Nutritional Supplement Based on Zinc, Prebiotics, Probiotics and Vitamins to Prevent Radiation-related Gastrointestinal Disorders

DANIELE SCARTONI, ISACCO DESIDERI, IRENE GIACOMELLI, VANESSA DI CATALDO, LUCIA DI BRINA, ANNA MANCUSO, ILARIA FURFARO, PIERLUIGI BONOMO, GABRIELE SIMONTACCHI and LORENZO LIVI

Department of Radiation Oncology, University of Florence, Florence, Italy

Abstract. *Aim: The present phase II study aimed to evaluate the tolerance and safety of Dixentil, a nutritional supplement based on zinc with the addition of prebiotics (galacto-oligosaccharides), tyndalized probiotics (Lactobacillus acidophilus and L. casei) and vitamins B1, B2 and B6, and nicotinamide), given as prophylaxis to patients undergoing pelvic radiotherapy and its efficacy in the prevention and reduction of radiation-related gastrointestinal disorders. Patients and Methods: Forty consecutive patients who were candidates for pelvic radiotherapy received Dixentil before starting and during radiotherapy. The primary end-point was to evaluate the safety and tolerance of Dixentil. Secondary end-points were incidence and severity of radiation-induced diarrhea and number of patients who discontinued radiotherapy because of diarrhea. Results: Radiation-induced enteritis occurred in 17 patients, grade I and grade II diarrhea was documented in 14 and 3 patients respectively; no grade III or IV diarrhea was observed. Radiotherapy was discontinued due to treatment-induced enteritis only in two patients for 6 days. Conclusion: Use of Dixentil is an easy, safe, and feasible approach to protect patients against the risk of radiation-induced diarrhea.*

The gastrointestinal tract is characterized by tissue with a high cell turnover and for this reason it is particularly sensitive to radiation damage (1). Side-effects on the gastrointestinal tract are common in patients treated with radiotherapy for abdominal and pelvic neoplasms (2). Gastrointestinal disorders usually occur after the second week of radiotherapy (2); acute symptoms, such as diarrhea and abdominal pain, develop during pelvic radiotherapy in 25-75% of patients (3). These side-effects may be related to the appearance of complications such as fatigue, malabsorption, dehydration, fecal incontinence and septicemia (2-4); in some cases, gastrointestinal disorders may result in a suspension of the treatment.

Currently, there exist no approved prophylactic agents for the prevention of enteritis related to radiotherapy treatment (5). Recently, probiotic agents have been identified as potential co-adjuvants in treatment of intestinal disorders; certain studies have evaluated their use for the prevention of radiation-related enteritis and their role in the production of anti-bacterial substances able to stimulate the immunological activity of the intestinal mucosa and re-establish a proper microenvironment (6). Besides probiotic agents, metallic chemical elements such as zinc seem to assist proper activity of the intestinal mucosa. In particular, a recent meta-analysis of more than 20 randomized controlled trials regarding diarrhea in children found zinc to be useful in cases of acute and persistent diarrhea. The authors showed that zinc supplementation is positively involved in reducing the duration and frequency of both severe and persistent diarrhea (7).

Dixentil (Gamfarma srl, Milano, Italy) is a nutritional supplement based on zinc with the addition of prebiotics (galacto-oligosaccharides), tyndalized probiotics (*Lactobacillus acidophilus* and *L. casei*) and vitamins B1, B2 and B6, and nicotinamide, useful for reducing the duration and frequency of severe and persistent diarrhea. Tyndalized probiotics differ from common lactic ferments because they are subjected to a particular pharmaceutical technology, tyndalization, which consists in their exposure to a temperature of 56˚C for 30 minutes; this technology makes these ferments resistant to gastric juices, digestive enzymes and bile acids. In this way, the probiotic bacteria do not require any refrigeration and are stable for 36 months at room temperature.

Our phase II study aimed to evaluate the tolerance and safety of Dixentil given as prophylaxis to patients

Correspondence to: Daniele Scartoni, MD, Department of Radiation Oncology, University of Florence, Largo G. A. Brambilla 3, 50134, Florence, Italy. Tel: +39 05579477018, Fax +39 0557947263, e-mail: scartoni_daniele@libero.it

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undergoing pelvic radiotherapy (with or without associated chemotherapy), and its efficacy in the prevention and reduction of radiation-related gastrointestinal disorders.

