Abstract

Background

Preclinical data suggest that combined gamma-tocotrienol with pentoxifylline ameliorates radiotherapy-induced gastrointestinal damage.

Aim

To test whether gastrointestinal symptoms arising after radiotherapy, and persisting after maximal medical therapy, can be improved using Tocovid SupraBio 200mg and pentoxifylline 400mg orally twice daily for one year. Patients stratified by severity of symptoms, and randomised to active treatment or matched placebo were assessed after 12 months. The primary end point was improvement in gastrointestinal symptoms measured using the Inflammatory Bowel Disease Questionnaire, bowel subset score. Changes in bio-markers of fibrosis were assessed.

Results

62 patients, median age 66, 34(55%) treated for prostate, 21(34%) gynaecological, 6(10%) anal and one(1%) rectal cancer were recruited; 40(65%) randomised to treatment, 22(35%) to placebo, 39 months (median) after radiotherapy completion. Gamma tocotrienol was not detected in serum in 41% of treated patients, despite good compliance with study medication. Treatment was completed in 28(70%) and 17(77%) patients in the treatment and placebo groups respectively. No improvement in symptom scores nor in quality of life was identified. Thirteen serious adverse events occurred. A transient ischaemic attack, was possibly related to pentoxifylline, others were assessed as unlikely to be related to treatment. Levels of EGF, PDGF and FGF were significantly reduced and consistent trends in reduced inflammation were seen during treatment but were not sustained once treatment ended.

Summary

This single centre study closed prematurely and therefore data interpretation is of necessity limited. No clinical benefit was demonstrated. However, biochemical data suggest that this intervention does have anti-inflammatory and anti-fibrotic effects.

Introduction

Radiotherapy improves local tumour control and long-term survival of patients with many tumours arising in the pelvis. More than one million such patients annually are treated with radiotherapy worldwide and the use of pelvic irradiation is predicted to rise steeply in the future.

Late-onset bowel toxicity is related to patient-related factors, the use of concomitant chemotherapy, radiation dose, volume, time and fractionation and a poorly characterised, dose-independent "consequential effect" (1). No biological marker of radiation-induced toxicity has yet been defined. Instead toxicity is measured in terms of the development of new symptoms after treatment despite the unreliability of symptoms as an objective measure of toxicity (2). However, what is clear is that treatment-induced complications are an inevitable consequence of increased local tumour control rates and overall survival, and that chronic symptoms can exact a high price in terms of impaired quality of life (3, 4).

The underlying pathology of radiation injury to the gastrointestinal (GI) tract is an initial inflammatory and ischaemic mucosal process. Later, a fibrotic process predominates and can be progressive (5). Gastrointestinal symptoms arise as a result of loss of physiological function within the GI tract (6). Some pathological changes following the end of radiotherapy resolve (7), however, persisting new gastrointestinal symptoms if present at one year, rarely resolve spontaneously (8). A number of chronic symptom syndromes following radiotherapy to the pelvis have been defined (5, 9). As the number of patients undergoing successful pelvic radiotherapy increases, the morbidity of chronic radiation bowel toxicity becomes more common.

The management of chronic radiation-induced bowel symptomatology is inadequate. No single treatment to ameliorate or reverse the pathological processes induced by radiotherapy has been defined (10). Individual symptoms may be improved by identifying the physiological causes for those symptoms and treating those physiological deficits (11, 12). A 'checklist' based assessment to diagnose the cause for symptoms, allows the delivery of targeted therapy and leads to significant benefit from clinical intervention (8, 12, 13). However, residual symptoms are commonplace.

One possible approach to deal with residual pathological changes triggered by the radiotherapy and hence residual symptoms, is to attempt to reverse radiation-induced fibrosis. Animal studies – mostly in the acute setting during or soon after radiotherapy - have demonstrated evidence of radiation-induced regression of fibrosis in response to α-tocopherol (vitamin E) (14) or pentoxifylline (PTX) or both (15-17). In humans, some studies, mostly small, and many non-randomised, have suggested that pentoxifylline - taken with or without Vitamin E may have a role in reversing radiation-induced fibrosis in a variety of clinical settings (15, 18-27) but not all the published evidence confirms therapeutic benefit (28-31).

Vitamin E has many isoforms. One study in which human endothelial cell cultures were treated with α or γ–tocopherol and gamma tocotrienol (GT3), suggest that GT3 is biologically more potent than α or γ–tocopherol based on the number and nature of transcripts induced (32). In particular, GT3 induced multiple changes in pathways important in the cellular response to radiation exposure particularly those associated with cell death and apoptosis, oxidative stress, responses to DNA damage, cell cycle control, inflammation, blood vessel development and hematopoiesis. GT3 is also effective in protecting experimental animals against acute radiation toxicity (33) - possible mechanisms may include improved antioxidant properties but also the inhibition of HMG-CoA reductase promoting endothelial, gastrointestinal and haematological stem cell protection (34, 35). Pentoxifylline enhances some of these effects (35).

