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File: ■ Cranberry (*Vaccinium macrocarpon*)
■ Urinary Tract Infection
■ Bladder Discomfort
■ Radiotherapy for Prostate Cancer

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RE: Cranberry Extract Supplementation Eases Bladder Discomfort and Infection following Radiotherapy for Prostate Cancer

Bonetta A, Di Pierro F. Enteric-coated, highly standardized cranberry extract reduces risk of UTIs and urinary symptoms during radiotherapy for prostate carcinoma. *Cancer Manag Res*. 2012;4:281-286.

Cranberry (*Vaccinium macrocarpon*) preparations have long been used for medicinal purposes, especially to treat urinary tract infections. The berries contain complex proanthocyanidins with A-type bonds. Several recent studies have demonstrated the clinical efficacy of cranberry preparations in patients with lower urinary tract infections (LUTIs).[1] Because LUTI is a frequent adverse event in patients with cancer who are being treated with external beam radiotherapy (EBRT) to the pelvis, the authors conducted a nonrandomized, single-center study to determine whether enteric-coated tablets containing highly standardized cranberry (ecVM) could prevent LUTIs and moderate the bladder irritation associated with the treatment.

From July 6, 2007 to September 3, 2010, 370 patients were enrolled at the Unità Operativa di Radioterapia Oncologica of Cremona Hospital in Cremona, Italy. The patients, diagnosed with prostatic adenocarcinoma, were treated with radiotherapy to the prostatic area (and to the pelvis in cases with a high risk of lymph node involvement). Only patients treated with radical, adjuvant, or salvage radiotherapy were enrolled in the study. Of the 370 patients, 186 had undergone surgery.

The patients were sorted into 2 groups: those treated with ecVM (n=184) and those serving as controls (n=186).

The patients in the ecVM group took 1 enteric-coated tablet daily of VO370® or MonoSelect Macrocarpon® (PharmExtracta; Pontenure, Italy), containing 200 mg of a highly standardized cranberry extract titered at 30% proanthocyanidins.

During the 6-7 weeks of treatment, all patients underwent weekly examinations to record their urinary symptoms and their use of nonsteroidal anti-inflammatory drugs. Urine cultures were performed at weeks 3 and 6 and in cases of intense dysuria. Urinary tract infection was diagnosed when bacteriuria exceeded 100,000 u/mL and specific symptoms of cystitis were present.

Compliance in the ecVM group was excellent; only 1 patient discontinued treatment for 10 days during the study. Two patients with chronic gastritis in the ecVm group complained of gastric pain and required treatment. No other unwanted effects or allergies were observed. All patients completed their planned EBRT.

In the control group, 45 (24.2%) patients suffered LUTIs; 8 (4.3%) had recurrent infection. In the ecVM group, 16 (8.7%) experienced urinary infections with no recurrence. The difference between the percent of patients that suffered LUTIs in each group was statistically significant.

Of the bacteria found in the urine cultures, *Escherichia coli* and bacteria of enteric origin were the most common, with a higher prevalence of coliform bacteria in the control group (21 cases) than in the ecVM group (5 cases).

Of the 8 relapses observed in the control group, 5 were caused by *E. coli*, 2 by enterococci, and 1 by a hemolytic staphylococcal strain.

Analysis of urinary symptomology, conducted in all but 2 patients independent of the presence of an infectious process, revealed a lower incidence of dysuria and milder symptoms in the ecVM group than in the control group. Absence of symptoms was observed in 62% of patients in the ecVM group and in 36% of those in the control group. Other degrees of dysuria (occasional burning, frequent burning, and constant pain) were significantly higher in the control group ($P<0.0001$).

Overall, the urinary symptoms due to radiotherapy were milder in the ecVM group than in the control group, with statistically significant differences in terms of nocturia (31% vs. 54% increase, $P<0.001$); urgency (31% vs. 54% increase, $P<0.0001$); and urine flow (14% vs. 21.5% decrease, $P=0.0066$). Daily urination frequency increased from 5.33 to 8.74 in the control group, and from 5.85 to only 7.55 in the treatment group ($P=0.0006$).

These results suggest that, "The benefits of cranberry extract in prevention of LUTIs can be observed also in nonphysiologic situations, such as the acute bladder damage associated with high-dose irradiation," say the authors.

According to the authors, only 2 studies have been reported on the use of cranberry extract in supportive cancer care. The first study, in 128 female patients treated with radiotherapy or a combination of radiotherapy and chemotherapy for uterine cancer, showed only a tendency toward reduced LUTI frequency in the treatment group compared with placebo, with the difference not statistically significant.[2] The second study[3] also used cranberry juice to prevent bladder symptoms in patients undergoing pelvic radiotherapy; no significant differences were reported between the cranberry-treated group and the controls. Both studies had design limitations.

Acknowledging the lack of randomization in their study, the authors conclude that the incidence of LUTIs and bladder discomfort associated with pelvic irradiation was lower

with the use of cranberry extract compared with placebo, with statistically significant differences in dysuria, nocturia, and urinary frequency. "It is possible that, because of its strong antioxidant properties, cranberry could attenuate actinic damage to the bladder mucosa, reducing the inflammatory process and, as a consequence, its symptoms," they explain. The authors fail to make a compelling case for their rationale of the use of an enteric coating in the formulation, which may have weakened the study outcome significantly.

—Shari Henson

References

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[3]Campbell G, Pickles T, D'yachkova Y. A randomised trial of cranberry versus apple juice in the management of urinary symptoms during external beam radiation therapy for prostate cancer. *Clin Oncol (R Coll Radiol)*. 2003;15(6):322-328.

Referenced article can be found at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3437800/pdf/cmar-4-281.pdf.