Patients and Methods

Forty consecutive patients were enrolled in this study, attending the Radiation Oncology Unit of Florence University (Florence, Italy) from April 2014 to June 2014. The eligibility criteria for participation in this phase II study were age >18 years, good performance status (Eastern Cooperative Oncology Group functional status ≤ 2) and a diagnosis of endometrial, cervical, anal canal, colorectal and prostate cancer requiring pelvic radiotherapy in neo/adjuvant or radical setting (with or without chemotherapy). The exclusion criteria were any acute or chronic gastrointestinal condition associated with diarrhea in the month before recruitment and performance status >2. Patients who were candidates to receive radiation therapy (radical or neo/adjuvant) for colorectal, cervical, anal, endometrial and prostate cancer were assigned to receive a daily 10 ml vial of Dixentil (Gamfarma srl, Milano Italy) starting from first day of the radiotherapy course until the end of the scheduled treatment. Each vial contains 500 mg of Galacto-oligosaccharides, 10 mg of *L. casei*, 10 mg of *Lactobacillus acidophilus* ,10 mg of zinc, 1 mg vitamin B1, 1 mg vitamin B2, 1 mg vitamin B6, and 10 mg nicotinamide. On the first day of treatment, two oral vials were administered, while on the remaining days only one vial was administered daily to the patients.

At baseline, patients provided a medical history and underwent a thorough physical examination. The study participants underwent clinical evaluation once weekly during the scheduled radiation therapy course and then 1 month after its completion. During each visit, clinical symptoms, concomitant medications, and any adverse events were reviewed, and a physical examination was performed.

Patients and treatment characteristics are described in Table I. The median prescribed total dose was 63.3 Gy (range=30-80 Gy). In the urological setting, the median dose was 68.4 Gy (range=30-80 Gy), and in the gastrointestinal and gynecological settings, 49.8 Gy (range=45-59.4) and 53.3 Gy (range=44-60 Gy), respectively. In almost half of the patients, a hypofractionated radiotherapy schedule was performed (2.70 Gy/day for radical radiotherapy in prostatic cancer, 2.12 Gy/day for treatment with simultaneous integrated boost technique). Concomitant chemotherapy with capecitabine for gastrointestinal cancer and cisplatin for gynecological cancer was performed in five cases (12.5%).

The primary end-point was to evaluate the safety and tolerance of Dixentil. Secondary endpoints were to evaluate the incidence and severity of radiation-induced diarrhea, the number of patients who discontinued radiotherapy because of diarrhea, and use of loperamide or other drugs as rescue medication for diarrhea. We evaluated any possible association between dosimetric volumes and occurrence of diarrhea. We also analyzed the hypothetical role of dixentil in diarrhea prevention, even in cases with the least favorable dosimetric values. Dose constraints used in different settings are summarized in Table II, and were obtained from various Radiation Treatment Oncology Group protocols and clinical trials (8-10).

Pelvic radiotherapy was delivered using 3D conformal radiotherapy techniques, intensity-modulated static techniques (IMRT-static) and IMRT elicoidal treatments with Tomotherapy (Accuray, Madison WI USA). For 3D conformal radiotherapy techniques, a combination of 15 MV and 18 MV photons was used with the patient in the supine position, depending on the proximity of the planning treatment volume (PTV) to the patient's posterior skin surface. Multi-leaf collimator (MLC) segments were used if necessary to optimize the coverage of the PTV by the 95% isodose, and were then used as a substitute for the wedge using a multisegment technique. Beam and wedge weightings were optimized to ensure coverage of the PTV by 95% isodose and limiting higher isodose levels to less than 107% in accordance with the International Commission on Radiation Units (ICRU) and Measurements Report No. 50 guidelines (11). The total X-ray dose prescribed was between 45 and 80 Gy.

IMRT plans were generated with seven fixed-gantry coplanar angles (0, 50, 100, 150, 210, 260 and 310) using inverse planning software (Pinnacle version 9.2, Philips Healthcare, Best, the Netherlands). The fluence of each modulated field was delivered with 120-leaf MLC which were 0.5 or 1 cm in width at the isocenter, using the sliding window technique with 6-15 MV photons. IMRT optimization was carried out by interactively adapting the objective dose constraints and their priorities. After optimization, the dose was calculated using the Anisotropic Analytical Algorithm (version 8.6.15) with a dose calculation grid of 2.5 mm. For treatment planning with Tomotherapy, CT scans with 3-mm slice thickness at full bladder and empty rectum were performed, and IMRT elicoidal plans were calculated with Tomoplan softare (Accuray, Madison WI

Table I. *Patients' and treatment characteristics.*

Characteristics	No. of patients	%
Neoplasm	40	
Urological cancer	28	70
Gastrointestinal cancer	6	15
Gynecological cancer	6	15
Gender		
Male	31	77.5
Female	9	22.5
PS		
0	28	70
1	11	27.5
2	1	2.5
Surgery		
Yes	18	45
No	22	55
Radiotherapy treatment		
Radical	18	45
Adjuvant	18	45
Neoadjuvant	4	10
Radiotherapy technique		
3D-CRT	18	45
IMRT	17	42.5
Tomotherapy	5	12.5
Radiotherapy fractionation		
Standard	26	65
Hypofractionated	14	35
Chemotherapy		
Yes	5	12.5
No	35	87.5

PS: Performance status, 3D-CRT: 3D conformal radiotherapy, IMRT: intensity-modulated radiotherapy.

