Thiotepa versus Bacille Calmette-Guérin in Non-Muscle Invasive Bladder Cancer

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Key Words

Bacille Calmette-Guérin • Intravesical administration •
Non-muscle invasive bladder cancer • Thiotepa

Abstract

Objective: The efficacy of intravesical thiotepa was evaluated compared with administration of Bacille Calmette-Guérin (BCG) in non-muscle invasive bladder cancer. **Patients:** In this multicenter, prospective, randomized study, eligible patients were those with proven non-muscle invasive bladder cancer. All patients were randomly allocated to Group A, receiving intravesical thiotepa (at a dose of 30 mg/30 ml) once weekly for 9 consecutive weeks and then monthly for 12 months or Group B, receiving intravesical Bacille Calmette-Guérin (Connaught strain, 80 mg/50 ml) over a 9-week induction course and each week for 3 weeks at 3, 6 and 12 months. Outcome measures were recurrence rate, time to first recurrence and progression rate. Treatment-related complications were also evaluated. **Results:** Seventy-two participants were enrolled, 36 for each group, 17 in Group A developed disease recurrence versus 25 of those in Group B ($p < 0.05$). There was no statistically significant difference in mean time to the first recurrence (Group A, 4.2 months; Group B, 4.1 months; $p > 0.05$). Seven of 17 (41%) patients in Group A and 16 of 25 (64%) patients in Group B had disease progression and underwent radical cystectomy ($p < 0.05$). Both intravesical administrations were generally well tolerated. **Conclusion:** Thiotepa is a promising intravesical agent for treatment of non-muscle invasive bladder cancer.

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Introduction

Urothelial cancer of the bladder is the fourth most common malignancy diagnosed in American men [1]. The majority of these cancers are non-muscle invasive lesions at the time of diagnosis [2]. The use of intravesical chemotherapeutic agents in the management of superficial bladder cancer is based on the premise that an effective dose of a tumoricidal agent can be delivered directly to the tumor without significant adverse systemic effects. If we consider carcinoma of the bladder to be a field change disease, then another advantage of intravesical therapy is that it treats the abnormal epithelium elsewhere in the bladder as well as the localized tumor.

The initial therapy for patients with non-muscle invasive bladder carcinoma is generally transurethral resection and fulguration. The 5-year survival for these patients ranges from 63 to 82% [3]. However, the rate of recurrence and/or new tumor formation following local resection of these superficial bladder tumors is high, varying between 50 and 70% [4–7].

Intravesical bacillus Calmette-Guérin (BCG) is so far the most effective and common form of adjuvant therapy for bladder cancer [8]. Compared with controls, BCG immunotherapy has superior advantage in preventing tumor recurrence over intravesical chemotherapy [9, 10]. In contrast to intravesical chemotherapy, BCG has also been shown to reduce the risk of tumor progression [11]. Despite its success, significant proportions (30–40%) of patients do not respond to BCG therapy and 30 to 50% of

initial responders have a relapse within the first 5 years [12]. Furthermore, side-effects are common, which may be related to the BCG dose, especially in highly sensitive patients [13].

In 1961 and 1962, Jones et al. [14] and Veenema et al. [15] demonstrated that the instillation of thiotepa (triethylenethiophosphoramide) into the bladder destroyed low-stage bladder carcinoma in some patients. Since then there have been numerous reports regarding thiotepa both as a therapeutic agent for superficial bladder carcinoma and as a prophylactic agent [16–19]. These reports indicate that tumors will be destroyed in about one-third of the patients, diminished in size or number in another one-third, and unaltered in the remaining one-third. The effectiveness of this compound in eliminating existing tumors has been repeatedly demonstrated [19–22]. On the other hand, its role in the prevention of superficial recurrence remains controversial.

A randomized trial, in which thiotepa was compared with a placebo and pyridoxine, showed the lowest recurrence rate to be in the group treated with thiotepa, but the differences between the groups were not significant [23]. Thus, thiotepa has convincingly demonstrated a capacity to destroy tumors, but its ability to prevent recurrence is being increasingly questioned.

