Prophilactic use of D-mannose and cranberry extract in the prevention of radio-induced acute and late cystitis.

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Conflict of interest statements: none declared.

KEY WORDS:

Radiotherapy, D-Mannose, Cranberry, Cystitis, Toxicity.

ABSTRACT:

AIM AND BACKGROUND:

The major criticism of radiotherapy on the pelvis is the presence of many dose-limiting organs, due to their low tolerance to radiation. Toxicity is conditioned by host and technique and affects particularly rectum, urinary bladder and small bowel. In the bladder the main side-effect is acute cystitis, with persistent hemorrhage, fibrosis of the tissues and loss of contractile capacity. Natural substances from cranberry and multivitamins have demonstrated their usefulness in the prevention of radio-induced bladder toxicity. CYSTOMAN100 is a natural product containing D-Mannose, cranberry and Vitamin C. In this paper we present our experience using Cystoman 100 to prevent bladder radio-induced toxicity.

MATERIALS AND METHODS:

From October 2009 to November 2011 in the Radiotherapy Department of San Filippo Neri Hospital in Rome, Cystoman100 was administered to 110 patients, treated with radiotherapy for prostate, gynaecological and anal-rectum tumours. 50 patients were instructed to assume the drug from the very first session until 30 days after the end of radiation course. 46 of them were valuable and 3 of them were lost during the follow-up. The patients were examined weekly during radiotherapy and then monthly for the first 6 months.

RESULTS:

All 46 patients completed the cycle of radiotherapy and no grade 4 (G4) bladder toxicity was observed: 24 patients did not develop any acute toxicity, 13 had grade 1 (G1), 8 grade 2 (G2) and only one grade 3 (G3). Regarding late toxicity, 36 had no symptoms, 6 presented grade 1 (G1) and only one grade 2 (G2).

CONCLUSIONS:

Cystoman100 was highly tolerable and useful as it allowed the completion of the radio or radio-chemotherapy course within the planned time As it has been demonstrated that any interruption is related to worse results in local control, there's the possibility that this treatment strongly affects tumour control. Longer follow up times are necessary to confirm these data.

Introduction

Radiotherapy alone or in association with surgery is an important therapy for the treatment of many tumors of the pelvic area, in particular gynecological, prostate and the anal-rectum. The major criticism of these treatments concerns the presence of many dose-limiting organs and structures, so called "critical organs", due to their relatively low tolerance to radiation. For this reason radiotherapy can be the cause of acute and/or late side-effects that appear during or within three months after the end of the treatment or later, particularly in the rectum, the urinary bladder and the small bowel.

Toxicity is conditioned by host factors (age, co-morbidities, other diseases) and radiation technique (volumes, total dose, fractionation, association with chemotherapy). [1] Furthermore, in recent years, there has been a tendency to use hypo-fractionated schedules (larger dose per fraction with a reduced total dose and time) and sequential or concomitant radio-chemotherapy regimens to increase the efficacy of radiotherapy.[2]

The main side-effect of the acute phase in the bladder is cystitis, connected to the inflammation of the internal mucosa lining, leading to its damage or loss, vasodilatation of the capillaries and bleeding. When the damage is very relevant, it can lead to symptoms of late toxicity, with persistent hemorrhage, fibrosis of the tissues and loss of contractile capacity of the bladder wall.

This acute actinic cystitis generally appears 2-3 weeks after the start of treatment: in these cases the radiation course could be interrupted, reducing the efficacy of the treatment.[3]

To date, there is no specific therapy recommended for radiation induced cystitis; generally steroids, FANS and antispasmodics are used for symptoms relief [4]. In case of severe cystitis, a urinary tract infection should be suspected: urine culture and sensitivity should be carried out and an antibiotic initiated.

Natural substances extracted from cranberry and multivitamins have demonstrated their usefulness in the prevention of radio-induced bladder toxicity.

CYSTOMAN100 is a natural food vitamin from D-Mannose, a concentrated extract from cranberry and Vitamin C. Clinical studies have shown the ability of these substances to protect the outer layer of the bladder mucosa, making it anti-adhesive. D-mannose inside the bladder adheres to the bacteria, preventing the colonization on the mucosa and expelling them through urine. Furthermore the anti-bacterial effect of D-Mannose is increased in association with the cranberry extract.

