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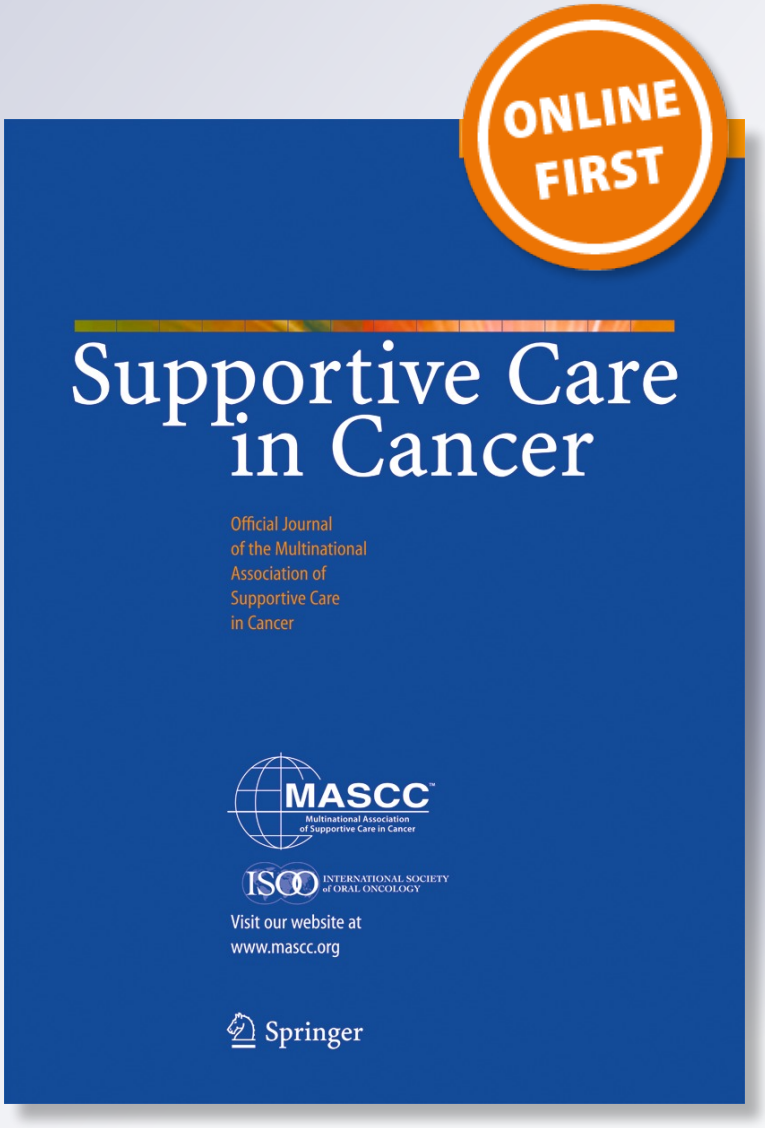
Supportive Care in Cancer

ISSN 0941-4355

Support Care Cancer
DOI 10.1007/s00520-014-2335-8



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ORIGINAL ARTICLE

Standardized cranberry capsules for radiation cystitis in prostate cancer patients in New Zealand: a randomized double blinded, placebo controlled pilot study

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Received: 26 March 2014 / Accepted: 22 June 2014

Abstract
Purpose Acute radiation cystitis, inflammation of the bladder, is a common side effect in men receiving external beam radiation for prostate cancer. Although several treatments provide symptomatic relief, there is no effective treatment to prevent or treat radiation cystitis. Cranberry products have been associated with urinary tract health. This study aimed to determine the effect of highly standardized cranberry capsules (containing 72 mg proanthocyanidins [PACS]) compared with that of placebo capsules on the incidence and severity of radiation cystitis.
Methods Forty-one men with prostate cancer participated in a double blinded randomized placebo controlled study. Men took one capsule a day at breakfast during treatment and for 2 weeks after treatment completion. Severity of urinary symptoms and the bother these caused were measured using the individual items of the urinary domain of the Modified Expanded Prostate Index Composite (EPIC).
Results The incidence of cystitis was lower in men taking cranberry capsules (65 %) compared with those that took placebo capsules (90 %) (p=0.058); severe cystitis was seen in 30 % of men in the cranberry arm and 45 % in the placebo arm (p=0.30). Overall, the incidence of pain/burning was significantly lower in the cranberry cohort (p=0.045). Men on the low hydration regimen who took cranberry had less pain/burning (p=0.038), stronger urine steam (p=0.030) and used significantly fewer pads/liners (p=0.042), which was significantly different from those on the high hydration regimen (p=0.028).
Conclusion Men receiving radiation therapy for prostate cancer may benefit from using cranberry capsules, particularly those on low hydration regimens or with baseline urinary symptoms.

