Randomized Controlled Trial of Oxybutynin Extended Release Versus Placebo for Urinary Symptoms During Intravesical Bacillus Calmette-Guérin Treatment

Michael H. Johnson, Kenneth G. Nepple,* Vicky Peck, Kathryn Trinkaus, Aleksandra Klim, Gurdarshan S. Sandhu and Adam S. Kibel†,‡

From the Division of Urologic Surgery (MHJ, KGN, VP, AK, GSS, ASK) and Division of Biostatistics (KT), Washington University School of Medicine, Saint Louis, Missouri, and Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (ASK)

Abbreviations and Acronyms

AUA = American Urological Association

BCG = bacillus Calmette-Guérin

EAT = evening after treatment

ER = extended release

MBT = morning before treatment

NMIBC = nonmuscle invasive bladder cancer

PD = posttreatment day

PVR = post-void residual

QSS = quantitative symptom score

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Study received institutional review board approval.

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† Correspondence: Division of Urology, Brigham and Women's Hospital, 45 Francis St., Boston, Massachusetts 02115 (telephone: 617-732-6325; FAX: 617-732-6665; e-mail: akibel@partners.org).

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Purpose: Intravesical bacillus Calmette-Guérin is used to decrease recurrence rates of nonmuscle invasive urothelial carcinoma. Irritative urinary symptoms are a common side effect of treatment and frequently limit treatment tolerance. While anticholinergic medications may be used for symptom prophylaxis, to our knowledge they have not been evaluated in a randomized controlled trial.

Materials and Methods: A total of 50 bacillus Calmette-Guérin naïve patients were randomized to 10 mg extended release oxybutynin daily or placebo starting the day before 6 weekly bacillus Calmette-Guérin treatments. A questionnaire assessing urinary symptoms (frequency, burning on urination, urgency, bladder pain, hematuria), systemic symptoms (flu-like symptoms, fever, arthralgia) and medication side effects (constipation, blurred vision, dry mouth) was recorded daily throughout the therapeutic course. A linear mixed repeated measures model tested the differences between each point and baseline score.

Results: The treatment group had a greater increase in urinary frequency and burning on urination compared to placebo ($p = 0.004$ and $p = 0.04$, respectively). There were no significant differences between groups for other urinary symptoms, which increased in severity after bacillus Calmette-Guérin but concomitantly returned to baseline in both groups. The treatment group experienced increases in fever, flu-like symptoms, dry mouth and constipation compared to placebo ($p < 0.0001$, $p = 0.0008$, $p = 0.045$ and $p = 0.001$, respectively). There were otherwise no significant differences in nonurinary symptoms or medication adverse reactions.

Conclusions: Oxybutynin increased urinary frequency and burning on urination compared to placebo in patients receiving intravesical bacillus Calmette-Guérin treatment. Our results do not support the routine use of oxybutynin as prophylaxis against urinary symptoms during bacillus Calmette-Guérin therapy.

Key Words: carcinoma, transitional cell; urinary bladder neoplasms; BCG vaccine; cholinergic antagonists; comparative effectiveness research

In 2012 in the United States bladder cancer had an estimated incidence of 73,500 new cases and accounted for nearly 15,000 deaths.[1] Approximately 70% of incident cases are nonmuscle invasive, invading no deeper than the lamina propria.[2] In the 1970s intravesical BCG, a live attenuated mycobacterium strain, emerged as an immunotherapeutic agent for the treatment of NMIBC.[3,4] It has since become a first line treatment option for NMIBC because of a

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reduction in disease recurrence and progression.[5–7]

Despite its efficacy, the side effects of BCG frequently limit a patient's ability to tolerate a full treatment course.[8–10] A 2003 study from the European Organisation for Research and Treatment of Cancer reported that 75% of patients had local side effects and 39% had systemic side effects from intravesical BCG.[11] Importantly a quarter of patients delayed treatment secondary to side effects (18.3% local, 6.2% systemic) and 20.3% stopped treatment altogether as a result of local side effects and/or systemic side effects. Symptomatic treatment of BCG induced lower urinary tract symptoms may include the use of anticholinergic medications.[12–14]

Oxybutynin chloride is a tertiary amine with a direct antispasmodic effect on smooth muscle, and anticholinergic, analgesic and local anesthetic effects. Oxybutynin chloride extended release is approved for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency.[15] To the best of our knowledge the efficacy of this treatment for urinary symptoms during BCG therapy is entirely anecdotal and has not been studied in a systematic method. Through a randomized controlled trial we evaluated the effectiveness of an anticholinergic prophylaxis on urinary symptoms during induction BCG treatment.

