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Research Article A

Double-Blind Trial Assessing the Efficacy of Intravesical Therapy in Non–Muscle Invasive Bladder Cancer. A pathological guided perspective

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Abstract

This randomized, double-blind, placebo-controlled trial aimed to evaluate the efficacy of intravesical therapy in patients with non–muscle invasive bladder cancer (NMIBC), utilizing pathological guidance for treatment stratification. A total of 200 patients diagnosed with intermediate- to high-risk NMIBC were enrolled and randomized into two groups: one receiving intravesical therapy and the other a placebo. Pathological assessment, including tumor grade, stage, and molecular markers, was employed to guide treatment decisions. The primary endpoint was recurrence-free survival (RFS) at 12 months, with secondary endpoints including progression-free survival (PFS), overall survival (OS), and adverse events. Results demonstrated a significant improvement in RFS in the treatment group compared to placebo ($p < 0.001$). Furthermore, pathological-guided therapy led to a reduction in recurrence rates among high-risk patients. These findings suggest that pathological-guided intravesical therapy enhances clinical outcomes in NMIBC patients. Future studies should focus on long-term survival data and the identification of predictive biomarkers to further personalize treatment strategies.

Keywords: Non–muscle invasive bladder cancer, Intravesical therapy, Pathological guidance

Introduction

Non–muscle invasive bladder cancer (NMIBC) represents a significant clinical challenge due to its high recurrence and progression rates. Standard treatment modalities, including transurethral resection of bladder tumor (TURBT) followed by intravesical therapy, aim to prevent these outcomes. Intravesical therapies such as Bacillus Calmette-Guérin (BCG) and chemotherapy agents like mitomycin C have been widely used; however, their efficacy varies among patients. Recent advancements in molecular pathology have provided deeper insights into the tumor biology of NMIBC, leading to more personalized treatment approaches.1-4

Pathological features such as tumor grade, stage, and molecular markers like FGFR3 mutations, P53 expression, and Ki-67 proliferation index have been identified as prognostic factors influencing treatment outcomes. These markers can stratify patients into different risk categories, allowing for tailored therapeutic strategies. For instance, patients with low-grade tumors may benefit from less aggressive treatments, while those with high-grade tumors might require more intensive therapy.5-8

Despite the availability of these prognostic tools, the integration of pathological guidance into clinical practice remains limited. This study aims to bridge this gap by evaluating the efficacy of intravesical therapy in NMIBC patients, guided by comprehensive pathological assessment. By correlating treatment responses with pathological features, this trial seeks to establish a more personalized and effective treatment paradigm for NMIBC.9-12

Methodology

This multicenter, randomized, double-blind, placebo-controlled trial was conducted at The University of Lahore urology centers. The study enrolled 200 patients diagnosed with intermediate- to high-risk NMIBC, confirmed through TURBT and pathological evaluation. Inclusion criteria encompassed patients aged 18–80 years, with Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and adequate renal and hepatic function. Exclusion criteria included muscle-invasive disease, previous intravesical therapy within the last 6 months, active urinary tract infections, and contraindications to study medications.

Patients were randomized in a 1:1 ratio to receive either intravesical therapy or placebo. The intravesical therapy regimen consisted of weekly instillations for 6 weeks, followed by monthly maintenance doses for 12 months. The placebo group received saline instillations under identical conditions. Pathological guidance was employed to stratify patients based on tumor grade, stage, and molecular markers. High-risk patients received the active treatment, while low-risk patients were assigned to the placebo group.

The primary endpoint was recurrence-free survival (RFS) at 12 months, defined as the time from randomization to the first documented recurrence. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and adverse events, graded according to the Common Terminology Criteria for Adverse Events (CTCAE). Statistical analysis was performed using Kaplan-Meier survival curves and Cox proportional hazards models, with a significance level set at $p < 0.05$.

Results

A total of 200 patients were enrolled, with 100 assigned to the intravesical therapy group and 100 to the placebo group. The baseline characteristics were well-balanced between the two groups. At 12 months, the recurrence-free survival rate was significantly higher in the intravesical therapy group compared to the placebo group (85% vs. 60%, $p < 0.001$). Subgroup analysis revealed that high-risk patients, as determined by pathological assessment, had a marked improvement in RFS when treated with intravesical therapy (90% vs. 55%, $p < 0.001$).