Keywords Cranberry capsules · Double blinded · Placebo capsules · Radiation cystitis · Randomized

Introduction

After skin cancer, prostate cancer is the most common cancer among older men in developed countries. The latest reports from the New Zealand Cancer Registry show an increasing trend in the number of men diagnosed with prostate cancer each year, from 2,484 in 2007 to 3,139 in 2012 [1]. Treatment for prostate cancer may include surgery, radiation therapy and hormone therapy, depending on stage, location, co-morbidities and patient preferences. Acute radiation-induced cystitis is a common side effect of radiation therapy for prostate cancer, with up to 60 % of men affected by cystitis to some extent [2-4]. Acute symptoms occur within 2–3 weeks of starting radiation treatment and include urinary urgency, frequency, dysuria, hematuria and an increased risk of urinary tract infections (UTIs) [5]. Although there are treatments that give symptom relief, there is currently no effective treatment to prevent radiation cystitis.

Acute radiation cystitis is caused by free radical damage to the umbrella cells that make up the apical part of the mucosal

Electronic supplementary material The online version of this article (doi:10.1007/s00520-014-2335-8) contains supplementary material, which is available to authorized users.

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Published online: 04 July 2014

lining of the bladder wall (urothelium). Disruption of urothelial integrity allows leakage of uric acid, urea, creatinine and electrolytes (chloride, sodium and potassium) as well as a range of dietary bladder irritants into the submucosa causing inflammation, which leads to further damage of the mucosa and fibrosis of the submucosa [5-8].

Anecdotally, cranberry products (*Vaccinium macrocarpon*) have been credited with preventing recurrent UTIs. Binding of proanthocyanidins to different types of fimbriae of uropathogenic bacteria (particularly *Escherichia coli*) blocks adherence of bacteria to the urothelium, preventing mucosal infection (reviewed in one study [9]). However, the most recent Cochrane systematic review does not support the use of cranberry products for the prevention of UTIs [10]. Cranberries are rich in polyphenols, including flavenoids, anthocyanins and proanthocyanidins, renowned for their strong anti-oxidant properties [11-15]. However, the bioavailability of anthocyanins and proanthocyanidins is very poor (<1–5 % of ingested dose) in both rats [16] and humans [17-19]. This demonstrates that cranberry products are unlikely to affect radiation cystitis through their radical scavenging abilities. It is conceivable that anthocyanins and proanthocyanidins in the bladder decrease radiation-induced inflammation in the submucosa by affecting cell signalling pathways in immune cells responsible for inflammation [20]. The effect of cranberries on radiation cystitis has been investigated in three clinical studies. Two of these studies tested the effect of cranberry juice [4, 21]; the open-label Canadian RCT compared the effect of cranberry juice with that of apple juice on radiation cystitis in 112 prostate cancer patients. Cystitis symptoms were scored using the modified International Prostate Symptom Score. This study did not find a significant difference between the two study arms [21]. A second Scottish trial was a double blinded RCT comparing the effect of cranberry juice and a similar control juice on the severity of radiation cystitis in 128 patients with bladder and cervical cancer [4]. Analysis was conducted on the intention to treat cohort (n=113) and the fully compliant cohort (n=32). Patients in the placebo arm experienced more severe cystitis symptoms (using Common Toxicity Criteria) and a greater incidence of UTIs than in the cranberry arm in both cohorts, but none of these differences were statistically significant [4]. A third Italian non-randomized study investigated the effect of standardized cranberry tablets on radiation cystitis against no treatment in a cohort of 370 prostate cancer patients but did not describe how the two groups were allocated [22]. The authors reported a significant decrease in UTI incidence and cystitis symptoms according to the Boyarski scale (frequency, nocturia, urgency, urine flow) in the treatment group. We hypothesize that taking cranberry capsules once a day may decrease the severity of acute radiation cystitis. This study is a pilot study to inform power calculations for a larger trial. We investigated the effect of highly standardized cranberry capsules with that of placebo capsules in a double blinded RCT on the incidence and severity of radiation cystitis in men with prostate cancer.