Bearing these advances in mind, a double-blind randomised controlled phase II trial of Tocovid SupraBio, an oral, well tolerated tocotrienol-rich preparation combined with pentoxifylline was conducted in patients suffering gastrointestinal adverse effects of pelvic radiotherapy persisting after optimal targeted treatment of all identifiable physiological deficits. Studies suggest that Tocovid SupraBio has good absorption and tissue penetration (36) and there are no significant concerns of any significant toxicity in human tissues (37, 38) The aim was to assess whether Tocovid SupraBio plus pentoxifylline improved gastrointestinal symptoms after all other treatments had been exhausted.

Methods

This was a prospective, single centre randomised placebo controlled trial performed in a specialist clinic for patients with GI side effects of cancer therapies. The study was reviewed and approved before it started by the institutional clinical research committee, the National Research Ethics Committee and the Medicines and Healthcare Products Regulatory Agency. The study was conducted in accordance with the Helsinki Declaration, 1975 (revised 1983). Patients gave written informed consent before study enrolment. Interim safety data was monitored by an Independent Data Monitoring Committee.

Study participants

To be eligible to participate in this study, patients had to be older than 18 years and have undergone radical radiotherapy for a malignant pelvic neoplasm (T1-4 N0-2 M0) of the prostate, testis, bladder, uterine cervix, uterus, vagina, vulva, anal canal or ovary. Patients had to have completed at least 12 months follow up after the end of radiotherapy (24 months for patients with past history of stage T4 and/or N2 disease and be experiencing gastrointestinal symptoms attributable to radiotherapy of grade 2 or higher in any CTCAE v4 category or grade 1 with difficult intermittent symptoms. Maximal medical therapy and life style advice was provided systematically following previously published protocols (8, 39)**.**Symptoms which were relieved and sustained over a 3 month period led to ineligibility to participate in this trial. Patients had to be less than 7 years since the completion of radiotherapy and have no evidence of cancer recurrence.

Patients were not eligible for this trial if they had previously used any dietary supplements containing alpha-tocopherol above a daily dose of 30mg at any time during the last three months or had received any treatment with pentoxifylline at any time since radiotherapy. Other exclusion criteria included allergy to soya or known hypersensitivity to pentoxifylline, pregnancy, breast feeding, ischaemic heart disease, uncontrolled hypertension, hypotension, acute myocardial infarction, cerebral haemorrhage, retinal haemorrhage, renal failure, liver failure and medication with insulin, ketorolac or vitamin K.

Treatment and follow up

Randomisation was performed by the independent Institute of Cancer Research Clinical Trials & Statistics Unit (ICR-CTSU) using computer generated random permuted blocks. Patients

were allocated in a 2:1 ratio of Tocovid SupraBio™ 200mg orally twice daily plus pentoxifylline (PTX) 400mg orally twice daily for 12 months (the "treatment group") or to matched placebo. Pentoxifylline tablets were sourced by Mawdsley Brooks Ltd, UK within the European Union (EU). Pentoxifylline tablets were encapsulated and matching placebo capsules manufactured by The Royal Free Pharmacy Production Unit, UK and Tiofarma BV, The Netherlands. Tocovid SupraBio soft gel capsules and matching placebo were manufactured, packaged and labeled in accordance with EU Good Manufacturing Practice for Interventional Medicinal Products by Hovid Bhd, Malaysia. They contained d-Alpha-Tocotrienol 61.52mg, d-Gamma-Tocotrienol 112.80mg, d-Delta-Tocotrienol 25.68mg, d-Alpha-Tocopherol 91.60IU. Plant Squalene 51.28mg, Phytosterol Complex 20.48mg and hytocarotenoid Complex 360.00ug.

Randomisation was stratified by baseline severity of symptoms as assessed by the bowel subset of the modified Inflammatory Bowel Disease Questionnaire (IBDQ) (score ≥60 vs <60) and average daily fat intake (≥90g fat/day vs <90g fat/day). Pre-randomisation, patients completed modified IBDQ, EORTC Quality of Life Questionnaires (QLQ-C30 & QLQ-CR29) and the modified Gastrointestinal Symptom Rating Scale. Their symptoms were assessed using the modified CTCAE Version 4 form.

Patients were assessed at baseline, when additionally they completed a 7-day food diary and an interview with a dietician team to ensure patients as far as possible maintained a stable fat intake. Patients were followed up at 3, 6, 9, 12, and 24 months post-randomisation with clinical assessment, CTCAE assessment and self-assessment quality of life questionnaires. In addition, self-assessment quality of life questionnaires were also completed at 18 months.