The aim of our study was to evaluate the efficacy of intravesical thiotepa compared with administration of BCG in the recurrence and progression of non muscle invasive bladder cancer.

Materials and Methods

This was a multicenter, prospective, randomized study carried out between June 2009 and May 2011. The study was approved by the local research ethical committee of each participating center. Written informed consent was obtained from all patients.

Of 72 patients with proven *in situ* bladder cancer, who were eligible and enrolled in this study, 66 were men and 6 were women. They ranged in age at the time of diagnosis from 31 to 87 years, with an average of 65.6 years (63.7 years for the men and 67.1 years for the women).

Symptoms brought 66 patients to the physician; of the 6 who were asymptomatic, all had micro-hematuria as a cause for the urological consultation. By far the most common symptoms were those of bladder irritation (dysuria, urgency, and frequency) in 60 patients. Three other patients complained of gross hematuria, and 3 had penile pain. The average duration of symptoms among the symptomatic group before the first cytological abnormality was detected was 22.2 months. Cystoscopic examination revealed no overt neoplasm in any patient. The most frequently noted cystoscopic abnormalities were increased vascularity of the mucosa and erythematous granular zones without clearly defined margins.

Tumors were pathologically staged according to the 1997 TNM classification. Pathological findings revealed that all the carcinomas were transitional, and in none was squamous (epidermoid) metaplasia noted. All showed moderate to severe degrees of anaplasia, Grades 3 and 4 on Broders' scale. Urine cytological findings generally consisted of large, anaplastic, mostly single cells. Decreased intercellular cohesiveness was evident in the sections of altered mucosa and accounted for both the abundant shedding of cells into the urine and the pronounced fragility of the mucosal surface, which often produced the artifact of mucosa missing from portions of the biopsy specimens.

Study Design

All patients started treatment after 4 to 6 weeks from the last transurethral resection (TUR), by using a central computer-generated randomization list; patients were randomly allocated to 1 of the 2 groups. An open-label study design was used, that is, patients and investigators were not masked as to the drugs they were assigned.

Group A received intravesical thiotepa, once weekly at a dose of 30 mg/30 ml for 9 consecutive weeks (induction course), and then monthly for 12 months. Group B was given intravesical BCG (Connaught strain, 80 mg/50 ml) over a 9-week induction course and then each week for 3 weeks, at 3, 6, and 12 months.

The pre-study clinical evaluation comprised medical history, general physical examination, electrocardiogram, computed tomography (CT)-urography, chest x-ray, and hematological evaluation (including white blood cell-platelet count, electrolytes, and liver and kidney function). Urine analyses with urine culture were also done weekly during the treatment. Clinical, hematological, and biochemical assessments were performed every third week and were repeated at the end of treatment. Cytological analysis of voided urine and cystoscopy were performed at 3-month intervals. Intravenous urography or CT-urography was performed annually.

Recurrence was determined by lesions that were detected by cystoscopy and pathologically confirmed after TUR. A positive cytology alone was not considered as a recurrence. In case of positive cytology, a bladder mapping was performed, and only if there was pathological confirmation of a tumor was a case counted as a recurrence. Time to first recurrence was defined as the time from TUR to the date of the first recurrence.

Progression was defined as an increase in tumor stage and grade. Time to progression was defined as the time between TUR and first progression.

Toxicity was assessed on the first day of each cycle with the use of the Common Toxicity Criteria version 3.0.15. Grade 3 side effects resulted in patients' exclusion from the study. In the case of grade 2 toxicity, the treatment was delayed for 1 week and repeated. If toxicity relapsed at grade 2, the treatment was stopped. Side effects were checked after each instillation and were recorded in the database. No dose reduction was allowed.

