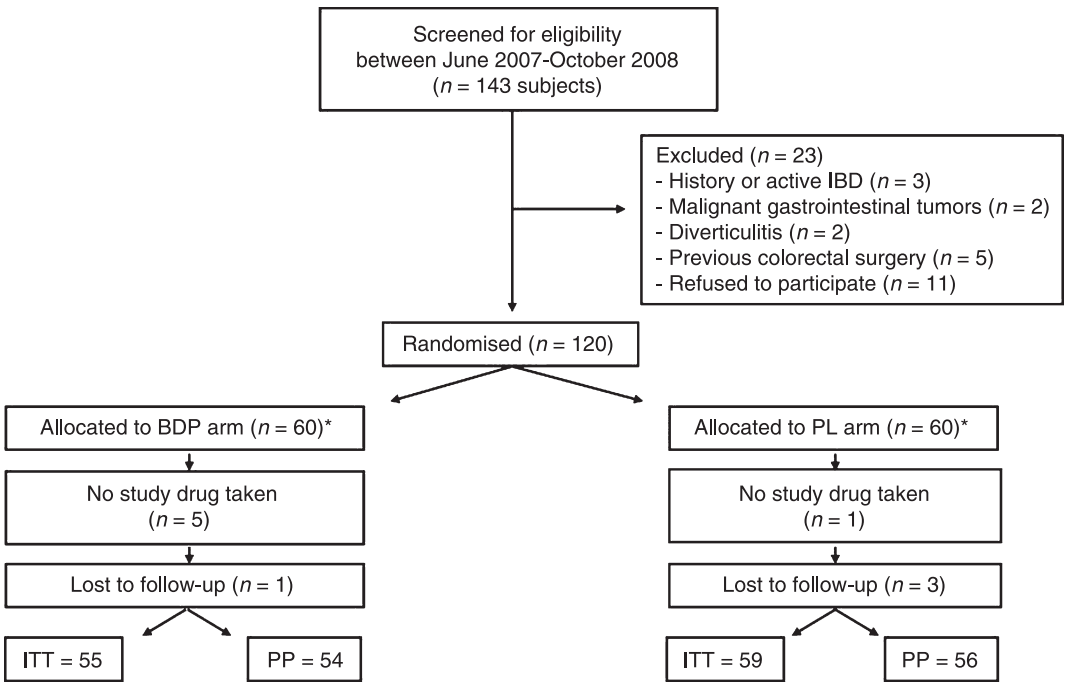

Figure 1 | Flow-chart of the study. IBD, inflammatory bowel disease; BDP, beclometasone dipropionate; PL, placebo; ITT, Intention-To-Treat; PP, Per Protocol. *Allocated intervention was given to all patients.

© 2011 Blackwell Publishing Ltd

RESULTS

Study population

The first patient was randomly assigned in June 2007 and the last patient was enrolled in October 2008. The follow-up of the last patient was completed in February 2010. Throughout the study period, 143 potentially eligible patients have been screened, out of whom 12 patients met at least one exclusion criterion and 11 declined participation. Therefore, 120 patients were eligible and randomly assigned; 60 patients in the beclomethasone dipropionate arm and 60 patients in the placebo arm. Six patients did not take any of the study drugs and were excluded from the analyses (ITT population = BDP arm: 55 patients; placebo arm: 59 patients); four more patients were lost to follow-up (PP population = beclomethasone dipropionate arm: 54 patients; placebo arm: 56 patients). A flow-chart of the study is shown in Figure 1.

Demographics and baseline characteristics

All patients were Caucasians. No statistically significant differences have been found between the two treatment groups (Table S1, published on-line). Furthermore, there were no differences in the distribution of pathological findings diagnosed at baseline rectosigmoidoscopy between the two treatment arms.