Methodology

This randomized double blinded placebo controlled trial obtained ethical approval from the Upper South Island Regional Ethics Committee (protocol number URA/11/08/038) and is registered with the Australian New Zealand Clinical Trials Registry: ACTRN12611000887976. All patients provided written informed consent before randomization.

Trial outcomes

We determined the effect of cranberry capsules and placebo capsules on (1) the incidence and severity of urinary symptoms and (2) the amount of bother these symptoms caused the men.

Participants

All men receiving image guided intensity modulated radiation therapy to their prostate, prostate and regional lymph nodes or prostate bed at the Southern Blood and Cancer Centre in Dunedin were eligible to enter the study. Men were excluded if they had received previous radiation therapy to the pelvis, metastatic disease, an allergy to cranberries, a history of kidney stones, a Karnofski performance status score of less than 70 or who were on warfarin. We recruited a total of 41 men from May 2012 to March 2013; the number of participants was not based on a power calculation as this was a pilot study.

Randomization and blinding

Cranberry and placebo capsules were indistinguishable in taste, colour and smell ensuring patients, clinicians and the research radiation therapist (RRT) were blinded with respect to the content of the capsules. Naturo Pharm LTD provided unmarked bottles with 70 coated cranberry capsules (containing 72 mg proanthocyanidins [PACs] each; content was tested using the UV-VISEP/CN standard method) and unmarked bottles with 70 coated placebo capsules (containing colloidal silica, magnesium stearate, cellulose and gelatin) free of charge. Bottles containing cranberry or placebo capsules were allocated a number between 1 and 41 using computer-generated randomization charts by the Principal Investigator (PMH), who was not involved with patient care. Each participant was given a numbered bottle by the RRT, corresponding to his place of enrolment (patient 01 was given bottle 01 and so on).

Radiation therapy treatment

Men receiving treatment to the prostate or prostate bed were prescribed a dose of 74 Gy in 37 fractions or 64 Gy in 32 fractions, respectively. All patients received 6MV photon beam intensity modulated radiation therapy with a consistent planning and treatment technique. Treatment was delivered with the patient in the supine position using seven fields (prostate or prostate bed), 12 fields (prostate and regional lymph nodes) or six fields (pre-existing metal hip). Daily cone beam CT scans were performed to assess prostate position and bowel and bladder status as per standard department protocol.

Procedure

Eligible patents were identified from their planning CT scan and given written information about the trial to take home with them. On their first day of treatment (approximately 4 weeks after CT), patients gave written informed consent before randomisation, if they elected to participate in the trial. Participants were given their numbered bottle of capsules on the first day of treatment and were asked to take one capsule a day during breakfast throughout their entire treatment course and for 2 weeks post treatment (9 weeks prostate bed, 10 weeks prostate and prostate nodes). Participants were specifically told not to consume any foods, drinks or supplements containing berries including cranberries, blueberries, blackberries and blackcurrants and were asked to limit their consumption of red grapes and red wine (1 glass/night). EPIC scores were obtained on the first day of treatment to provide baseline scores, then twice weekly during treatment and once a week over the phone during the 2 weeks post treatment.

Measurements

Modified Expanded Prostate Index Composite (EPIC)

EPIC was specifically designed to evaluate patient quality of life (QoL) after prostate cancer treatment [23]. EPIC is divided into four domains that address urinary, bowel and hormonal-related side effects as well as sexual function. Each of the domains consists of a number of items that address symptoms and the bother that these symptoms cause. Each item is scored using a Likert scale. The domains have been validated together as well as separately and can be used as a stand-alone measure [23, 24]. We used the urinary domain which consists of five symptom items (how often have you experienced: pain or burning upon urination, blood in urine, leakage, overall control, number of pads or liners) and seven bother items (how big a problem for you was: pain or burning upon urination, weak urine stream or incomplete emptying, daytime frequency, night time frequency, blood in urine, leaking or dribbling, overall problem (Table S1). It was modified by restricting questions to the last week. We compared the raw scores of each of these items, which was an a priori analysis, rather than convert them into percentage scores to determine the overall percentage QoL score. In this pilot study, we were more interested in the individual items to identify any specific effects of the cranberry capsules on radiation cystitis rather than the overall QoL of the men in the trial.