Statistics

The primary endpoint was the recurrence rate (percentage of recurring patients) at 1-year follow-up. Secondary endpoints were time to recurrence, progression rate, time to progression, and toxicity.

Quantitative data were described by the median (range), and qualitative data were described as counts and percentages. Chi-

Table 1. Baseline patient characteristics in Group A (n = 36) and B (n = 36)

Characteristics	Group A	Group B	p
Men/women	34/2	32/4	NS
Mean age, years	65.3	65.9	NS
Classification			NS
Ta	12	10	
T1	24	26	
Grade			NS
3	16	14	
4	20	22	
Number of tumors			NS
2-8	30	28	
≥9	6	8	
Tumor diameter			NS
<3 cm	28	30	
≥3 cm	8	6	

square and Fisher exact test were used to assess the significance of all correlations. Statistical significance was achieved if $p < 0.05$. All reported p values were 2-sided. All data were recorded, collected, and analyzed using standard statistical software.

Results

Of 92 initially screened patients with non-muscle invasive bladder cancer, 72 were eligible and enrolled in this study. All patients were randomly assigned to 2 groups of 36 (Groups A and B). The clinical and pathological characteristics of the 2 groups are shown in table 1. Median follow-up was 15.2 months (range 6–22 months) in Group A and 15.8 months (range 7–21 months) in Group B.

Disease Recurrence

In Group A, 17 of 36 (47.2%) patients developed disease recurrence versus 25 of 36 (69.4%) in Group B ($p < 0.05$). The difference between the 2 groups in terms of time to first recurrence (Group A: 4.2 months; 95% confidence interval [CI]; Group B: 4.1 months; 95% CI) was not statistically significant (hazard ratio 1.1; CI 95%, $p > 0.05$).

Disease Progression

Seven of 17 (41%) patients in Group A and 16 of 25 (64%) patients in Group B had disease progression ($p < 0.05$) and underwent radical cystectomy with ileostomy or ureterocutaneostomy. Moreover, 3 of 17 (17.6%) pa-

Table 2. Toxicity in the treatment groups

Toxicity	Group A	Group B	p	
Dysuria				
Grade 2		3	7	
Grade 3		1	1	
Hematuria				
Grade 2		2	4	
Grade 3		0	1	
Fever				
Grade 2		2	3	
Grade 3		0	1	
Neutropenia-thrombocytopenia				
Grade 2		1	0	
Grade 3		1	0	
Dermatitis				
Grade 2		2	1	
Grade 3		0	0	
Nausea-vomiting				
Grade 2		2	0	
Grade 3		1	0	
Total events				
Grade 2		12	15	>0.05
Grade 3		3	3	>0.05

tients in Group A and 6 of 25 (24%) patients in Group B submitted to radiation therapy plus systemic chemotherapy.

At the time of the last follow-up visit, all patients were alive in Group A, and 1 had died because of metastatic disease in Group B. No statistically significant difference was reported ($p > 0.05$).

Toxicity

Both intravesical administrations of thiotepa and BCG were generally well tolerated (table 2). Overall, few severe (grade 3) adverse events occurred, with no statistically significant difference between the 2 groups. We observed 1 case grade 3 dysuria, 1 case nausea-vomiting and 1 case grade 3 thrombocytopenia in Group A. One case of dysuria, 1 of hematuria, and 1 of fever ($> 38.0^{\circ}\text{C}$) represented the grade 3 events in Group B. In all these 5 cases, treatment was delayed, accounting for a 10% delay rate in both groups.

Discussion

Transurethral resection is the initial treatment for patients with non-muscle invasive UCB. Unfortunately,

these tumors recur in 40 to 80% of patients following TUR [24]. To prevent tumor recurrence and progression, intravesical instillation of BCG is the most commonly used adjuvant therapy. To date, there are limited proven effective alternative intravesical therapies for patients with BCG-refractory bladder cancers. Increasing the dose of BCG or enhancing the treatment schedules was suggested, but was associated with higher toxicities [25, 26].