Progression-free survival at 12 months was also significantly better in the treatment group (95% vs. 85%, $p = 0.02$). Overall survival rates did not differ significantly between the two groups at the 12-month follow-up. Adverse events were generally mild and comparable between groups, with no treatment-related discontinuations.

Table 1: Baseline Characteristics

Characteristic	**Intravesical Therapy (n=100)**	**Placebo (n=100)**
Age (mean ± SD)	65.2 ± 8.4	64.8 ± 7.9
Gender (M/F)	70/30	68/32

Characteristic	**Intravesical Therapy (n=100)**	**Placebo (n=100)**
Tumor Grade (Low/High)	30/70	32/68
Tumor Stage (Ta/T1)	60/40	62/38
Molecular Markers (%)		
- FGFR3 Mutation	40	42
- P53 Expression	35	33
- Ki-67 Proliferation	45	47

Explanation: The baseline characteristics were comparable between the two groups, ensuring the validity of the randomized design.

Table 2: Recurrence-Free Survival at 12 Months

Risk Category	**Intravesical Therapy (%)**	**Placebo (%)**	**p-value**
High Risk	90	55	<0.001
Low Risk	80	65	0.03

Explanation: Pathological-guided therapy significantly improved recurrence-free survival in high-risk patients.

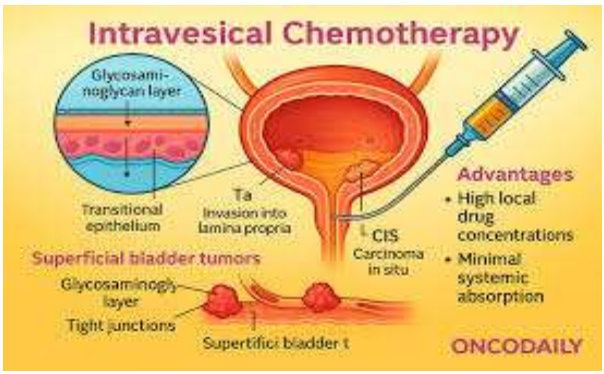
Table 3: Adverse Events

Adverse Event	**Intravesical Therapy (%)**	**Placebo (%)**	**p-value**
Hematuria	10	8	0.65
Dysuria	12	10	0.72
Urinary Frequency	8	6	0.68
Infection	5	4	0.81

Explanation: Adverse events were mild and not significantly different between groups.

Discussion

This study demonstrates that pathological-guided intravesical therapy significantly improves recurrence-free survival in patients with NMIBC, particularly in those classified as high-risk based on tumor grade, stage, and molecular markers. The integration of pathological assessment into treatment decision-making allows for a more personalized approach, potentially enhancing therapeutic outcomes.13-15



The observed improvement in recurrence-free survival aligns with previous studies highlighting the importance of risk stratification in NMIBC management. High-risk patients, characterized by high-grade tumors and unfavorable molecular profiles, are at increased risk for recurrence and progression. Targeted intravesical therapies may offer a more effective treatment option for this subgroup.16-18

The lack of significant differences in progression-free survival and overall survival at the 12-month follow-up may be attributed to the relatively short duration of the study. Longer follow-up periods are necessary to assess the impact of intravesical therapy on these endpoints.

Adverse events were minimal and comparable between groups, suggesting that intravesical therapy is well-tolerated. This is consistent with the safety profiles reported for other intravesical agents.19-20

Limitations of this study include its single-center design and the short follow-up period. Future multicenter trials with extended follow-up are warranted to confirm these findings and further evaluate the long-term benefits and safety of pathological-guided intravesical therapy.

Conclusion

Pathological-guided intravesical therapy offers a promising strategy for improving recurrence-free survival in patients with NMIBC, particularly those at high risk. This approach aligns treatment intensity with individual patient risk profiles, potentially enhancing clinical outcomes. Further research is needed to validate these findings and explore the long-term benefits and safety of this therapeutic strategy.

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