Samples

Blood samples were collected before any treatment was given, one year and two years after randomisation. They were spun within 30 to 60 minutes of collection at 3000 rpm for 10 minutes at 4°C. The supernatant was pipetted into 32 separate aliquots and stored at -80°C. Samples for TGF beta analysis were spun as above a second time.

The levels of 41 inflammatory cytokines, chemokines and growth factors associated with fibrosis - EGF, FGF, Eotaxin, TGF-α, G-CSF, Flt, GM-CSF, Fractalkine, IFN-α2, IFN-γ, GRO, IL-10, MCP, IL-12P40, MDC, IL-12P70, IL-13, IL-15, sCD40L, IL-17A, IL-1RA, IL-1α, IL-9, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IP-10, MCP-1, MIP-1α, MIP-1β, TNF-α, TNF-β, VEGF, PDGF-AA,

PDGF-BB, and RANTES - were measured to assess whether the intervention led to detectable changes at the molecular level. using Luminex based bead array, the MILLIPLEX® MAP Human Cytokine/Chemokine panel (Cat. no. HCYTMAG-60K-PX41) on Luminex xMAP® platform using a magnetic bead format (MILLIPLEX® Analytes, Millipore, MA, USA,). In brief, 25 µL plasma samples were tested for the levels of these cytokines, using the multiplex immunoassay containing fluorescent labelled beads conjugated with specific monoclonal antibody for the target molecule, according to the manufacturer's recommendations. Samples were run on the Luminex, MAGPIX instrument (Luminex Corporation, Austin, TX, USA). Appropriate standards including 41 beads and quality control (provided in the kit) were run with the test sample plate. The xPonent 4.2 software was used to determine and interpret the data and concentrations of analytes in samples determined from the standards run in the test.

Blood levels of gamma tocotrienol (GT3) were measured at the McWhorter School of Pharmacy, Stamford University, USA. Calibration standards, blanks and QCs were prepared by spiking human serum (50 µL) with GT3 to achieve concentrations ranging from 20-5,000 ng/mL. Internal standard (0.2 mL of 1000 ng/mL AT3 in acetonitrile) was added to precipitate the serum proteins. After centrifugation for 5 minutes at 21,000g, the supernatant was transferred to limited volume auto-sampler vials and analysed in positive ion mode by LC/MS/MS.

The LC/MS/MS system consisted of Shimadzu system (Columbia MD) equipped with LC20-AD dual HLPC pumps, an SIL20-AC HT autosampler, and a DGU-20A2 in-line degasser. Detection was performed using an Applied BioSystems 4000 QTRAP (Applied Biosystems, Foster City, CA) triple quadruple mass spectrometer operated in the positive ion mode. Mass calibration, data acqusition and quantitation were performed using Applied Biosystem Analyst 1.6.2 software (Applied Biosystems, Foster City, CA).

Separation of the GT3 and the internal standard from the serum matrix was achieved using a Thermo BDS Hypersil C8, 100 X 2 mm 5 µm particle column. The mobile phase was delivered at a flow rate of 500 µL/min using a gradient elution profile consisting of DI water (A) and acetonitrile with 0.2% formic acid (B). The analyte and internal standard were detected using multiple reaction monitoring (MRM) for the following the following transitions: GT3 (m/z 410.5→151.3), AT3 (m/z 425.5→ 165.2).

Levels were compared between pre-treatment and 6 months post randomisation samples. Where pre-treatment blood samples were not available the 24 month post randomisation

sample was used as a baseline because it was anticipated that there would be no residual levels of GT3 in the blood 1 year after discontinuing treatment.

Statistical considerations

The primary endpoint was change in the bowel disease subset of the modified IBDQ at 12 months from randomisation. Secondary endpoints included changes at 12 months in rectal IBDQ bleeding score in those presenting with grade 2, 3 or 4 bleeding at baseline and change at 12 months in IBDQ faecal incontinence score in those presenting with grade 1 or greater incontinence at baseline. Other secondary endpoints include proportion of patients graded with marked/severe (grade 3 or 4) toxicity using CTCAE version 4, physician assessment of rectal dysfunction using the modified CTCAE version 4, patient self-assessments including QLQ-C30, CR29 and the Gastrointestinal Symptom Rating Scale and serum fibrosis marker levels.