Baseline EPIC scores

All baseline EPIC scores were taken on the first day of treatment.

Dose volume histograms

Dose volume histograms (DVHs) were obtained for trial patients using the Xio (version 4.70; Elekta) planning system. Participant anatomy was contoured using the 3D helical planning CT scan. Information on bladder volume (cc), maximum, minimum and average bladder doses across the IMRT dosimetry plans for the two trial arms are shown in Table 1.

Data collection, entry and statistical analysis

EPIC scores were analysed with SAS v9.3 (SAS Institute Inc., Cary, NC, USA). The mean and maximum scores were compared with non-parametric Wilcoxon rank-sum tests and analysis of variance on the ranked data [25] with adjustment for whether or not the symptom was present at baseline. Analysis of variance on the rank data with terms for study group and either whether the patient had baseline symptoms or whether they had the high or low hydration regimen, and their interactions, were used to assess the statistical significance of any differences between sub-groups. A p value <0.05 was considered statistically significant.

Results

Patient demographics

Patients were recruited between May 2012 and March 2013, resulting in a cohort of 41 men. Two men did not comply with the protocol, and one of these pulled out of the trial after 2 weeks. Analysis on an intent-to-treat basis was performed on 40 patient data sets (20 in the cranberry arm and 20 in the control arm) (Fig. 1). The average age of the men was 68 years, the vast majority of men (93 %) identified as New Zealand European, two as Maori/NZ European and one as Maori. Approximately half (55 %) of the participants presented with stage T1 disease at the time of diagnosis and three quarters

Table 1 Patient demographics

	Total	Cranberry arm	Placebo arm
Patient numbers	40 (100 %)	20 (50 %)	20 (50 %)
Personal construct			
Age	68 (51–82)	68 (52–82)	68 (51–76)
Ethnicity			
NZ European	37 (93)	20 (100 %)	17 (85 %)
Maori/NZ European	2 (5 %)		2 (10 %)
Maori	1 (3 %)		1 (5 %)
Smoker			
Never	29 (73 %)	14 (70 %)	15 (75 %)
Past/current	11 (28 %)	6 (30 %)	5 (25 %)
Alcohol intake			
<3 a week	26 (65 %)	13 (65 %)	13 (65 %)
≥3 a week	14 (35 %)	7 (35 %)	7 (35 %)
Family history of PC	14 (35 %)	7 (35 %)	7 (35 %)
Cancer construct			
Gleason's score			
6 or 7	30 (75 %)	15 (75 %)	15 (75 %)
8 or 9	10 (25 %)	5 (25 %)	5 (25 %)
Stage/Grade			
T1 (a–c)	22 (55 %)	12 (60 %)	10 (50 %)
T2 (a–c)	9 (23 %)	4 (20 %)	5 (25 %)
T3	7 (18 %)	4 (20 %)	3 (15 %)
T4	2 (5 %)	0 (0 %)	2 (10 %)
Nodal involvement	9 (23 %)	5 (25 %)	4 (20 %)
RT construct			
Prescription Gy/# fractions			
74/37 (prostate)	24 (60 %)	12 (60 %)	12 (60 %)
74/37 (prostate plus nodes)	8 (20 %)	4 (20 %)	4 (20 %)
64/32 (prostate bed)	7 (18)	3 (15%)	4 (20 %)
64/32 (prostate bed plus nodes)	1 (3 %)	1 (5 %)	
Min dose (Gy)	9 (0.2–28)	9 (0.3–28)	8 (0.2–26)
Max dose (Gy)	77 (67–80)	77 (67–80)	76 (67–80)
Mean dose (Gy)	40 (14–65)	40 (21–65)	40 (14–53)
Bladder volume in field (ml)	228 (71–536)	216 (71–474)	240 (81–536)
Adjuvant therapy			
Surgery	13 (33 %)	7 (35 %)	6 (30 %)
Hormone therapy	19 (47 %)	7 (35 %)	12 (60 %)
Stratification			
Hydration regimen			
High	14 (35 %)	8 (40 %)	6 (30 %)
Low	26 (65 %)	12 (60 %)	14 (70 %)
Baseline EPIC scores			
Yes	21 (53 %)	9 (45 %)	12 (60 %)
No	19 (47 %)	11 (55 %)	8 (40 %)

(75 %) of men had a Gleeson score of 6 or 7. A small number of men had nodal involvement (Table 1). Patient-related factors (smoking, alcohol intake), family history of prostate cancer) and treatment-related factors (fractionation regimen, bladder volume in the radiation field and dose to the bladder, as well as previous surgery and concurrent androgen therapy) were evenly distributed between the cranberry and placebo arms (see Table 1).