Modified Simple Clinical Colitis Activity Index. Three and 12 months after the end of radiotherapy, the analyses of the SCCAI total score did not show any difference between the two treatment arms. However, when each item of the SCCAI score was separately considered, the analysis showed a statistically significant lower bleeding rate in the BDP arm (Table S2, published on-line). Indeed, 12 of 55 patients (22%) in the BDP arm and 25 of 59 patients (42%) in the placebo arm presented blood in the stool, at least once a week, yielding an OR of 0.38 (95% CI: 0.17–0.86), with a number needed to treat of 5 (Figure 2). The survival analysis that evaluated the time for the first occurrence of blood in stools showed that patients randomised to the BDP arm presented later onset of blood in the stool than patients on placebo (Log-rank test 4.587; $P = 0.032$; Figure 3).

Radiation Therapy Oncology Group acute and late toxicity scales. Three and 12 months after the end of radiotherapy, no differences were found between the two treatment groups based on the RTOG/EORTC toxicity scales (Figure 4).

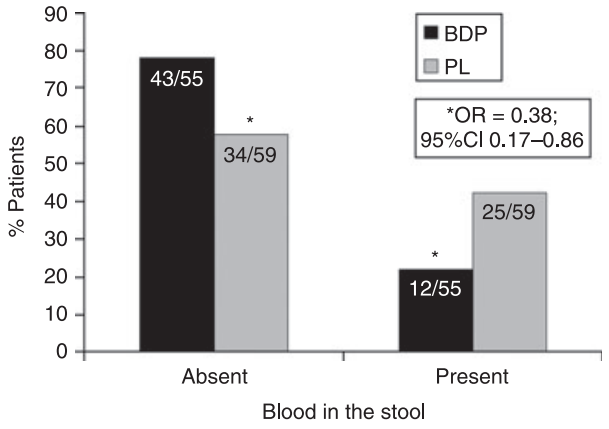

Figure 2 | Patients on beclomethasone dipropionate treatment present a significantly lower rectal bleeding rate than patients randomised to placebo, yielding an OR of 0.38 (95% CI: 0.17–0.86), with a number needed to treat of 5. BDP, beclomethasone dipropionate; PL, placebo.

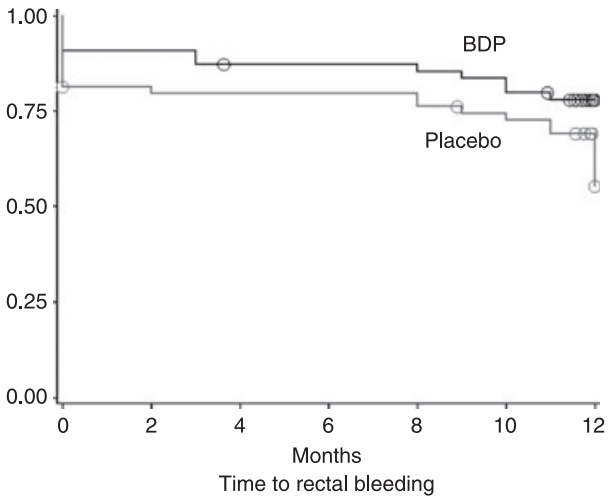

Figure 3 | Kaplan–Meier graph indicating time to rectal bleeding from the end of radiotherapy. Patients randomised to the beclomethasone dipropionate (BDP) arm presented later onset of blood in the stool than patients on placebo (Log-rank test 4.587; $P = 0.032$).

Inflammatory Bowel disease Quality of Life Index

After 12 months of follow-up, as shown in Figure 5, the reduction of the total IBDQ scores between the two groups of treatment was significantly more pronounced for patients on placebo ($P = 0.034$). In particular, a subanalysis of the four categories showed that the difference between the two groups of treatment was mostly evident