Table II. *Dose constraints for small bowel used in different groups of patients.*

Neoplasm	Dose constraints		
Endometrial cancer	V35 <180 cc	V40 <100 cc	40 Gy <30%
Rectal cancer	V35 <180 cc	V40 <100 cc	
Anal cancer	V30 <200 cc	V35 <150 cc	
Prostate cancer (prostate only)	D_{max}: 52 Gy		
Prostate cancer (prostate + pelvic lymph nodes)	V35 <180 cc	V40 <100 cc	

V##: Volume receiving ## Gy; D_{max}: maximum dose.

USA). Triangulation marks were used to make sure the patient did not roll and to quickly position the patient in the correct location. Before each treatment, a 3.5 MV fan beam CT image was acquired and matched to the planning CT image. If necessary, the patient's position was corrected.

Diarrhea was evaluated according to the Common Toxicity Criteria of the National Cancer Institute, version 4.0 (12).

Table III. *Incidence and severity of radiation-induced diarrhea.*

	Grade I	Grade II
Urologic cancer	21.4%	7.1%
Gastrointestinal cancer	50%	16%
Gynecologic cancer	83%	0%

Results

All patients completed the study protocol. The study product was well-tolerated, and no related adverse events were reported; no patients discontinued Dixentil. No tumor or treatment-related deaths or deaths from other causes were recorded during the period of radiation therapy, and no case of bacteremia, sepsis, or septic shock was reported.

Radiation-induced enteritis and colitis occurred in 17 patients (42.5%), in particular in eight (28.5%), five (83%), four (66%) urological, gynecological and gastrointestinal cases, respectively.

Grade I and grade II diarrhea was documented in 14 (35%) and three (7.5%) patients respectively, no grade III or IV diarrhea was observed. Grade II diarrhea occurred in urological and gastrointestinal settings. The incidence and severity of radiation-induced enteritis are summarized in Table III.

The highest toxicity occurred at a mean dose of 34 Gy (30 Gy, 23 Gy and 42 Gy for gynecological, gastrointestinal and urological patients, respectively), on average 23 days after starting radiotherapy (19, 18 and 28 days for gynaecological, gastrointestinal and urological patients, respectively). Radiotherapy was discontinued due to treatment-induced enteritis in two patients only (5%) for 6 days. Rescue medication for diarrhea was administered to eight patients (20%): loperamide was given to six patients, two patients received a combination of loperamide and lactic acid. Rescue medication for diarrhea was prescribed for a mean of 3 days. From a dosimetric point of view, diarrhea as a toxicity end-point is currently not well-defined. In fact, when taking into account the dosimetric values from our series in order to assess any correlation with gastrointestinal toxicity, we were forced to choose values correlated with more serious adverse events (*e.g.* obstruction, perforation, and fistula). In Table IV, dosimetric parameters in patients experiencing any grade of diarrhea are reported.

Most radiation-induced enteritis occurred in patients undergoing 3D conformal radiotherapy (11 patients *vs.* 6 patients treated with IMRT or Tomotherapy) and treatments with standard fractionation (only three out of 14 patients who underwent a hypofractionated schedule presented diarrhea). The onset of diarrhea can be caused by a different number of factors; in fact it was reported in almost all patients treated with chemoradiotherapy (four out of five patients).

Discussion

Our phase II study demonstrates the safety and good tolerance to Dixentil for the prevention or reduction of both the incidence and severity of radiation-induced enteritis and colitis. Indeed, the incidence of diarrhea recorded was relatively low, or at least in agreement with those published in the literature (3). Few studies have been published regarding the use of probiotics in the prevention of radiation-induced diarrhea. To our knowledge, there are only five human clinical studies published on the prevention of acute radiation-induced diarrhea using probiotics (13-17) and one study for the treatment of diarrhea within 4 weeks after radiotherapy (18).