In this paper we present our experience using Cystoman 100 to prevent bladder radio-induced toxicity in patients irradiated for pelvic tumours, with particular emphasis on prostate and rectal cancers, carried out in San Filippo Neri Hospital.

Materials and Methods

From October 2009 to November 2011 in the Department of Radiotherapy in the San Filippo Neri Hospital in Rome, Cystoman100 was administered to 110 patients, consecutively treated with radiotherapy for prostate, gynaecological and anal-rectum tumours.

Cystoman100 was prescribed in 60 patients during the course of the radiotherapy for symptomatic treatment of radio-induced bladder symptoms, while the other 50 were instructed to assume the drug from the very first session until 30 days after the end of radiation course .

Our observation was limited to these 50 patients assuming Cystoman100 with prophylactic intent. Out of these, two were excluded due to the premature interruption of radiotherapy and two others spontaneously interrupted the drug before the end .

The prescribed Cystoman 100 dosage consisted of two tablets a day during and for at least one month after the end of radiotherapy .The patients were instructed to assume the tablets after the first and the last urine every day. The pelvic radiotherapy consisted of absolute or equivalent total doses ≥ 45 Gy, delivered with 3D conformal (3D-RT) or intensity-modulated (IMRT) radiation technique.

The patients were examined weekly during radiotherapy and then monthly for the first 6 months .

Toxicity was evaluated according to the EORTC/RTOG scales [22].

Results

The reported results only concern the group of 46 patients treated with prophylactic intent.

Out of these patients prostate was the primary site in 22, rectum in 19, uterus in 4 and anus in one . The characteristics of the patient sample are reported in Table 1.

All 46 patients completed the cycle of radiotherapy and no grade 4 (G4) bladder toxicity was observed.

In particular, twenty-four patients did not develop any acute toxicity (52,2%), 13 (28,3%) had grade 1 (G1), 8 (17,4%) grade 2 (G2) and only one (2,2%) presented grade 3 (G3).

Regarding late toxicity, apart from the 3 patients lost during the follow-up, 36 (83,7%) had no symptoms, 6 (13,9%) presented grade1 (G1) and only one patient (2,3%) grade 2 (G2). (Fig.1)

The patients with toxicity equal or greater than G2, were treated with FANS and/or systemic steroids.

Antibiotic therapy was added only in patients with positive urine culture. The results are reported in Table 2.

It is overwhelming to note that none of the 46 patients reported any toxicity or adverse reactions due to Cystoman100.

The two groups of patients affected by prostate and rectal tumours were analyzed separately and the results are shown in tables 3 and 4.

Out of the 22 patients affected by prostate tumours, 14 underwent post-operative adjuvant radiation course and 8 received radiotherapy as a single curative modality.

Radiation was carried out with conventional fractionation (2 Gy/Fr) in 16 patients and with hypo-fractionated regimen (3.10 Gy/Fr) in 6. The absolute or equivalent total prescribed dose was greater than 74 Gy in all patients.

Regarding the acute toxicity, in this group 10 patients (45,4%) did not report any symptoms (G0), 7 (31,8%) had grade 1 (G1), 4 (18,2%) grade 2 (G2) and only one patient (4,6%) had grade 3 (G3) toxicity.

For the late toxicity, 12 (55,5%) were free of toxicity (G0), 9 (38,9%) showed grade 1 (G1) and only one patient (5,6%) presented grade 2 (G2). These results are shown in Table 3.

In the cohort of 19 patients with rectal tumours, 17 underwent pre-operative neo-adjuvant radio or chemo-radiotherapy and 2 received post-operative adjuvant chemo-radiotherapy. Of the former group, 11 patients underwent radiotherapy with conventional fractionation (50,4 Gy/28 fr), with concomitant i.v. 5-Fluorouracil or oral Capecitabine. The other 5, deemed *"unfit"* because of general conditions, age and/ or co-morbidities, received hypo fractionated radiotherapy only (25 Gy/5 fr). All 17 patients underwent subsequent surgery.