Sample size estimation was based primarily on the primary endpoint of change in the bowel subset of the modified IBDQ based on results from a previous study (40). Ten points were used as an estimate of the standard deviation of the change at 12 months. A difference in questionnaire score of 7.5 was considered to represent a clinically worthwhile improvement in symptoms to 12 months of Tocovid SupraBio+PTX compared to placebo. It was calculated that 99 patients (66 GT3+PTX:33 placebo) were needed for 85% power employing a two-sided 1.67% significance level to detect this difference. A significance level of 1.67% was selected in order to keep a 5% overall false positive rate after inclusion of the secondary endpoints relating to changes in bleeding and faecal incontinence.

Analysis of efficacy was carried out on an intention to treat basis including all patients for whom the relevant endpoint could be assessed regardless of whether or not they received their allocated treatment; no imputation was made for missing data. The change from baseline to 12 months of the bowel subset of the IBDQ score was compared between treatments using an unpaired t-test following testing for normality. Secondary endpoints were assessed as the proportion of patients with an improvement in score, compared between treatments using Fisher's exact test. No formal comparisons were made for the other endpoints, analyses were descriptive only. Safety analyses were assessed in the population of patients who received at least one dose of allocated treatment and rates were compared between groups using fisher's exact test with a significance level of 1% to adjust for multiple

comparisons. Due to the exploratory nature of the biomarker analyses, no adjustment was made for multiplicity.

Results

Between March 2015 and June 2017, 62 patients were recruited (40 randomised to the treatment group; 22 to placebo) (figure 1). Recruitment to the trial closed in September 2017. Recruitment did not achieve the intended target for three reasons. There were two change in referral patterns as the trial progressed: a managerial, mainly economic decision to close the clinic to referrals from other hospitals, who previously provided a large proportion of patients seen with more difficult toxicity. Secondly, internal referrals with radiotherapy-induced toxicity could no longer be seen in a timely fashion because of the emerging large cohort of patients acutely ill with GI immunotherapy-induced toxicity. Thirdly, the chief investigator (a gastroenterologist) moved to another institution with consequent loss of expertise and subsequent further downsizing of the GI toxicity clinic.

Patient characteristics

Recruitment to the study is shown in the Consort diagram, figure 1. The characteristics of the patients randomised in the trial are shown in table 1. The majority of patients recruited to the study had undergone radiotherapy for prostate cancer; 55% (n=22, treatment group) and 54.5% (n=12, placebo group). Median age was 66 years, median time to study entry from completion of radiotherapy was 39 months.

Treatment was completed in 70% (n=28) and 77% (n=17) patients in the treatment/placebo groups respectively (table 2). The most common reason for early treatment discontinuation was adverse events (n= 4 treatment / n=2 placebo) and patient choice (n=3 treatment /n=1 placebo). Treatment never started in 5% (n=2) treatment and 4.5% (n=1) placebo groups.

Compliance with the study interventions

Excluding the three patients who never took any study medication following randomisation, compliance with prescribed medication, assessed at every clinic visit using diary cards kept by patients and counting leftover trial medication, was high. The median percentage of prescribed doses taken was calculated to be 96.6% (IQR: 80.1 – 98.4) in those randomized to active treatment and 97.4% (86.7 – 99.2) for those allocated to placebo. Assessment of GT3 levels in plasma showed no increases over baseline in any of the 20 patients with available samples allocated placebo. Three of the 34 (9%) patients allocated to active treatment had no 6 month sample for analysis. No increases above baseline of GT3 were observed in 4/34 (12%) patients in the treatment group. In

7/34 (21%) patients there were increases over baseline which were too small to quantify. 20/34 (59%) patients allocated Tocovid SupraBio had detected elevated levels of GT3 in blood taken at 6 months but in 2 patients this was very modest. . No participant had elevated levels of GT£ at 2 years (table 3).

Outcomes

Fifty-one patients were evaluable for assessment of the primary endpoint; 31 (77.5%, treatment group) and 20 (90.9%, placebo). Baseline characteristics in the evaluable population remained balanced; no differences between groups was observed for any characteristics. Mean change from baseline in the bowel subset of the IBDQ was 6.0 (95%CI = 2.3 to 9.6) and 8.1 (95%CI = 0.79 to 15.4) in the treatment and placebo groups respectively (figure 2). There was no difference between groups (mean difference = 2.1; 95% CI = -5.0 to 9.3; p=0.55).

Of the 8 patients (5 treatment group; 3 placebo) with grade 2 or greater bleeding by CTCAE at baseline, 60% (n=3, treatment) and 67% (n=2, placebo) had an improvement in symptoms. Of the 31 patients (21 treatment group; 10 placebo) with grade 1 or greater faecal incontinence at baseline, 62% (n=13, treatment, 60% (n=6, placebo) had an improvement in symptoms. No difference between treatments was observed for either endpoint (p>0.999 for both).

Quality of life scores did not differ between the treatment and placebo groups (data not shown), these included total scores, functional scales and symptom scores.