© 2011 Blackwell Publishing Ltd

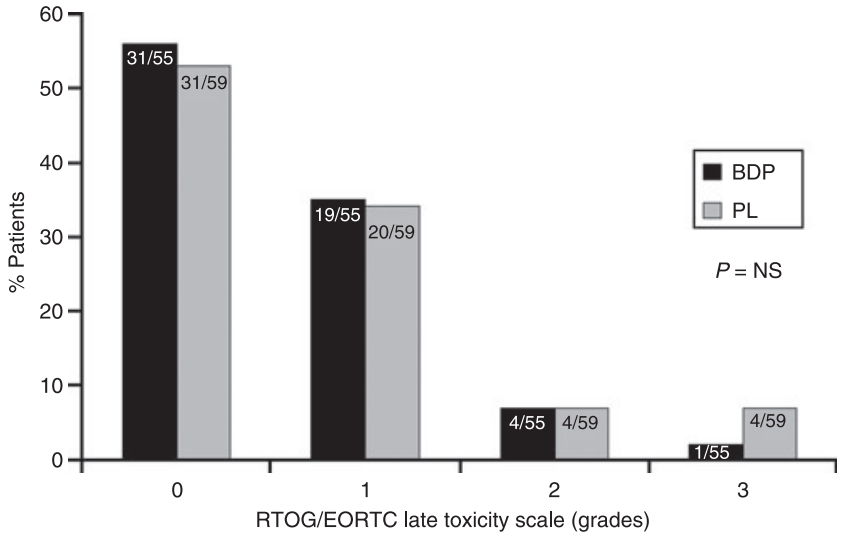

Figure 4 | Morbidity grade according to the Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC) toxicity scales after 12 months of follow-up. The two treatment groups did not show any statistical difference. BDP, beclomethasone dipropionate; PL, placebo.

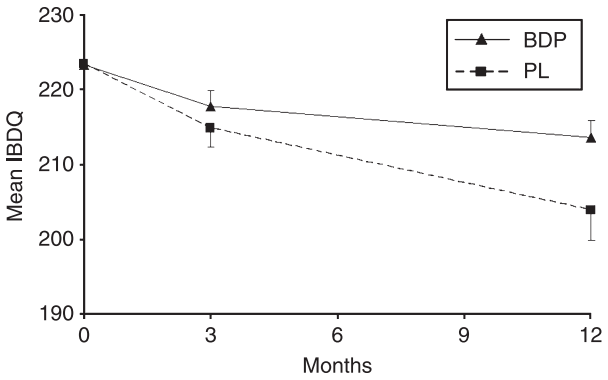

Figure 5 | Changes of the mean IBDQ scores during follow-up after radiotherapy treatment. After 12 months of follow-up, the reduction of the total IBDQ scores between the two groups of treatment was significantly more pronounced for patients on placebo (P = 0.034).

for the emotional status (P = 0.028). The lower reduction of IBDQ score reported by patients randomised to BDP treatment may be attributed to the different rectal bleeding rates reported in the two arms of treatment. Indeed, patients who reported episodes of rectal bleeding during follow-up had significantly lower IBDQ total scores (P < 0.001) than patients without rectal bleeding, regardless of the treatment group; this finding was also confirmed when the emotional score was separately considered (P < 0.001). Patients in the placebo group had a significantly higher bleeding rate than those on BDP and this probably explains why the total IBDQ score at 12 months was lower in the placebo than the BDP arm, although the total SCCAI and RTOG/EORTC scores were similar in the two groups.

Vienna rectoscopy score

Three months after the end of radiotherapy, no difference was noted between the two treatment groups. However, after 12 months of follow-up, the Vienna Rectoscopy Score was significantly lower in the beclomethasone dipropionate group (Figure 6). Patients randomised to the BDP treatment presented a significantly lower risk of developing mucosal changes (p 0.028).

Severe hemorrhagic proctopathy

During the whole period of the study, severe haemorrhagic proctopathy, defined as the development of anaemia and a drop of the haemoglobin level of at least 1.5 g/dL, was diagnosed in 10 patients, four in the BDP arm and six in the placebo arm. Three cases developed severe haemorrhagic proctopathy within 3 months from the end of radiotherapy (one patient on beclomethasone dipropionate and two patients on placebo) and seven cases thereafter. All patients reported anaemia (mean haemoglobin value 11.0 ± 1.2 g/dL) and were successfully managed with APC endoscopic treatment (four patients), hyperbaric oxygen treatment (four patients) or a combination of both (two patients), with resolution of