Of these 19 patients, 8 (42,1%) did not develop any acute toxicity, 5 (26,3%) had grade 1 (G1) and 6 (31,58%) grade 2 (G2) toxicity .

None of the patients presented late toxicity during the follow-up. These results are shown in table 4.

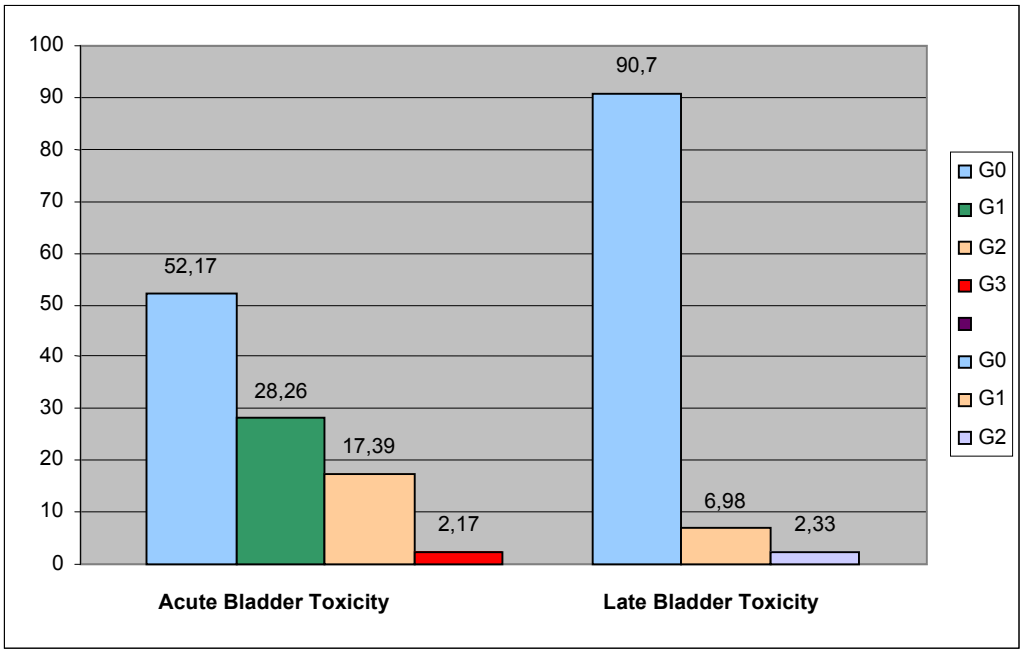

Fig. 1

Discussion

Damage caused by pelvic radiotherapy to the bladder has been evaluated in many clinical studies.

The acute symptoms of radio-induced cystitis consist of dysuria, tenesmus, hematuria, nocturia, urgency and pain during sexual intercourse. These symptoms disappear

gradually at the end of treatment, however, they can be prolonged for several months and in some cases (10%) become permanent.

From the histological point of view, acute alterations include inflammation and oedema of the mucosa and the bladder sub mucosa, superficial ulcers and signs of perineural flogosis.[6]

The most frequent late symptoms are represented by changes in the urinary function, such as frequency, dysuria and incontinence. More debilitating symptoms, such as the formation of ulcers and bladder-rectal fistulas are actually very rare thanks to an improvement in radiotherapy techniques.

Late histopathological damage is caused by ischemic lesions of the bladder walls for radio-induced vessel alterations: blockage, vascular ecstasies and endothelial necrosis; in these conditions ischemia causes inflammation, which may become chronic and result in fibrosis with an irreversible loss of elasticity of the bladder walls.

There may also appear atypical epithelium in the bladder mucosa, with nuclear pleomorphyism and cytoplasmatic inclusions.[7]

Data regarding the frequency in bladder complications during radiotherapy may vary according to the dose, fractionation and the technique, as well as differences in data interpretation and the scale used for the toxicity evaluation.

