

Patient Compliance With Maintenance Intravesical Therapy for Nonmuscle Invasive Bladder Cancer

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OBJECTIVE	To assess patient adherence to intravesical instillation therapy for nonmuscle invasive urothelial carcinoma outside of clinical trials.
MATERIALS AND METHODS	We reviewed the records of patients from 2000 to 2013 who received intravesical therapy for nonmuscle invasive urothelial carcinoma. Patients with evidence of tumor recurrence or progression were excluded. We performed univariable and multivariable regression analyses to predict adherence to intravesical therapy.
RESULTS	A total of 729 patients started 861 induction cycles, 63% with bacillus Calmette-Guèrin (BCG) and 37% with mitomycin C (MMC). The rate of completion of 6 weeks induction therapy with BCG and MMC was similar (86% and 87%, respectively). Within the BCG cohort, 161 (35%) patients commenced the Southwest Oncology Group (SWOG) maintenance protocol after induction and 16 (10%) completed all 21 treatments. A monthly protocol for BCG was started by 87 patients (19%) and 48 (55%) completed all 9 treatments. MMC therapy was started in 270 patients, 97 of whom (36%) commenced monthly maintenance treatment, and 46 (47%) completed treatments. Median number of instillations was 7 for patients undergoing monthly maintenance therapy (MMC or BCG) and 9 for patients allocated to 3 years BCG. On multivariable analysis, recurrence after prior treatment of urothelial carcinoma was predictive of patients' adherence to treatment.
CONCLUSION	Compliance with intravesical therapy is low in clinical practice, notably for longer treatment schedules. UROLOGY ■■■: ■■■–■■■, 2018. © 2018 Elsevier Inc.

High recurrence rates of nonmuscle invasive bladder cancer (NMIBC) and the risk of tumor progression reflect the need for adjuvant bladder instillation following transurethral resection of bladder tumor (TURBT).^{1,2} Intravesical therapy is a well-established modality for the treatment of NMIBC and its application has been shown to reduce the rate of disease recurrence in several randomized trials and meta-analyses.³⁻⁵ Treatment guidelines published by the American Urological Association and the European Association of Urology advocate the use of adjuvant intravesical therapy using bacillus Calmette-Guèrin (BCG) or mitomycin C (MMC), depending on tumor stage, grade, and risk of recurrence.^{6,7} Common treatment protocols consist of single postoperative instillation, short-term induction therapy, and longer maintenance therapy. At least 1 year of BCG maintenance

therapy is recommended, whereas maintenance therapy with MMC should not exceed 1 year.⁸

The use of BCG and MMC for the treatment of NMIBC is associated with adverse effects ranging from mild local irritative symptoms to life-threatening systemic complications. Rate of completion of maintenance therapy in clinical trials is low, ranging from 16% to 35% for 3-year schedule.^{3,9,10} Treatment discontinuation can be only partially attributed to toxicity.^{3,9,10} The results of randomized controlled trials, although relevant and representing the basis for the correct management of NMIBC, are often not reproducible in everyday clinical practice. Moreover, the strict selection criteria in randomized controlled trials are not applicable in common practice and patient compliance with intravesical therapy outside the controlled environment of a clinical trial has been poorly characterized. The aims of this study are to assess patient compliance in “real-world” clinical settings and to describe factors predicting adherence to maintenance protocols in patients with NMIBC.

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MATERIALS AND METHODS

After obtaining approval from the institutional ethics committee, we reviewed the medical records of 729 patients who were

treated with intravesical instillation therapy at our institution's outpatient clinic from January 2000 to December 2013. All patients were followed up either until completion of designated maintenance protocol or discontinuation of protocol. All patients had been diagnosed with histologically proven urothelial carcinoma (pTa, pT1, or carcinoma in situ). After the diagnosis of NMIBC had been confirmed, patients started an induction course of intravesical therapy. Instillation agent (MMC or BCG) was selected based on patient risk group stratification for recurrence and progression. Following the completion of induction course patients were assigned to receive either maintenance therapy or surveillance. Because the purpose of the study was to describe adherence to maintenance, we excluded patients with recurrence or progression at any time during therapy or by the time they were scheduled to start maintenance treatment. Primary end point was the completion of maintenance protocol, and noncompliance was defined as premature termination of instillation protocol without disease recurrence or progression. Evidence of disease recurrence or progression requires termination of bladder instillations and therefore such patients were not considered as noncompliant.