© 2011 Blackwell Publishing Ltd

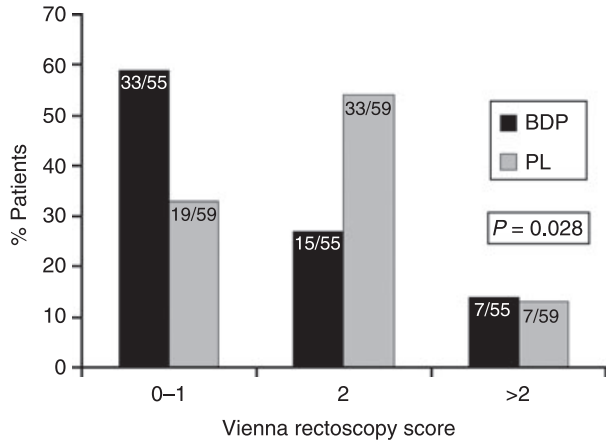

Figure 6 | Vienna Rectoscopy Score after 12 months of follow-up. After 12 months of follow-up, the Vienna Rectoscopy Score was significantly lower in the beclomethasone dipropionate group; in particular, patients randomised to the BDP treatment presented a significantly lower risk of developing mucosal changes (*P* 0.028), mainly multiple angiectasias (VRS ≥2). BDP, beclomethasone dipropionate; PL, placebo.

both bleeding and anaemia. One patient, 8 months after the end of APC treatment, presented a rectal severe fibrotic stenosis, that was successfully managed with endoscopic balloon dilation; the patient was in the placebo arm.

Risk factors associated with the development of radiation-induced proctopathy

The analysis of the risk factors associated with the development of radiation-induced proctopathy demonstrated a significant association between the percentage of rectum volume receiving at least 60Gy (V60) and the development of rectal bleeding, yielding an OR of 1.134 (95% CI 1.037–1.239). In particular, patients with a V60 > 45% presented a three-fold increased risk of bleeding than patients with lower values (OR 3.0; 95% CI 1.3–7.1).

Compliance and adverse events

Compliance to the treatments was similar in the two randomisation groups: 90.2 ± 14.5% in the BDP group and 89.7 ± 14.5% in the placebo group ($P = 0.861$). No patient reported adverse events related to the study treatments.

DISCUSSION

The main finding of our study is that topical rectal treatment with BDP, during radiotherapy for prostate cancer, reduces significantly the post-radiation risk of bleeding and of rectal mucosal changes. Furthermore, beclomethasone dipropionate preventive treatment significantly improves the patient's quality of life. However, beclomethasone dipropionate treatment does not influence the occurrence of other radiation-induced symptoms (changes in defaecatory frequency and/or continence).

Soon after the beginning of radiotherapy, an intense acute mucosal inflammatory reaction develops in those areas exposed to the radiation-treatment. Subsequently, this acute reaction can either induce a regenerative process or, alternatively, proceed to a more severe condition with prominent vascular involvement and fibrotic changes.[11–15] Angiogenesis is an integral and crucial component of the chronic inflammatory process.[16, 17] Indeed, within weeks to months after radiation treatment, the normal endothelium is replaced by thickened fibrous layer, leading to the narrowing or even occlusion of the vasculatures, with progressive ischaemia and necrosis of the supplied tissue.[11–15, 18, 19] Prophylactic treatment with beclomethasone dipropionate during radiotherapy may reduce the acute inflammatory process, thus reducing the development of a chronic inflammatory reaction and of vascular changes. Vascular Endothelial Growth Factor (VEGF) is an essential mediator of pathological angiogenesis during chronic inflammation[20] and several lines of evidence have shown a modulator effect of corticosteroid treatment on the pro-angiogenic VEGF-mediated pathway.[21–23] In our study, the effect of BDP treatment on the radiation-induced inflammatory process and neo-angiogenesis was represented by the significantly lower Vienna Rectoscopy Score and the consequent lower bleeding risk.