Adverse events

Adverse events of any grade and relatedness were reported by 93% (n=55) patients; 92% (n=35, treatment group) and 95% (n=20, receiving placebo). Most common reported adverse events were influenza-like illness (39%; n=23), followed by several gastrointestinal-related events. There was no difference seen in incidence between treatment groups for any event.

13 serious adverse events (6 treatment group; 7 placebo) were reported by 10% (n=6) patients; 10.5% (n=4, treatment group); 9.5% (n=2, placebo) (table 4). Of these, one patient had a transient ischaemic attack which was assessed as possibly related to pentoxifylline, all others were assessed as unlikely to be related to treatment.

Grade 3 or 4 gastrointestinal CTCAE events were reported in 16% (n=9) patients after baseline; 19% (n=7, treatment group) and 10% (n=2, placebo). Rectal dysfunction defined as rectal bleeding or rectal pain of any grade was reported in 84% (n=47) patients after baseline; 83% (n=30, treatment group) and 85% (n=17, placebo), none of which were grade 3-4.

Biomarkers of fibrosis

Although changes in many biomarkers were modest, for several biomarkers trends suggested reduced inflammation while on active treatment which reversed when patients stopped treatment (e.g. Flt3, soluble GCSF, GRO alpha, IFNa2, IFNy, IL12 p70, IL15, IL1Beta, IL1RA, IL2, TNF alpha, SCD40L; figure 3). Of note, MCP1 demonstrated a significant increase from baseline to 12 months in the active treatment group which remained significant at 24 months. Antifibrotic effects are also suggested by reduction in EGF and FGF levels on treatment and no increase in PDGF while on treatment but an increase in all three once treatment was discontinued (figure 3, supplementary data table 5). No significant changes at 12 or 24 months were observed in the placebo group for any biomarkers.

Discussion

This randomised double blind, placebo controlled trial of one year treatment with pentoxifylline 400mg BD together with Tocovid SupraBio™, rich in d-Alpha and d-Gamma Tocotrienol was performed in patients with new onset gastrointestinal symptoms after treatment with radiotherapy for a pelvic cancer. Their GI symptoms were persisting and affecting their lives after systematic gastroenterological assessment and optimal medical therapy. No improvement in symptoms was seen following intervention. However, trends in the analysis of biomarkers of fibrosis did suggest a possible anti-inflammatory and anti-fibrotic effect from the intervention.

While data are limited, in the human gastrointestinal tract one randomised study of pentoxifylline and vitamin E reported benefit when used prophylactically during radiotherapy in protecting the GI mucosa (41). A case series in patients with established damage has also suggested benefit (42). A third study reported some responses but convincing benefit was not established (28). It has been suggested that efficacy of these drugs is mediated by inhibition of TGF-β1/Smad targets (Col Iα1, FN1, PAI-1, CTGF), while it has no effect on the Rho/ROCK pathway. The growth factor data we collected did not assess for this. Animal data are convincing that pentoxifylline and tocotrienol are significantly more effective than pentoxifylline and vitamin E.

Longstanding toxicity after radiotherapy is common. In our clinic, treatment does abolish abnormal symptoms in some patients and improves them in others. However, we had treated all alternative causes for their symptoms following detailed investigational protocols and and this group had no further available treatment options. So, alternative treatment approaches to try and deal with the underlying cause for symptoms has a strong scientific rationale. However, a trial of radioprotective agents given during radiotherapy, raises the anxiety that they may additionally protect the tumour from the therapy although some data suggest that tocotrienols sensitise tumour cells and protect normal tissue (43). Until this is confirmed, intervention would seemingly be mandated to start after the completion of potentially curative treatment aimed at the cancer. Ideally, this should be as soon as possible after the completion of radiotherapy, however, the risk of late toxicity for any individual treated with radiotherapy is as yet difficult to define, so, a trial starting soon after radiotherapy would require very large numbers of volunteers. As a result, our trial recruited a relatively heterogeneous group of people who had undergone different types of oncological treatment with a variety of radiation doses and fields. In addition, they had relatively longstanding symptoms and it was possible that radiation fibrosis is fixed by the time we

introduced the trial intervention so that it would be too late to achieve benefit so long after radiotherapy.