Treatment Protocol Schedule

Following TURBT and histopathological confirmation, patients started induction therapy, consisted of a weekly instillation for 6 consecutive weeks. This was followed by a maintenance protocol of 9 monthly treatments, starting 3 months after induction. The monthly maintenance protocol was applied for both MMC and BCG. An additional maintenance protocol, as described in Southwest Oncology Group (SWOG) 8507 trial,³ was offered to patients undergoing intravesical instillation with BCG only. This consisted of 3 weekly BCG instillations at 3 and 6 months after starting induction therapy, and every 6 months thereafter for 3 years. The intent for every patient on SWOG protocol was to complete 3 years of treatment. The choice of maintenance therapy protocol (1 year or 3 years) was at the surgeon's discretion, following discussion with the patient.

Before treatment, bladder was drained using a urethral catheter. BCG (81 mg) or MMC (40 mg) was delivered into the bladder via a catheter, suspended in 50 mL saline 0.9% solution. Patients were instructed to remain in supine position for 15 minutes and to hold the solution in the bladder for 2 hours.

Data Analysis

Demographics, disease-related data, and the number of treatments were analyzed using descriptive statistics. To test predictors of compliance with intravesical treatment, we performed univariable and multivariable binary logistic regression analyses. Compliance was defined as completion of at least 9 instillations because this represents completion of 1 year of therapy and, in addition, was the median number of treatments completed by a patient undergoing maintenance therapy for 3 years. Covariates consisted of age, gender, country of origin, distance from hospital, pathologic stage and grade, and prior history of bladder cancer. Tests were considered significant if *P* value was less than .05. All tests were 2-tailed. All analyses were performed using SPSS statistics 20 (IBM Corp, Armonk, NY).

RESULTS

Patients' Characteristics and Type of Intravesical Therapy

Demographic, clinical, and pathologic data are shown in Table 1. Seven hundred and twenty-nine patients started

Table 1. Patient characteristics

Age (y)	
Median	73
Interquartile range	65-79
Gender	
Male	612 (84%)
Female	117 (16%)
Country of origin	
Israel	184 (25%)
Other	545 (75%)
Distance from hospital	
<20 km	517 (71%)
20-40 km	117 (16%)
>40 km	95 (13%)
Pathologic stage and grade	
Ta low grade	201 (27%)
Ta high grade	217 (30%)
T1	255 (35%)
CIS	56 (8%)
Prior diagnosis of NMIBC	
Yes	317 (44%)
No	412 (56%)
Intravesical instillation	
Induction MMC only	173 (24%)
Induction BCG only	211 (29%)
Monthly maintenance	97 (13%)
MMC	
Monthly maintenance BCG	87 (12%)
SWOG maintenance BCG	161 (22%)

BCG, bacillus Calmette-Guèrin; CIS, carcinoma in situ; MMC, mitomycin C; NMIBC, nonmuscle invasive bladder cancer; SWOG, Southwest Oncology Group.

induction protocol, 459 (63%) with BCG and 270 (37%) with MMC. A total of 861 induction cycles were commenced. One hundred and thirteen patients (16%) started more than 1 induction protocol, 44 of whom were treated with both MMC and BCG. The majority of patients with high-grade urothelial carcinoma were assigned to receive instillations with BCG (68%, 90%, and 94% of patients with Ta high grade, T1, and carcinoma in situ, respectively), whereas 80% of patients with Ta low grade were treated with MMC. Of all patients with high-grade urothelial carcinoma, 44% started maintenance treatment with BCG following induction therapy.

Treatment Adherence

From 270 patients who received the MMC induction protocol, 235 (87%) completed all 6 instillations; 97 (36%) started monthly maintenance protocol and 138 patients (51%) were clinically followed up. Forty-six patients (47%) completed all 9 maintenance instillations (Fig. 1A). Of the patients treated with BCG, 395 of 459 (86%) completed the induction cycle; 19%, 35%, and 32% were subsequently assigned to 9 monthly instillations, 3-year SWOG protocol (21 instillations), or surveillance, respectively. Adherence to full schedule was attained in 55% of patients receiving monthly maintenance instillations and in 10% of those on the SWOG protocol (Fig. 1B). Nineteen patients were treated with reduced BCG dose (27 mg). Overall, completion of induction therapy was similar

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