In our study, endoscopic and hyperbaric oxygen treatments were performed only in those patients in whom rectal bleeding caused anaemia. In the common clinical practice, the presence of rectal bleeding, despite its severity, is considered a sufficient indication for endoscopic and hyperbaric oxygen treatments.[24, 25] Our choice was to avoid unnecessary treatments, as bleeding may spontaneously improve over time.[26] Therefore, patients with rectal bleeding but without anaemia were reassured about their condition and invited to strictly monitor their symptoms.

Topical preventive beclomethasone dipropionate treatment does not seem to substantially influence neither diarrhoea nor urgency rates. These symptoms have a multi-factorial pathogenesis.[4] Diarrhoea might be in relation to different pathogenic mechanisms not influenced by topical corticosteroid (i.e. bile-salt malabsorption,

Aliment Pharmacol Ther 2011; 34: 628–637
© 2011 Blackwell Publishing Ltd

bacterial overgrowth). Of note, in our population, the frequency of diarrhoea (5–6%), was substantially lower than that reported in other studies (about 25–50%).[4] Different selection criteria, assessing methods and different definitions may partly explain this discrepancy. Similarly, urgency of defecation and faecal incontinence present a multi-factorial pathogenesis and have been correlated to the deterioration of ano-rectal function, because of the alteration of the rectal capacity, the basal sphincter function and to the irradiation of the anal region.[27–29] The formulation used in our study, enema and suppository, might not be the best choice to protect the anal region from the irradiation; a topical gel formulation might be preferable. Finally, it should be noted that, based on the rates of diarrhoea and of urgency observed in our study, thousands of patients would be needed to show a difference between treatment groups, which is beyond the capacity of our centre's recruitment.

Radiation-induced syndrome affects the quality of life in up to 50% of patients.[30] Most of the published trials do not include a quality-of-life assessment. However, the potential impact of radiation therapy on patient's quality of life needs careful attention and should be exposed to the patient before the beginning of treatment. Beclomethasone dipropionate preventive treatment seemed to better preserve the patient's quality of life; in particular the emotional status (e.g., anger, depression, irritability) was less frequently altered.

Higher radiation doses are associated with improved tumour control outcomes, however are also associated with increased risk of late radiation-induced side effects; therefore, the significant association between the percentage of rectum volume receiving at least 60Gy (V60) and the development of rectal bleeding was not unexpected.

Several studies have investigated the efficacy of preventive topical or systemic treatments showing no beneficial or even harmful effects.[31–36] However, most of these studies presented several methodological limitations (lack of placebo or inadequate blinding), limited follow-up (<3 months), lack of endoscopic controls or were based on small sample size populations. At the moment, there is only one randomised, double-blind, placebo-controlled, multicentre study investigating the effect of an other corticosteroid, budesonide, for the prevention of radiation-induced proctopathy (ClinicalTrials.gov identifier: NCT00828230); the study is currently still recruiting the 32 estimated participants, therefore any comparison is not yet feasible.

In our study, all bias influencing the internal validity were adequately minimised.[37] The baseline rectosigmoidoscopy allowed excluding patients with baseline pathological conditions that could have altered the results. The implementation of endoscopic controls provided a more accurate assessment of the effects of radiotherapy.[38] Unavoidably, symptoms are translated into various grades of toxicity when different grading systems are used and there is no general and widely accepted consensus on which system should be preferred. The RTOG/EORTC questionnaire is the most used scoring system for the assessment of radiation-induced side effects; however, it presents several limitations because all symptoms are not adequately evaluated. We implemented two more questionnaires, to complete the clinical assessment and investigate the patient's quality of life. These two questionnaires are usually implemented for patients with inflammatory bowel diseases but not for radiation-induced proctopathy; nevertheless, the similarities between these two pathological conditions have been broadly underlined.[39, 40] In addition, questionnaires used in benign gastrointestinal diseases have shown to be more sensitive and much easier to use than questionnaires specific for radiation-induced toxicity.[8, 41] The external validity of our findings cannot be extended to patients irradiated for other pelvic cancers or with different type of radiotherapy (i.e., intensity-modulated radiotherapy).