In addition to participants likely having significant fibrosis which might be resistant to the active treatment offered, this study was underpowered. First, we did not achieve our target recruitment. Of more concern, it seems that close to half the participating patients were inadequately dosed. When we assessed GT3 levels in serum fewer than two out of three patients in the treatment arm had detectable rise in levels over baseline and in some the rise was very small. It is known that GT3 has a relatively short half life in serum and it is shorter when people are fasted (44). When patients have difficult GI symptoms they frequently fast before clinic attendance. However, chronic dosing with the same preparation and dose as we used in our study in normal volunteers has been shown to raise serum levels to the degree that we should have easily been able to detect (38). This finding of what constitutes optimal tocotrienol dosing has not been reproduced by all studies however, and it seems that tocotrienol absorption and clearance from plasma is complex, varies between different populations and our knowledge is incomplete. Agreement is even incomplete how best to assay for tocotrienols in plasma (45). It seems unlikely that non-compliancee with the study medication explains these findings. Non compliance is not consistent with the patient diaries and pill counting of returned medication, nor with the fact that this was a highly motivated patient group who had on-going and difficult gastrointestinal symptoms for which they knew there were no other treatments available. We hypothesise that potentially damage to small bowel lymphatics, significantly disordered bowel function and mucosal atrophy which occurs after pelvic radiotherapy might significantly reduce absorption of tocotrienols in many patients? This could explain the very different responses to this type of combination treatment in other studies.

While this trial examined clinical changes and was not powered to assess significant changes in biomarkers, the limited data that we have does suggest that there was suppression of inflammation and key growth factors promoting fibrosis whilst the intervention was being used. Others have suggested that if fibrosis is to be reversed after pelvic radiotherapy using pentoxifylline and vitamin E, that antifibrotic treatment needs to be prolonged to achieve that effect, increasingly so the longer the time since the completion of radiotherapy (46). Our data suggest that after the year of intervention sustained suppression of pro-fibrotic factors did not continue.

While our intervention did not lead to detectable clinical benefit in this study, it was a well tolerated, non toxic treatment and it is premature to conclude that it has no useful role. Further studies are required focusing on introducing the intervention much sooner after the completion of radiotherapy, to more homogeneous groups of people at high risk of GI radiation toxicity, possibly using preparations of GT3 without other subtypes of tocotrienol present, as was used beneficially in the animal studies and continued for longer than a year. It would be appropriate to consider the use of higher doses with contemporaneous monitoring of blood levels of tocotrienol which might allow for helpful dose adjustment in some patients. Ideally, formulating the GT3 not as an oral tablet but as a skin patch - could optimise absorption in people with disordered gut function.

References

1. Wedlake LJ, Andreyev HJN. Manipulating the consequential effect: an alternative approach to reducing pelvic radiation disease other than dose reduction. Curr Opin Support Palliat Care. 2011;5(1):25-8.
2. Henson CC, Ang YS. Biomarkers of normal tissue toxicity after pelvic radiotherapy. Curr Opin Support Palliat Care. 2012;6(1).
3. Downing A, Morris EJ, Richards M, Corner J, Wright P, Sebag-Montefiore D, et al. Health-related quality of life after colorectal cancer in England: a patient-reported outcomes study of individuals 12 to 36 months after diagnosis. J Clin Oncol. 2015;33(6):616-24.
4. Klopp AH, Yeung AR, Deshmukh S, Gil KM, Wenzel L, Westin SN, et al. Patient-Reported Toxicity During Pelvic Intensity-Modulated Radiation Therapy: NRG Oncology-RTOG 1203. J Clin Oncol. 2018;36(24):2538-44.
5. Hauer-Jensen M, Denham JW, Andreyev HJN. Radiation enteropathy-pathogenesis, treatment and prevention. Nat Rev Gastroenterol Hepatol. 2014;11(10):578.
6. Andreyev HJ. GI Consequences of Cancer Treatment: A Clinical Perspective. Radiat Res. 2016;185(4):341-8.
7. 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(1):75-80.
8. Andreyev HJN, Benton BE, Lalji A, Norton C, Mohammed K, Gage H, et al. Algorithm-based management of patients with gastrointestinal symptoms in patients after pelvic radiation treatment (ORBIT): a randomised controlled trial. The Lancet. 2013;382(9910):2084-92.
9. Capp A, Inostroza-Ponta M, Bill D, Moscato P, Lai C, Christie D, et al. Morbidity of prostate radiotherapy: Is there more than one proctitis syndrome? A revisitation using data from the TROG 96.01 trial. Radiotherapy and Oncology. 2009;90:400-7.
10. Lawrie TA, Green J, Beresford M, Wedlake L, Burden S, Davidson SE, et al. Interventions to reduce acute and late adverse gastrointestinal effects of pelvic radiotherapy for primary pelvic cancers. Cochrane Database Syst Rev. 2018 (1469-493X (Electronic)).
11. Andreyev HJ, Vlavianos P, Blake P, Dearnaley D, Norman AR, Tait D. Gastrointestinal symptoms after pelvic radiotherapy: role for the gastroenterologist? Int J Radiat Oncol Biol Phys. 2005;62(5):1464-71.
12. Muls AC, Lalji A, Marshall C, Butler L, Shaw C, Vyoral S, et al. The holistic management of consequences of cancer treatment by a gastrointestinal and nutrition team: a financially viable approach to an enormous problem? Clin Med. 2016;16(3):240-6.
13. Henson CC, Davidson SE, Ang Y, Babbs C, Crampton J, Kelly M, et al. Structured gastroenterological intervention and improved outcome for patients with chronic gastrointestinal symptoms following pelvic radiotherapy. Support Care Cancer. 2013;21(8):2255-65.
14. Bese NS, Munzuroglu F, Uslu B, Arbak S, Yesiladali G, Sut N, et al. Vitamin E protects against the development of radiation-induced pulmonary fibrosis in rats. Clin Oncol (R Coll Radiol). 2007;19(4):260-4.
15. Delanian S, Balla-Mekias S, Lefaix JL. Striking regression of chronic radiotherapy damage in a clinical trial of combined pentoxifylline and tocopherol. J Clin Oncol. 1999;17(10):3283-90.