Zelefsky et al. reported that high-grade acute bladder toxicity is one of the principal factors leading to late complications.[16]Michalskj et al. reported a close link between the development of cystitis, the total dose and the percentage of irradiated bladder walls.[13]

Other identified risk factors were the dose per fraction, the type of fractionation (a dose greater than 2 Gy/fraction increases the risk of acute/late cystitis)[14] and the age of the patient.[15]

Lips et al.[8] reported a clinically significant incidence of acute genito-urinary complications after radiotherapy for prostate cancer : 47% for G2 and 3% for G3. In the same study, after a follow up of at least 2 years, the late toxicity was almost 21% for G2 and about 4% for G3-G4. In this work they also report the results published by other authors regarding acute and late toxicity after prostate radiotherapy (Tab. 5).

Table 5

Authors	**Acute Genitourinary Toxicity (GU)%**			**Late Genitourinary Toxicity (GU)%**		
3D-Conformal RT (3D-CRT)	**G2**	**G3**	**G4**	**G2**	**G3**	**G4**
Storey, 2000 [18], Pollack 2002 [2]	24	4	1	10	3	-
Beckendorf, 2004 [15]	30	7	-	-	-	-

Michalski, 2005 [16]	41	3	0	17	4	0
Zietman, 2005 [3]	49	1	1	20	1	0
Peeters, 2005/2006 [1,17]	42	13	0	26	13	-
Intensity Modulated RT (IMRT)						
Zelefsky, 2002/2006 [8,11]	28	0.1	0	9	3	0
De Meerleer, 2004/2007 [7,12]	36	7	0	19	3	0
Teh, 2005 [23]	35	0	0	-	-	-
Skala, 2007 [9]	-	-	-	9	1	-
Lips, 2008 [3,15]	47	3	0	21	4	0.3

According to the literature, the average incidence of acute bladder complications after conformal radiotherapy with doses between 70 and 78 Gy is equal to 65% (G1-2) and 4-9% (G3-G4) respectively.[9,10,11]

Thanks to higher conformation of the doses to target, IMRT, seems able to save healthy tissue and reduce the complications from radiotherapy to critical organs. However, not all the studies agree on the significance of these data.

The radio-induced changes in the bladder may become clinically evident and/or worsen due to infection. Actinic damage in fact predisposes the mucosa to the development of acute cystitis caused by Escherichia Coli (E. Coli) transferred to the bladder from the colon through the urethra and responsible for more than 90% of bladder infections.

The adhesion of bacteria to the mucosa, represents the first pathogenic phase of the infection [17] , which is mediated by the presence of fimbriae, protein filament appendices, similar to tentacles on the bacteria walls.

D-Mannose is a mono-saccharide extracted from birch or larch wood. It is absorbed in the large intestine, and does not affect the glucose metabolism; thus, it is not altered in the urinary tract and is expelled with the urine.

Lectin, present on the fimbriae of most pathogenic bacteria, has a pocket that specifically binds to D-Mannose and represents the first site for the adhesion of E. Coli and other pathogenic bacteria of the bladder[18.] In studies carried out on mice, D-Mannose has shown to be capable of inhibiting the bacterial invasion and adhesion to the bladder mucosa, mechanically inhibiting the colonization; the consequence is the expulsion of the bacteria with the urine. [19]

Tao et al. found that cranberry is able to render anti-adhesive the surface of the urinary mucosa and inhibit the formation of biofilm by uro-pathogenic bacteria in the bladder.[20]

Cranberry increases the antibacterial effects of D-Mannose as it contains flavonoids and other organic acids that have anti-bacterial properties.

Head et al. therefore forwarded D-Mannose and cranberry as the best natural options for long-term prevention of the development of bladder infections.[21]

In our experience we identify the prophylactic use of Cystoman100 for the prevention of actinic cystitis in patients undergoing pelvic radiotherapy as recommended. The drug was highly tolerable and useful for all the analysed patients.

One of the main difficulties of the analysis concerning the use of Cystoman is that most of the clinical data is based on symptoms reported by patients, and therefore often conditioned by individual sensitivity.

In our study the patients were always examined by the same radiotherapist with wide experience, in order to ensure the maximum accuracy for symptom registration, reducing the inter-observer variability and creating a relationship of trust between patient and physician.

Further, Cystoman100 for preventive purposes increased the patient compliance to the treatment, allowing the completion of the radio or radio-chemotherapy course within the planned time As it has been demonstrated that any interruption is related to worse results in terms of local control , there's the possibility that this continuative treatment modality strongly affects tumour control. Longer follow up times are necessary to confirm these data.