Liquid enemas reach all sites potentially irradiated during radiotherapy, as this formulation may move even up to the splenic flexure.[42] The choice to provide suppositories after the end of radiotherapy was mainly due to two reasons: (i) protection of the more probably irradiated site, as this formulation normally reaches the upper rectum[42] and (ii) avoiding a drop of compliance. Indeed, the compliance to the study drugs was high (about 90%), although a lower rate might be expected in the clinical practice.

While radiation-induced syndrome is usually described at a median of eight to 12 months after the completion of radiotherapy,[43, 44] proctopathy may appear even several years after.[45] Therefore, 1 year of follow-up could have not been sufficient to completely investigate the preventive effect of beclomethasone dipropionate treatment.

Our study is the first trial that shows the preventive efficacy of BDP for radiation-induced rectal bleeding. Therefore, although encouraging, any clinical implication seems premature and further trials should be performed before providing any suggestions. Furthermore, longer follow-up is needed to ascertain whether beclomethasone dipropionate preventive treatment reduces or simply

© 2011 Blackwell Publishing Ltd

delays the time of first occurrence of blood in the stools. Finally, BDP treatment does not seem to prevent other radiation-induced symptoms (changes in bowel frequency and/or continence). Since the incidence of radiation-induced proctopathy is substantially higher than other gastrointestinal disorders with comparable deterioration of the quality of life (e.g., IBD), the lack of interest on this disease is astonishing.[39] This is mainly attributed to the fact that radiation-induced chronic toxicity is often overlooked and not seen as a 'disease'.[40] We expect our study to turn the focus of attention towards the radiation-induced syndrome and promote further studies.

ACKNOWLEDGEMENTS

Declaration of personal interests: Professor Franco Bazzoli has been part of the scientific board of Axcan Pharma Inc. *Declaration of funding interests*: Sofar s.p.a., (Trezzano Rosa, Milan, Italy) provided both the beclomethasone dipropionate and the placebo used in our trial and funded the study logistics. This study was designed by the investigators. Statistical analyses were performed by the Contract Research Organization GB Pharma (Pavia, Italy). The investigators interpreted and reviewed the results and were responsible for the manuscript writing and submission for publication.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Baseline characteristics of the randomised cohort. The two treatment arms did not present significant differences. BDP, beclomethasone dipropionate; PL, placebo.

Table S2. Separated analysis of each Simple Clinical Colitis Activity Index (SCCAI) score item. Twelve months after the end of radiotherapy, patients randomised in the BDP arm showed a statistically significant lower bleeding rate than patients in the placebo arm. At opposite, the analysis of the other items did not show any statistical difference. BDP, beclomethasone dipropionate; PL, placebo.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**: 74–108.
2. Denham JW, O'Brien PC, Dunstan RH, *et al.* Is there more than one late radiation proctitis syndrome? *Radiother Oncol* 1999; **51**: 43–53.
3. Denton A, Forbes A, Andreyev J, Maher EJ. Non surgical interventions for late radiation proctitis in patients who have received radical radiotherapy to the pelvis. *Cochrane Database Syst Rev* 2002; **1**: CD003455.
4. Andreyev J. Gastrointestinal symptoms after pelvic radiotherapy: a new understanding to improve management of symptomatic patients. *Lancet Oncol* 2007; **8**: 1007–17.
5. Hanauer SB. New steroids for IBD: progress report. *Gut* 2002; **51**: 182–3.
6. Walmsley RS, Ayres RC, Pounder RE, Allan RN. A simple clinical colitis activity index. *Gut* 1998; **43**: 29–32.
7. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995; **31**: 1341–6.
8. Olopade FA, Norman A, Blake P, *et al.* A modified Inflammatory Bowel Disease questionnaire and the Vaizey Incontinence questionnaire are simple ways to identify patients with significant gastrointestinal symptoms after pelvic radiotherapy. *Br J Cancer* 2005; **92**: 1663–70.
9. Crespi M, Delvaux M, Schaprio M, Venables C, Zwiebel F. Working Party Report by the Committee for Minimal Standards of Terminology and Documentation in Digestive Endoscopy of the European Society of Gastrointestinal Endoscopy. Minimal standard terminology for a computerized endoscopic database. Ad hoc Task Force of the Committee. *Am J Gastroenterol* 1996; **91**: 191–216.
10. Wachter S, Gerstner N, Goldner G, Potzi R, Wambersie A, Potter R. Endoscopic scoring of late rectal mucosal damage after conformal radiotherapy for prostatic carcinoma. *Radiother Oncol* 2000; **54**: 11–9.
11. Hasleton PS, Carr N, Schofield PF. Vascular changes in radiation bowel disease. *Histopathology* 1985; **9**: 517–34.
12. Brenn T, Fletcher CD. Postradiation vascular proliferations: an increasing problem. *Histopathology* 2006; **48**: 106–14.
13. Hovdenak N, Fajardo LF, Hauer-Jensen M. Acute radiation proctitis: a sequential clinicopathologic study during pelvic radiotherapy. *Int J Radiat Oncol Biol Phys* 2000; **48**: 1111–7.
14. Sedgwick DM, Howard GC, Ferguson A. Pathogenesis of acute radiation injury to the rectum. A prospective study in patients. *Int J Colorectal Dis* 1994; **9**: 23–30.
15. Haboubi NY, Schofield PF, Rowland PL. The light and electron microscopic features of early and late phase radiation-induced proctitis. *Am J Gastroenterol* 1988; **83**: 1140–4.
16. Szekanecz Z, Koch AE. Vascular endothelium and immune responses: implications for inflammation and angiogenesis. *Rheum Dis Clin North Am* 2004; **30**: 97–114.
17. Jackson JR, Seed MP, Kircher CH, Willoughby DA, Winkler JD. The codependence of angiogenesis and chronic inflammation. *FASEB J* 1997; **11**: 457–65.
18. Martin M, Lefaix J, Delanian S. TGF-beta1 and radiation fibrosis: a master switch and a specific therapeutic target? *Int J Radiat Oncol Biol Phys* 2000; **47**: 277–90.