MATERIALS AND METHODS

After obtaining institutional review board approval we initiated a prospective, randomized, placebo controlled, double-blind trial to determine if oxybutynin ER improved urinary symptoms during induction with intravesical BCG immunotherapy.

Patient Eligibility

A total of 50 BCG naïve patients were enrolled in the study. Study inclusion criteria were patients older than age 18 years with pathologically demonstrated NMIBC (CIS, Ta or T1). Patients were excluded from study for an AUA symptom score greater than 20, the use of medications for overactive bladder, pelvic surgery within the previous 6 months, a PVR greater than 50 ml or other medical conditions that would be adversely affected by anticholinergics (fig. 1).

Treatment and Randomization

As participants were enrolled in the study they were randomly assigned an identification number corresponding to a course of medication. Of the 50 patients 25 received active medication with 10 mg oxybutynin ER and 25 received placebo medication. Patients were in-

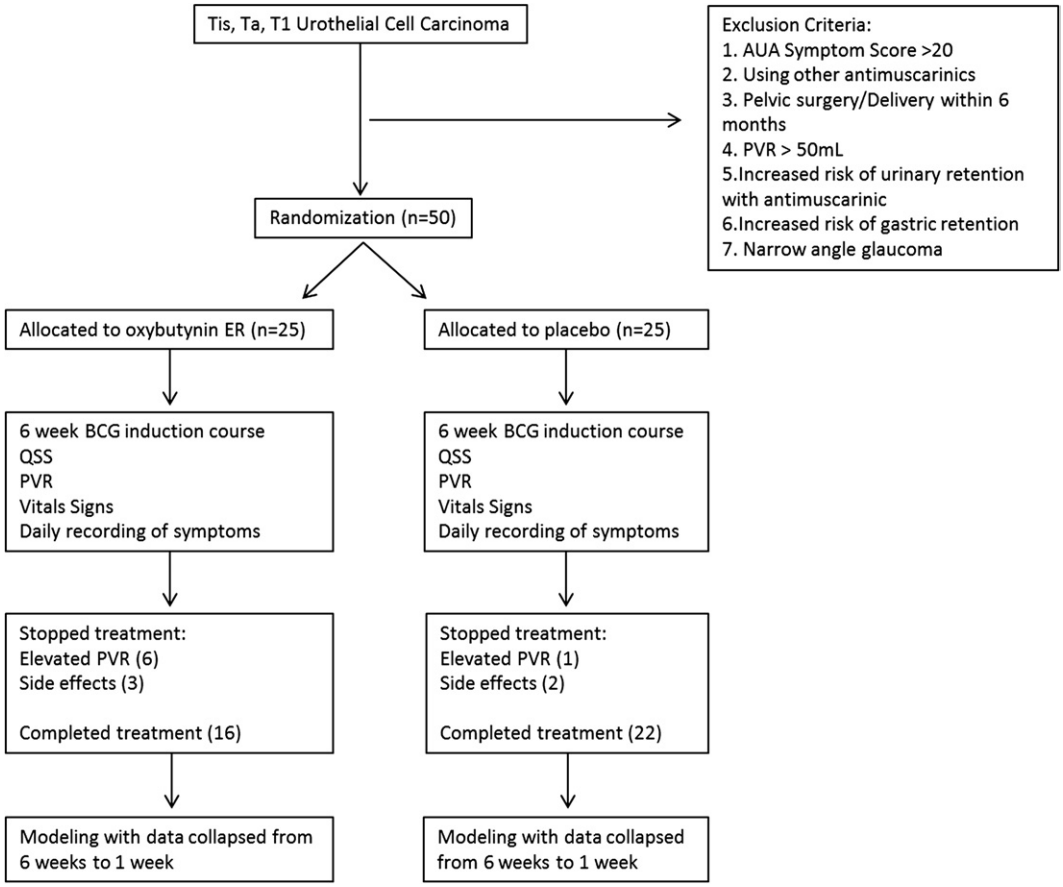

Figure 1. Outline of study design