Conclusions

Bladder toxicity is one of the major causes of morbidity in patients treated with pelvic radiotherapy.

In this study, the use of natural food supplements based on D-Mannose and a dry concentrated extract of cranberry, (Cystoman 100) has demonstrated promising results for the reduction of acute and late bladder toxicity, bringing about an improvement in patients quality of life and the possibility of continuing the radiation course without interruption.

Our experience permitted 90% of patients to complete radiation therapy in the planned time and, as the data in literature have established the benefit of continuity to obtain the best results in cancer care, a longer follow-up is needed to confirm the clinical significance of respecting the overall treatment time.

These promising results obtained with the prophylactic use of Cystoman 100 in the reduction of bladder toxicity are encouraging and need to be validated in multi-centric studies.

Table 1- Patients characteristics (N=46)

Characteristics	**Values**
Total number of patients	**46**
Age	
Mean±SD	67,63±7,98
Range	47-81
Sex	
Male	36 (78,26%)
Female	10 (21,74%)
Type of cancer:	
Anus	1 (2,17%)
Prostate	21 (45,65%)
Rectum	19 (41,30%)
Uterus	4 (8,7%)
Prostate and Rectum	1 (2,17%)
Type of RT fractionation:	
Conventional	35 (76,09%)
Hypofractionation	11 (23,91%)

Table 2- Bladder Toxicity in the whole group

Acute Bladder Toxicity	**N= 46**
G0	24 pts (52,17%)
G1	13 pts (28,26%)
G2	8 pts (17,39%)
G3	1 pts (2,17%)
Late Bladder Toxicity	**N=43**
G0	39 pts (90,7%)
G1	3 pts (6,98%)

G2	1 pts (2,33%)

Table 3 - Prostate cancer patients characteristics

Prostate cancer patients	**N=22**
Age Median Range	 69,18 60-81
RT fractionation: Conventional Hypofractionation	 **16** (**72,73%**) **6** (**27,27%**)
Acute Bladder Toxicity	**N= 22**
G0	10 pts (45,45%)
G1	7 pts (31,82%)
G2	4 pts (18,18%)
G3	1 pts (4,55%)
Late Bladder Toxicity	N= 20
G0	10 pts (55,56%)
G1	7 pts (38,89%)
G2	1 pts (5,56%)

Table 4- Rectal cancer patients

Rectal cancer patients characteristics	**N=19**
Age Median Range	 66,26 47-79
Post-operative Adjuvant CT-RT	**2 (RT + CT)**

Pre-operative Neo-adjuvant RT/CT-RT: RT Fractionation: Conventional Hypofrationation	**17** 12 (RT + CT) 5
Acute Bladder Toxicity	**N=19**
G0	9 pts (47,37%)
G1	6 pts (31,58%)
G2	4 pts (21,05%)
Late Bladder Toxicity	**N=18**
G0	18 pts (100%)

References

1. Dean RJ, Lytton B: Urologic complications of pelvic irradiation. J Urol, 119: 64 - 67, 1978.
2. Miles EF, Lee WR: Hypofractionation for prostate cancer: a critical review. Semin Radiat Oncol, 18(1):41-7, 2008.
3. Revathy B. Iyer, Anuja Jhingran, Hassan Sawaf and Herman I. Libshitz: Imaging Findings After Radiotherapy to the Pelvis. AJR, 177 No. 5: 1083-1089, 2001.
4. Shaun G. Smit & Chris F. Heyns: Management of radiation cystitis. Nature Reviews Urology 7: 206-214, 2010.
5. Pavlidakey PG, MacLennan GT: Radiation cystitis. J Urol, 182(3):1172-3, 2009.
6. U R Suresh, V J Smith, E W Lupton, and N Y Haboubi: Radiation disease of the urinary tract: histological features of 18 cases. J Clin Pathol, 46(3): 228–231, 1993.
7. Chan TY, Epstein JI: Radiation or chemotherapy cystitis with "pseudocarcinomatous" features. Am J Surg Pathol, 28(7):909-13, 2004.
8. Lips IM, Dehnad H, van Gils CH, Boeken Kruger AE, van der Heide UA, van Vulpen M: High-dose intensity-modulated radiotherapy for prostate cancer using daily fiducial marker-based position verification: acute and late toxicity in 331 patients. *Radiat Oncol*, 21:3-15, 2008.
9. Zietman AL, DeSilvio ML, Slater JD, Rossi CJ, Miller DW, Adams JA, Shipley WU: Comparison of Conventional-Dose vs High-Dose Conformal Radiation Therapy in Clinically Localized Adenocarcinoma of the Prostate A Randomized