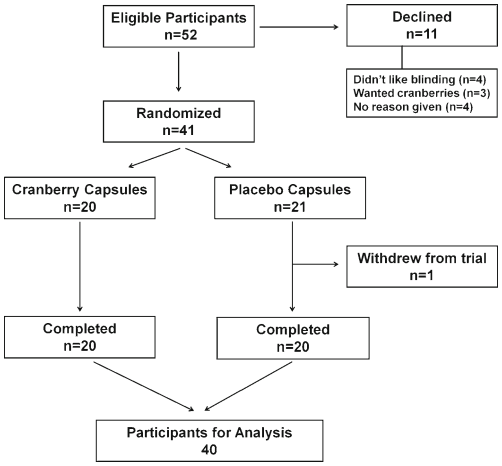

Fig. 1 Diagram showing flow of patients through the trial. Of the 41 patients that entered into the trial, two patients did not comply with protocol, and one of these left the trial after 2 weeks

The effect of cranberry capsules on incidence of cystitis

We defined cystitis as having at least one maximum score of 2 in any of the symptoms or bother items. Severe cystitis was then defined having at least one maximum score of 4 (3 for urinary control and number of pads). Using this definition 13/20 (65 %) patients in the cranberry arm and 18/20 (90 %) patients in the placebo arm developed cystitis (p=0.058, chi-square test) and 6/20 (30 %) of patients in the cranberry arm and 9/20 (45 %) patients in the placebo arm developed severe cystitis (p=0.30, chi-square test). None of the men in the trial developed a UTI.

The effect of cranberry capsules on EPIC scores

We calculated both the mean and maximum EPIC scores for patients in both cohorts (see Fig. 2). Scores for all items (with the exception of blood in urine) were consistently lower for the cranberry cohort than for the placebo cohort. Because the scores were not normally distributed, we used the non-parametric Wilcoxon signed-rank test to determine which of these differences were statistically significant. We found that the pain/burning scores were significantly lower for the cranberry cohort both for the mean (p=0.045) and maximum (p=0.019). Patients in the placebo arms had a significantly weaker mean urine stream (p=0.022), but the difference was not significant after controlling for baseline symptoms (p=0.14) (Table S2).

The effect of having urinary symptoms at the start of treatment on EPIC scores

With respect to baseline EPIC scores, 21 (53 %) of the men in our cohort had urinary symptoms in at least one of the items of the EPIC measure. Patients with urinary symptoms at the start of treatment experienced worse urinary symptoms and were more bothered by these symptoms than patients with no baseline EPIC scores. Differences between cranberry and placebo cohorts were significantly different for leaking/dribbling between those with and without baseline scores for both mean (p=0.039) and maximum (p=0.045) scores (Table S3). This difference was significant for those with baseline EPIC scores (mean p=0.024, maximum p=0.021), but not significant for those without baseline EPIC scores