© 2011 Blackwell Publishing Ltd

19. Herskind C, Bamberg M, Rodemann HP. The role of cytokines in the development of normal-tissue reactions after radiotherapy. *Strahlenther Onkol* 1998; **174**(Suppl. 3): 12–5.
20. Carmeliet P. Angiogenesis in life, disease and medicine. *Nature* 2005; **438**: 932–6.
21. Pousa ID, Algaba A, Linares PM, *et al.* Corticosteroids modulate angiogenic soluble factors in ulcerative colitis patients. *Dig Dis Sci* 2010; **56**: 871–9.
22. Taha Y, Raab Y, Carlson M, *et al.* Steroids reduce local inflammatory mediator secretion and mucosal permeability in collagenous colitis patients. *World J Gastroenterol* 2006; **12**: 7012–8.
23. Greenberger S, Boscolo E, Adini I, Mulliken JB, Bischoff J. Corticosteroid suppression of VEGF-A in infantile hemangioma-derived stem cells. *N Engl J Med* 2010; **362**: 1005–13.
24. Postgate A, Saunders B, Tjandra J, Vargo J. Argon plasma coagulation in chronic radiation proctitis. *Endoscopy* 2007; **39**: 361–5.
25. Clarke RE, Tenorio LM, Hussey JR, *et al.* Hyperbaric oxygen treatment of chronic refractory radiation proctitis: a randomized and controlled double-blind crossover trial with long-term follow-up. *Int J Radiat Oncol Biol Phys* 2008; **72**: 134–43.
26. O'Brien PC, Hamilton CS, Denham JW, Gourlay R, Franklin CI. Spontaneous improvement in late rectal mucosal changes after radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2004; **58**: 75–80.
27. Heemsbergen WD, Hoogeman MS, Hart GA, Lebesque JV, Koper PC. Gastrointestinal toxicity and its relation to dose distributions in the anorectal region of prostate cancer patients treated with radiotherapy. *Int J Radiat Oncol Biol Phys* 2005; **61**: 1011–8.
28. Yeoh EE, Botten R, Russo A, *et al.* Chronic effects of therapeutic irradiation for localized prostatic carcinoma on anorectal function. *Int J Radiat Oncol Biol Phys* 2000; **47**: 915–24.
29. Yeoh EK, Holloway RH, Fraser RJ, *et al.* Anorectal function after three- versus two-dimensional radiation therapy for carcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 2009; **73**: 46–52.
30. Gami B, Harrington K, Blake P, *et al.* How patients manage gastrointestinal symptoms after pelvic radiotherapy. *Aliment Pharmacol Ther* 2003; **18**: 987–94.
31. Sanguineti G, Franzone P, Marcenaro M, Foppiano F, Vitale V. Sucralfate versus mesalazine versus hydrocortisone in the prevention of acute radiation proctitis during conformal radiotherapy for prostate carcinoma. A randomized study. *Strahlenther Onkol* 2003; **179**: 464–70.
32. Kertesz T, Herrmann MK, Zapf A, *et al.* Effect of a prostaglandin – given rectally for prevention of radiation-induced acute proctitis–on late rectal toxicity. Results of a phase III randomized, placebo-controlled, double-blind study. *Strahlenther Onkol* 2009; **185**: 596–602.