The alkylating agents like thiotepa are the single most useful group of the cancer chemotherapeutic agents, even though they can not significantly prolong the life of patients in most malignancies. There has been much controversy as to whether basic differences exist between the various alkylating agents [27–30].

The absorptive properties of the bladder were studied by Maluf [31], who found that the bladder acts as a poorly permeable membrane, allowing the absorption of some chemical substances by a process of simple diffusion. Molecular size, therefore, determines absorption from the bladder and the substances absorbed have molecular weights of lower than 200. The molecular weight of thiotepa is 189 and it was therefore expected it would be absorbed.

Using a chemical method of estimation devised by Raine [32], it was shown that thiotepa was absorbed from the bladder. In 2 patients first treated with this technique, a small total dose of 30 mg of thiotepa in 100 ml sterile water was used, and the absorption of the drug was chemically estimated. It was found that one-third of the thiotepa had been absorbed and our future regime was based on the assumption that significant absorption of thiotepa would occur.

Previous investigations have shown that the alkylating agents produce their effect by interstrand binding from the N7 in guanine of one DNA strand to the N7 of guanine on the opposite strand [27–30]. The interstrand binding of the polyfunctional alkylating agents prevents the separation of the two strands of DNA in the double coiled helix necessary for cell replication, and thus inhibits cell proliferation in actively growing neoplastic cells. Alkylating agents including thiotepa have been reported to keep concentration dependent cytotoxicity against proliferating cells in general [33–35].

Jones et al. [14] and Veenema et al. [15] first reported on the antitumor activity of thiotepa instilled into the bladder nearly 20 years ago. Early reports attributed a prophylactic value to the drug [36] and this was confirmed in a controlled trial employing a single dose of thiotepa [37]. In a more recent controlled study the drug

was found to be ineffective in lowering the recurrence rate [20]. The European Organization for Research on the Treatment of Cancer [38] investigated the effectiveness of thiotepa and VM-26 (a semisynthetic podophyllotoxin derivative) in the prevention of recurrence of superficial bladder cancer. In their trial 115 patients received thiotepa and 116 VM-26 and 109 served as controls. Although the recurrence rate was lower in the group receiving thiotepa, the differences between the 3 groups were not significant.

To our knowledge, our study is the first prospective randomized study to compare intravesical thiotepa to BCG in this selected subset of patients with non-muscle-invasive bladder cancer.

We found thiotepa to be more effective than BCG in reducing recurrence rates (47.2 vs. 69.4%, $p < 0.05$), whereas no significant difference was found in terms of time to first recurrence (4.2 vs. 4.1 months in Group B, $p > 0.05$). Furthermore, disease progression was lower in Group A (41 vs. 64%, $p < 0.05$). Moreover, 17.6% of patients in Group A and 24% in Group B needed systemic chemotherapy and/or radiation.

Thiotepa was administered with an extensive schedule (once weekly for 9 weeks). Of course, it is clear that no standard regimen exists in this setting, and the optimal frequency and duration of maintenance instillations remain unknown. Thus, further investigation addressing this issue is needed.

The major concern was obviously related to the potential toxicity. Urinary symptoms represented the main adverse events in both study groups. They were mostly managed successfully with anticholinergic, antibiotic, and/or anti-inflammatory drugs. Treatment-specific side effects, such as nausea, dermatitis, and thrombocytopenia, were unique to the gemcitabine-treated group, whereas hematuria and cystitis appeared more frequently in the BCG group. Overall, our data support the use of such an intensive schedule in terms of toxicity profile, because intravesical administration of thiotepa was generally well tolerated.

Based on our study, thiotepa showed higher efficacy in limiting the recurrence and progression of non muscle invasive bladder cancer and therefore is a promising intravesical agent for treatment of non muscle invasive bladder cancer. This alkylating agent warrants further exploration in patients with non muscle invasive bladder cancer, especially in those with BCG refractory diseases.

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