Controlled Trial. JAMA, 294(10):1233-1239, 2005.
10. Beckendorf V, Guérif S, Le Prisé E, Cosset JM, Lefloch O, Chauvet B, Salem N, Chapet O, Bourdin S, Bachaud JM, Maingon P, Lagrange JL, Malissard L, Simon JM, Pommier P, Hay MH, Dubray B, Luporsi E, Bey P: The GETUG 70 Gy vs. 80 Gy randomized trial for localized prostate cancer: feasibility and acute toxicity. Int J Radiat Oncol Biol Phys, 60(4):1056-65, 2004.
11. Storey MR, Pollack A, Zagars G, Smith L, Antolak J, Rosen I: Complications from radiotherapy dose escalation in prostate cancer: preliminary results of a randomized trial. Int J Radiat Oncol Biol Phys, 48(3):635-42, 2000.
12. Zelefsky MJ, Chan H, Hunt M, Yamada Y, Shippy AM, Amols H: Long-term outcome of high dose intensity modulated radiation therapy for patients with clinically localized prostate cancer. J Urol, 176(4 Pt 1):1415-9, 2006.
13. Michalski JM, Purdy JA, Winter K, Roach M 3rd, Vijayakumar S, Sandler HM, Markoe AM, Ritter MA, Russell KJ, Sailer S, Harms WB, Perez CA, Wilder RB, Hanks GE, Cox JD: Preliminary report of toxicity following 3D radiation therapy for prostate cancer on 3DOG/RTOG 9406. Int J Radiat Oncol Biol Phys, 46(2):391-402, 2000.
14. Pointreau Y, Atean I, Durdux C: Normal tissue tolerance to external beam radiation therapy: bladder. Cancer Radiother, 14(4-5):363-8, 2010.
15. Hanks GE, Schultheiss TE, Hunt MA, Epstein B: Factors influencing incidence of acute grade 2 morbidity in conformal and standard radiationtreatment of prostate cancer. Int J Radiat Oncol Biol Phys, 31(1):25-9, 1995.
16. Zelefsky Michael J., Levin Emily J., Hunt Margie, Yamada Yoshiya, Shippy Alison M., Jackson Andrew, Amols Howard I.: Incidence of Late Rectal and Urinary Toxicities After Three-Dimensional Conformal Radiotherapy and Intensity-Modulated Radiotherapy for Localized Prostate Cancer. Int J Radiat Oncol Biol Phys, 70 (4): 1124–1129, 2008.
17. Ofek I, Beachey EH: Mannose binding and epithelial cell adherence of Escherichia coli. Infect Immun, 22:247-254, 1978.
18. Hung CS, Bouckaert J, Hung D, et al: Structural basis of tropism of Escherichia coli to the bladder during urinary tract infection. Mol Microbiol, 44:903-915, 2002.
19. Wellens A, Garofalo C, Nguyen H, Van Gerven N, Slättegård R, Hernalsteens JP, Wyns L, Oscarson S, De Greve H, Hultgren S, Bouckaert J : Intervening with urinary tract infections using anti-adhesives based on the crystal structure of the FimHoligomannose-3 complex. PLoS ONE, 3:e2040, 2008.
20. Tao Y, Pinzón-Arango PA, Howell AB, Camesano TA: Oral consumption of cranberry juice cocktail inhibits molecular-scale adhesion of clinical uropathogenic Escherichia coli. J Med Food, 14(7-8):739-45, 2011.
21. Head KA: Natural approaches to prevention and treatment of infections of the lower urinary tract. Altern Med Rev, 13(3):227-44, 2008.
22. 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, 31(5):1341-6, 1995.