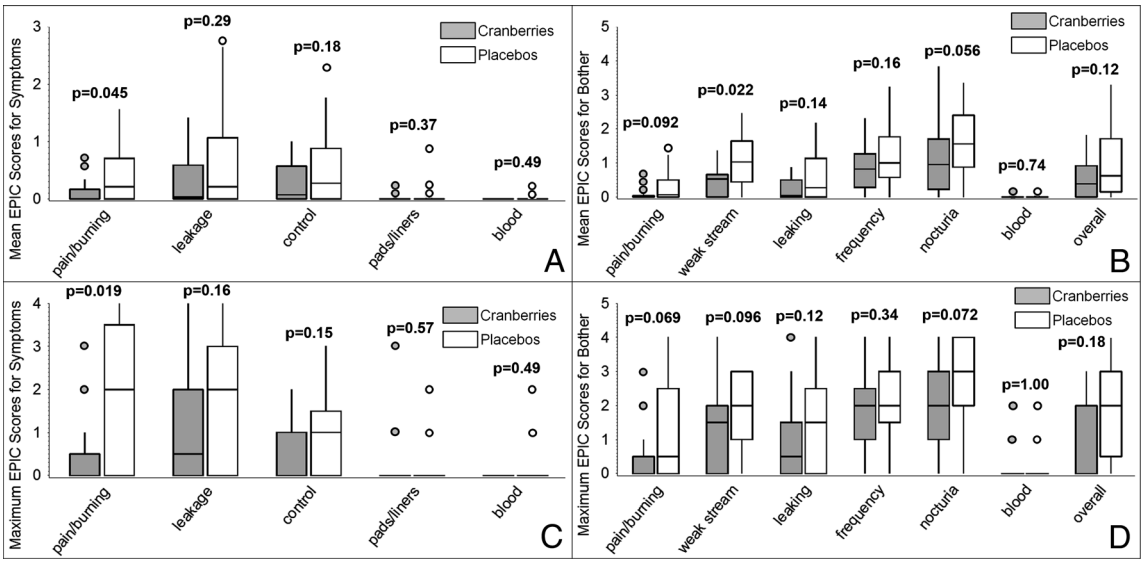

Fig. 2 Box plot of differences in EPIC scores between cranberry arm (*grey*) and placebo arm (*white*) on mean (**a**, **b**) and maximum (**c**, **d**) urinary symptoms (**a**, **c**) and bother symptoms (**b**, **d**). The *bottom* and *top edges* of the box represent 25th and 75th percentiles, with a *line* at the median. The *vertical lines* are drawn to the most extreme point within 1.5 of the interquartile range from the box, with additional *dots* for the most extreme scores

(mean p=0.47, maximum p=0.57). There were no significant differences for patients with no baseline scores. For patients with baseline scores taking cranberry capsules also significantly decreased pain/burning (symptoms: mean p=0.042, maximum p=0.009; bother: maximum p=0.036), control (maximum p=0.034), and weak urine stream (mean p=0.036), but these decreases were not significantly different from the differences for those without baseline scores (Table S3).

The effect of hydration on EPIC scores

Initially men were instructed to drink eight cups of water (2 l) daily and to have a full bladder and empty bowels for their computed tomography (CT) scan and subsequently for each day of their treatment. To achieve this, department guidelines suggested emptying both the bladder and bowels an hour before treatment then consuming two or three cups of water and holding this until after CT or treatment. However, many of the men in our cohort were elderly and not used to drinking large volumes of water on top of their normal consumption of fluids. We had noticed that many of them were very uncomfortable following this regimen and felt that at least in some of the smaller older men, this hydration regimen may have caused overstretching of their bladder. Overstretching of the bladder wall increases urothelial permeability [26], which may contribute to cystitis severity (particularly urgency and frequency). The research team consisting of the principal investigator (PI), the RRT, the charge radiation therapist (RT), the radiation oncologist and the oncology nurses therefore decided to change the hydration guidelines to a more comfortable four to six cups of water a day and one to two cups after emptying the bladder. We felt justified changing the hydration regimen partway through the trial because this was a pilot study meant to inform the protocol and participant numbers for a larger multicentre study. The switch to the new regimen occurred after 14 patients (eight patients in cranberry arm and six patients in placebo arm) with the next 26 patients following the less strenuous hydration regimen (12 patients in the cranberry arm and 14 patients in the placebo arm). Differences between cranberry and placebo cohorts were significantly different between those on high and low hydration regimens for the number of pads/liners used (mean p=0.028 and maximum p=0.027) (Table S4). The difference was significant for those on low hydration regimens (mean p=0.042, maximum p=0.047), but not significant for those on high hydration regimens. There were no significant differences for patients on the high hydration regimen. For patients on the low hydration regimen taking cranberry capsules also significantly decreased pain/burning (maximum symptoms p=0.038, bother p=0.036), and weak urine stream (maximum p=0.030), but these decreases were not significantly different from the differences for men on a high hydration regimen (Table S4).

Discussion

In this paper we report that taking highly standardized cranberry capsules once a day, during and for 2 weeks after completion of radiation therapy, decreased the incidence and severity of certain aspects of cystitis, including incidence of pain/burning, in men with prostate cancer compared with placebo capsules. We based the cranberry capsule dosage (72 mg PACs/capsule) on a study by Howell and colleagues who conducted a detailed in-depth comparative PACs dose study with cross-over design in 32 healthy female volunteers from Japan, Hungary, Spain and France [27]. We measured and analysed the individual items of the urinary domain of the EPIC measure to determine the effect of cranberry capsules on different urinary symptoms as well as the effect of these symptoms on the amount of bother they caused the men.