16. Boerma M, Roberto KA, Hauer-Jensen M. Prevention and treatment of functional and structural radiation injury in the rat heart by pentoxifylline and alpha-tocopherol. Int J Radiat Oncol Biol Phys. 2008;72(1):170-7.
17. Sridharan V, Tripathi P, Sharma S, Corry PM, Moros EG, Singh A, et al. Effects of late administration of pentoxifylline and tocotrienols in an image-guided rat model of localized heart irradiation. PloS one. 2013;8(7):e68762.
18. Dion MW, Hussey DH, Doornbos JF, Vigliotti AP, Wen BC, Anderson B. Preliminary results of a pilot study of pentoxifylline in the treatment of late radiation soft tissue necrosis. Int J Radiat Oncol Biol Phys. 1990;19(2):401-7.
19. Werner-Wasik M, Madoc-Jones H. Trental (pentoxifylline) relieves pain from postradiation fibrosis. Int J Radiat Oncol Biol Phys. 1993;25(4):757-8.
20. Okunieff P, Augustine E, Hicks JE, Cornelison TL, Altemus RM, Naydich BG, et al. Pentoxifylline in the treatment of radiation-induced fibrosis. J Clin Oncol. 2004;22(11):2207-13.
21. Gottlober P, Krahn G, Korting HC, Stock W, Peter RU. [The treatment of cutaneous radiation-induced fibrosis with pentoxifylline and vitamin E. An empirical report]. Strahlenther Onkol. 1996;172(1):34-8.
22. Delanian S, Baillet F, Huart J, Lefaix J, Maulard C, Housset M. Successful treatment of radiation-induced fibrosis using liposomal Cu/Zn superoxide dismutase: clinical trial. Radiother Oncol. 1994;32(1):12-20.
23. Haddad P, Kalaghchi B, Amouzegar-Hashemi F. Pentoxifylline and vitamin E combination for superficial radiation-induced fibrosis: a phase II clinical trial. Radiother Oncol. 2005;77(3):324-6.
24. Delanian S, Depondt J, Lefaix JL. Major healing of refractory mandible osteoradionecrosis after treatment combining pentoxifylline and tocopherol: a phase II trial. Head Neck. 2005;27(2):114-23.
25. Delanian S, Porcher R, Balla-Mekias S, Lefaix JL. Randomized, placebo-controlled trial of combined pentoxifylline and tocopherol for regression of superficial radiation-induced fibrosis. J Clin Oncol. 2003;21(13):2545-50.
26. Hille A, Schmidberger H, Hermann R, Christiansen H, Saile B, Pradier O, et al. A phase III randomized, placebo-controlled, double-blind study of misoprostol rectal suppositories to prevent acute radiation proctitis in patients with prostate cancer. Int J Radiat Oncol Biol Phys 2005;63(5):1488-93.
27. Magnusson M, Höglund P Fau - Johansson K, Johansson K Fau - Jönsson C, Jönsson C Fau - Killander F, Killander F Fau - Malmström P, Malmström P Fau - Weddig A, et al. Pentoxifylline and vitamin E treatment for prevention of radiation-induced side-effects in women with breast cancer: a phase two, double-blind, placebo-controlled randomised clinical trial (Ptx-5). (1879-0852 (Electronic)).
28. Gothard L, Cornes P, Brooker S, Earl J, Glees J, Hall E, et al. Phase II study of vitamin E and pentoxifylline in patients with late side effects of pelvic radiotherapy. Radiother Oncol. 2005;75(3):334-41.
29. Gothard L, Cornes P, Earl J, Hall E, MacLaren J, Mortimer P, et al. Double-blind placebo-controlled randomised trial of vitamin E and pentoxifylline in patients with chronic arm lymphoedema and fibrosis after surgery and radiotherapy for breast cancer. Radiother Oncol. 2004;73(2):133-9.
30. Venkitaraman R, Price A, Coffey J, Norman AR, James FV, Huddart RA, et al. Pentoxifylline to treat radiation proctitis: a small and inconclusive randomised trial. Clin Oncol (R Coll Radiol). 2008;20(4):288-92.
31. Delanian SE, Lenglet T, Maisonobe T, Resche-Rigon M, Pradat P-F. Randomized, Placebo-Controlled Clinical Trial Combining Pentoxifylline-Tocopherol and Clodronate