Salminen and colleagues performed a randomized, controlled trial to investigate the efficacy of probiotic supplementation for prevention of radiation-induced diarrhea compared to only dietary restriction (16). Twenty-one

Table IV. *Dosimetric characteristics small bowel-related in patients with radiation-induced diarrhea.*

Patient no.	Neoplasm	Toxicity grade	V30	V35	V40	40 Gy	D_{max}
1	Rectal cancer	1		80 cc	46 cc		
2	Rectal cancer	2		315 cc	275 cc		
3	Rectal cancer	1		182 cc	166 cc		
4	Anal cancer	1	304 cc	256 cc		20%	
5	Endometrial cancer	1	198 cc	140 cc		0%	
6	Endometrial cancer	1	1 cc	0.33 cc		24%	
7	Endometrial cancer	1	530 cc	260 cc		18%	
8	Endometrial cancer	1	180 cc	148 cc		69%	
9	Endometrial cancer	1	305 cc	290 cc		20%	
10	Prostate cancer	1					52%
11	Prostate cancer	1					50%
12	Prostate cancer	1					48%
13	Prostate cancer	2					54%
14	Prostate cancer	1					42%
15	Prostate cancer	2					63%
16	Prostate cancer	1					54%
17	Prostate cancer	1					54%

V##: Volume receiving ## Gy; D_{max}: maximum dose.

patients with cervical or uterine carcinoma received either a daily dose of live *Lactobacillus acidophilus* strain during the whole treatment period or only dietary restriction. The authors showed less diarrhea and need for rescue medication in the probiotic group. Delia *et al*. reported positive results with the probiotic VSL#3 for preventing radiation-induced diarrhea (13). They reported a statistically significant reduction in the incidence of diarrhea, the number of daily bowel movements, and the time to loperamide use. In their study, Urbancsek *et al*. showed patients in the group supplemented with *Lactobacillus* rhamnosus needed antidiarrheal drugs less frequently and the onset of loose stools was delayed (19).

A meta-analysis involving several trials analyzed the positive role of zinc supplementation in reducing the duration and frequency of both severe and persistent diarrhea, especially in children (7). There are many data regarding the use of zinc supplementation for mucositis prevention in patients with head and neck cancer undergoing radiotherapy, with controversial results (20-22) but to our knowledge there exist no data to support its use for prevention of radiation-induced enteritis.

This phase II trial is, therefore, the first study to evaluate a nutritional supplement based both on zinc, prebiotics, tyndalized probiotics and vitamins used for reducing the duration and frequency of severe and or persistent diarrhea. During the study period, Dixentil was well-tolerated by the patients. Indeed no patient complained of any difficulties using this nutritional supplement related to a possible poor tolerance to the product. The excellent tolerance is a very important aspect to be considered, especially in patients who have olfactory and taste problems during or after chemotherapy; often these disorders may limit the use of such supplements.

In a recent report by Banerjee *et al*. regarding patients treated for rectal cancer with neoadjuvant intent, a small bowel V35 (cc of small bowel volume receiving 35 Gy) and V40 of less than 238 cc and 217 cc, respectively, were associated with a less than 10% risk of grade 3 or more acute toxicity (23). When examining the dosimetric parameters for patients with the onset of diarrhea during treatment in our study, patients with 'unfavorable' dosimetric parameters developed a maximum of grade 2 toxicity. Even if based on a low number of patients, we could then hypothesize that the supplement of Dixentil during radiation treatment was able to overcome the toxic effect of radiotherapy.

Only two patients required radiation treatment interruption for an average of 6 days. This is a very important aspect to keep in mind because the literature shows that a delay or lengthening of the total treatment time negatively affects the overall survival of the patients (24). Dixentil, in addition to having a positive impact on the incidence and severity of diarrhea, appears to have a role in delaying the timing of these disorders. Indeed, the highest grade of toxicity occurred after a mean of 23 days from the start of radiotherapy (19, 18 and 28 days for gynecological, gastrointestinal and urological patients respectively).

It is important to highlight that four out of five patients treated with concomitant chemoradiotherapy experienced diarrhea, which is a confirmation of how chemotherapy increases the incidence of treatment-related enteritis. However, even in this sub-type of patient, Dixentil seemed to reduce the severity of diarrhea (only one patient had grade II diarrhea) and delay its onset (on average after 19 days of treatment). Various studies have evaluated the incidence and temporal pattern of the side-effects of pelvic radiotherapy with and without chemotherapy association. In those studies, side-effects appear to have occurred earlier compared to our results (25, 26). For instance, Gilinsky *et al*. reported that diarrhea was encountered in patients receiving abdomen and pelvic radiotherapy and occurred in approximately 75% of patients, usually beginning in the second or third week of radiotherapy (25).

As hypothesized, from our analysis we highlight a higher occurrence of diarrhea in patients treated with 3D conformal radiotherapy technique. However, even in these patients, grade III or IV diarrhea was not observed.

In conclusion, comparing our results with data in the literature, we can assert that the use of Dixentil allows reduction of the risk and severity of radiation-induced diarrhea. This consequently leads to a reduction of radiation treatment suspension and the need for rescue medication.

Data from our study are encouraging, phase III studies are needed to confirm these results and to compare Dixentil with placebo or standard supplementation for the prevention of radiation-induced diarrhea.

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