Urinary symptoms before treatment

A significant proportion of prostate cancer patients are likely to present with one or more urinary symptoms before starting radiation therapy. Figures reported in the literature range from 44 % [4] to 62 % [21]. Two of the trials investigating the effect of cranberry products on radiation cystitis excluded men with urinary symptoms at the start of treatment from participation [4, 22]. Cowan et al. [4] identified that having so many men presenting with baseline urinary symptoms, an exclusion criteria for this study, severely affected recruitment. Campbell et al. [21] stratified between patients with and without baseline urinary symptoms (35/55 in cranberry juice arm and 34/57 in apple juice arm). The authors reported significantly worse urinary symptoms and QoL in patients who presented with urinary symptoms at the start of treatment. We also saw significantly worse EPIC scores for most of the items in men who presented with baseline urinary symptoms. Interestingly, significantly less pain/burning, better control, a stronger urine stream and less leaking/dribbling was only experienced by men taking cranberry capsules who presented with baseline urinary symptoms and not by men who did not have baseline cystitis scores. The difference was significant for leaking/dribbling, a result that suggests that cranberry capsules may have a greater effect on those with worse urinary symptoms.

Hydration regimen

The rationale behind full bladders and empty bowels during CT scanning and daily radiation treatment is to minimize the volume of bladder and rectum in the radiation field, to avoid acute and chronic radiation cystitis. In order to facilitate this, different departments have different guidelines but most include drinking a lot of water every day and immediately prior to treatment. However, many elderly men find it difficult to

adhere to this regimen and are not always compliant, possibly due to having uncomfortably stretched bladders. Erickson and colleagues [26] showed a 4-fold increase in urothelial permeability over controls following bladder distension of patients, with overstretched bladders causing worse urinary symptoms particularly with respect to urgency and frequency. In our study, only men on the low hydration regimen experienced significantly less pain/burning, used fewer pads/liners and had a stronger urine stream than men on the low hydration regimen taking placebo capsules. This was not the case for men in the high hydration cohort. This discrepancy could perhaps be explained by the fact that at least some of the urinary symptoms experienced by men on high hydration were caused by mechanical overstretching rather than a result of radiation damage. Perhaps cranberry products are better at preventing radiation cystitis than mechanically induced cystitis.

Recommendations for future trials

Future trials should use highly standardized cranberry capsules/tablets that have been analysed for PAC and other antioxidant content. Based on the results of this trial it is important that consistent advice is given to patients regarding hydration, particularly in multicentre studies. With respect to men who present with baseline urinary symptoms, we found that men presenting with urinary symptoms at the start of treatment benefitted more from taking cranberry capsules than men who did not have baseline EPIC scores. Future trials could incorporate both cohorts, adjusting for having baseline symptoms during analysis and be sufficiently powered for subgroup analysis. With respect to the timing of taking the capsules, pharmacokinetic studies have shown that a single dose of elderberry extract [17] and cranberry juice [18, 19] produced maximum anthocyanin levels in urine 3–6 h after consumption [18, 19], indicating that breakfast would be the best time to take the capsules. It may also be useful to consider taking one capsule twice a day, as the bioavailability of proanthocyanidins in humans is poor [17-19].

Limitations

This study was limited by analysing the raw scores of the individual items from the EPIC measure rather than converting these into a single overall QoL percentage. Using EPIC items in this way has not been validated; however, we wanted to identify any specific effects of the cranberry capsules on radiation cystitis rather than on the overall QoL of the men in the trial. The randomized double blinded placebo controlled design of this trial minimized patient and researcher bias and minimized confounding by patient and treatment related factors.

Conclusion

Men receiving radiation therapy for prostate cancer may benefit from using cranberry capsules, particularly those on low hydration regimens or presenting with urinary symptoms before radiation treatment.

Acknowledgements This research was funded by grants from the University of Otago and the Health Otago Charitable Trust and by the Southern Blood and Cancer centre. Cranberry and placebo capsules were provided free of charge by Naturo Pharm LTD.

Conflict of interest The authors declare no conflict of interest. Although Naturo Pharm LTD provided the capsules, the firm had no input into study design, execution, analysis or publication of this research.

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