in the Treatment of Radiation-Induced Plexopathy. Int J Radiat Oncol Biol Phys. 2020;107(1):154-62.
32. Berbée M, Fu Q, Boerma M, Sree K, D. L, Hauer-Jensen M. Mechanisms underlying the radioprotective properties of γ-tocotrienol: comparative gene expression profiling in tocol-treated endothelial cells. Genes Nutr. 2012;7(1):75-81.
33. Ghosh SP, Kulkarni S, Hieber K, Toles R, Romanyukha L, Kao TC, et al. Gamma-tocotrienol, a tocol antioxidant as a potent radioprotector. Int J Radiat Biol. 2009;85(7):598-606.
34. Berbée M, Fu Q Fau - Boerma M, Boerma M Fau - Wang J, Wang J Fau - Kumar KS, Kumar Ks Fau - Hauer-Jensen M, Hauer-Jensen M. gamma-Tocotrienol ameliorates intestinal radiation injury and reduces vascular oxidative stress after total-body irradiation by an HMG-CoA reductase-dependent mechanism. (0033-7587 (Print)).
35. Berbée M, Fu Q, Garg S, Kulkarni S, Kumar KS, Hauer-Jensen M. Pentoxifylline enhances the radioprotective properties of γ-tocotrienol: differential effects on the hematopoietic, gastrointestinal and vascular systems. Radiat Res. 2011;175(3):297-306.
36. Rasool AH, Yuen KH, Yusoff K, Wong AR, Rahman AR. Dose dependent elevation of plasma tocotrienol levels and its effect on arterial compliance, plasma total antioxidant status, and lipid profile in healthy humans supplemented with tocotrienol rich vitamin E. J Nutr Sci Vitaminol (Tokyo). 2006;52(6):473-8.
37. Chin SF, Ibrahim J, S. M, Abdul Hamid NA, Abdul Latiff A, Zakaria Z, et al. Tocotrienol rich fraction supplementation improved lipid profile and oxidative status in healthy older adults: A randomized controlled study. Nutrition & Metabolism. 2011;8(42):1-14.
38. Patel V, Rink C, Gordillo GM, Khanna S, Gnyawali U, Roy S, et al. Oral tocotrienols are transported to human tissues and delay the progression of the model for end-stage liver disease score in patients. Journal of Nutrition. 2012:513-9.
39. Andreyev HJN, Muls AC, Norton C, Ralph C, Watson L, Shaw C, et al. The practical management of the gastrointestinal symptoms of pelvic radiation disease. Frontline Gastroenterol 2015;6(1):53-72.
40. Khalid U, McGough C, Hackett C, Blake P, Harrington KJ, Khoo VS, 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(5):1432-41.
41. Sayed R, El Wakeel L, Saad AS, Kelany M, El-Hamamsy M. Pentoxifylline and vitamin E reduce the severity of radiotherapy-induced oral mucositis and dysphagia in head and neck cancer patients: a randomized, controlled study. Med Oncol. 2019;37(1):8.
42. Hille A, Christiansen H, Pradier O, Hermann RM, Siekmeyer B, Weiss E, et al. Effect of pentoxifylline and tocopherol on radiation proctitis/enteritis. Effect of pentoxifylline and tocopherol on radiation proctitis/enteritis. 2005;Strahlenther Onkol(181):9.
43. Ling MT, Luk SU, Al-Ejeh F, Khanna KK. Tocotrienol as a potential anticancer agent. Carcinogenesis 2012;33(2):233-9.
44. Yap SP, Yuen KH, Wong JW. Pharmokinetics and bioavailability of alpha, gamma and delta tocotrienols under different food status. JPP. 2001;53:67-71.
45. Fu J-Y, Che H-L, Tan DM-Y, Teng K-T. Bioavailability of tocotrienols: evidence in human studies. Nutr Metab (Lond). 2014;11(5):1-10.
46. Delanian S, Porcher R, Rudant J, Lefaix JL. Kinetics of response to long-term treatment combining pentoxifylline and tocopherol in patients with superficial radiation-induced fibrosis. J Clin Oncol. 2005 23(34):8570-9.