33. Martenson JA, Bollinger JW, Sloan JA, *et al.* Sucralfate in the prevention of treatment-induced diarrhea in patients receiving pelvic radiation therapy: a North Central Cancer Treatment Group phase III double-blind placebo-controlled trial. *J Clin Oncol* 2000; **18**: 1239–45.
34. O'Brien PC, Franklin CI, Dear KB, *et al.* A phase III double-blind randomised study of rectal sucralfate suspension in the prevention of acute radiation proctitis. *Radiother Oncol* 1997; **45**: 117–23.
35. Khan AM, Birk JW, Anderson JC, *et al.* A prospective randomized placebo-controlled double-blinded pilot study of misoprostol rectal suppositories in the prevention of acute and chronic radiation proctitis symptoms in prostate cancer patients. *Am J Gastroenterol* 2000; **95**: 1961–6.
36. Fuccio L, Guido A, Eusebi LH, *et al.* Effects of probiotics for the prevention and treatment of radiation-induced diarrhea. *J Clin Gastroenterol* 2009; **43**: 506–13.
37. Juni P, Altman DG, Egger M. Systematic reviews in health care: assessing the quality of controlled clinical trials. *BMJ* 2001; **323**: 42–6.
38. Williams HR, Vlavianos P, Blake P, Dearnaley DP, Tait D, Andreyev HJ. The significance of rectal bleeding after pelvic radiotherapy. *Aliment Pharmacol Ther* 2005; **21**: 1085–90.
39. Andreyev J. Gastrointestinal complications of pelvic radiotherapy: are they of any importance? *Gut* 2005; **54**: 1051–4.
40. Andreyev HJ, Wotherspoon A, Denham JW, Hauer-Jensen M. Defining pelvic-radiation disease for the survivorship era. *Lancet Oncol* 2010; **11**: 310–2.
41. Khalid U, McGough C, Hackett C, *et al.* A modified inflammatory bowel disease questionnaire and the Vaizey Incontinence questionnaire are more sensitive measures of acute gastrointestinal toxicity during pelvic radiotherapy than RTOG grading. *Int J Radiat Oncol Biol Phys* 2006; **64**: 1432–41.
42. Regueiro M, Loftus EV Jr, , Steinhart AH, Cohen RD. Clinical guidelines for the medical management of left-sided ulcerative colitis and ulcerative proctitis: summary statement. *Inflamm Bowel Dis* 2006; **12**: 972–8.
43. Eifel PJ, Levenback C, Wharton JT, Oswald MJ. Time course and incidence of late complications in patients treated with radiation therapy for FIGO stage IB carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys* 1995; **32**: 1289–300.
44. Fischer L, Kimose HH, Spjeldnaes N, Wara P. Late progress of radiation-induced proctitis. *Acta Chir Scand* 1990; **156**: 801–5.
45. Lee HL. Images in clinical medicine. Radiation proctitis. *N Engl J Med* 2010; **363**: 1163.

© 2011 Blackwell Publishing Ltd