NONMUSCLE INVASIVE TRANSITIONAL CELL CARCINOMA OF URINARY BLADDER – ADJUVANT INTRAVESICAL THERAPIES AFTER TRANSURETHRAL TUMOR RESECTION

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ABSTRACT

Introduction. More than 70% of all bladder cancers are nonmuscle invasive involving only the mucosa and the submucosa. A large percentage of patients present local recurrence after endoscopic surgery, and many of them progress to muscle invasive disease necessitating radical cystectomy. The high recurrence and progression rate is the reason to use intravesical therapy to prevent recurrences. The aim of this study is to compare the efficacity and safety of intravesical immunotherapy with Bacillus Calmette Guerin (BCG) vs. chemotherapy (Pharmoribicin) after TUR-B for NMIBC.

Material and methods. Following TURB and pathological analysis, NMIBC was stratified into low, intermediate and high-risk groups depending on the probability of recurrence and progression to muscle-invasive disease. Patients were treated with adjuvant intravesical therapies, BCG or Pharmorubicin.

Results. Between 2008 and 2012, a total of 125 patients with NMIBC were diagnosed in the Urology Department Sibiu. Histopathological data show: pT1 G1 – 48 patients (38.4%), pT1 G2 – 69 patients (55.2%), pT1G3 and or Tis – 8 patients (6.4%). Adjuvant intravesical therapies with Pharmorubicin was administered to 83 patients (66.4%) and with BCG 42 patients (33.6%). Pharmorubicin, the recurrence rate was 22.8% in the first year and at 5 years there was a recurrence of 36.1%. For the group of patients treated with BCG recurrent rate was 14.2% in the first year and 33,3% at 5 years. For the whole group of patients tumor progression was 2.4% in the first year and 9.6% at 5 years. For the Pharmorubicin group, in the first year, the progression was 2.4% compared with 2.3% tumor progression in the BCG-treated group.

Conclusions. Intravesical instillation treatment after TURB reduce the recurrence rate and tumor progresion. In our series there are no major differences between efficacity of intravesical immunotherapy (BCG) vs. chemotherapy (Pharmoribicin). Disease-free survival and progression-free survival are comparable to the two studied lots.

Keywords: non muscular invasive bladder tumor, BCG, Pharmorubicin, intravesical therapy, tumor progression

INTRODUCTION

Bladder cancer is the eleventh most common cause of neoplasm, sixth most common cancer in men and the nineteenth most common cancer in women. The incidence in Europe is 9.6 cases per 100,000 inhabitants (1). More than 70% of all bladder cancers are nonmuscle invasive involving only the mucosa and the submucosa (2).

The most common symptom at presentation is haematuria and diagnosis is usually made following transurethral resection (TUR). The main objective of the diagnosis is to establish the clinical and histopathological stage for differentiate beetwen nonmuscle invasive bladder cancer (NMIBC) and muscle invasive bladder cancer (MIBC).

Patients with high-risk NMIBC (T1, with high grade/G3, and/ or CIS) represent a challenging group with an increased 5-year risk of recurrence (up to 80%) and progression (up to 50%) (3).

The treatment of NMIBC is transurethral resection of the bladder (TUR-B). A large percentage of patients present local recurrence after surgery, and many of them progress to muscle invasive disease necessitating radical cystectomy (4). The high recurrence and progression rate is the reason to use intravesical therapy to prevent recurrences. Intravesical Bacillus Calmette Guerin (BCG) or Pharmorubicin are standard adjuvant therapy for NMIBC following TUR-B (5,6). Despite this, around 30-45% of patients receiving adjuvant intravesical therapy develop recurrence of their cancer (7,8).

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The aim of this paper is to compare the efficacity and safety of intravesical immunotherapy (BCG) vs. chemotherapy (Pharmorubicin) after TUR-B for NMIBC.

MATERIAL AND METHODS

We have reviewed patients who were treated with bladder tumors between 2008 and 2012. Demographic data were recorded including age, gender, histological diagnosis, concomitant carcinoma in situ (Tis), recurrent versus de novo tumor, the number of bladder tumors, the size of the largest tumor, prostatic urethral involvement. Baseline blood count, renal and liver function tests, urine cytology were done before TURB.

Following TURB and pathological analysis, NMIBC was stratified into low, intermediate and high-risk groups depending on the probability of recurrence and progression to muscle-invasive disease. Progression-free survival was calculated from the date of initiation of therapy till recurrence.

Important dates were recorded: first and last intravesical instillations with BCG or Pharmorubicin, number of weekly instillations, adverse events, follow up protocol, recurrence and tumor progression.

Vesical instillations were classically given according to the empirical 6-weekly induction schedule and after that, one instilation monthly, 6 months It was used BCG or Pharmorubicin on patient demand. Because it is a retrospective study we did not use a control group of patients.

Follow-up protocol consisted in clinical examination, urinary echography and cystoscopy every 3 months, in the first year, twice a year in the second year, then annually up to 5 years.

Patients with pT1 disease were classified as risk groups according to G1-3 and monitored to highlight tumor recurrence. Patients with tumor recurrences underwent another TURB. Those with tumor progression have been systemic chemotherapy-induced, radiotherapy or radical surgical treatment.

RESULTS

Between 2008 and 2012, a total of 324 patients with bladder tumors were diagnosed in the Urology Department Sibiu. The onset of symptoms was haematuria in 92% of cases. The diagnosis was confirmed histopathologically as transitional cell carcinoma pT1 at 125 patients. These patients were included in the study group of comparing the efficacity and safety of intravesical immunotherapy vs. intravesical chemotherapy. The mean age of patients was 64.5 years (range 45-78) and sex ratio was 2.6:1 (85 males and 32 females). Cystoscopic examination reveals the unique tumor with a diameter of 1-4 cm at 20 patients (25%), multiple tumors in 81 patients (64.8%) and prostatic urethral involvement in 5 patients. (4%).

Histopathological data show: pT1 G1 – 48 patients (38.4%), pT1 G2 – 69 patients (55.2%), pT1G3 and/or Tis – 8 patients. (6.4%) (Table 1).

TABLE 1. *Risk groups*

Risk Group	Patients	%
Low – pT1G1	48	38,4
Intermediate – pT1G2	69	55,2
High – pT1G3, Tis	8	7,1
Total	125	100

All patients received adjuvant intravesical therapies consisting in Pharmorubicin in 83 patients (66.4%) and BCG in 42 cases (33.6%) (Table 2).

TABLE 2. *Bladder instillations – risk groups*

Risk Group	Pharmorubicin		BCG	
Low – pT1G1	28	33,7%	20	47,6%
Intermediate – pT1G2	50	60,2%	19	45,2%
High – pT1G3, Tis	5	6 %	3	7,1%
Total	83	100 %	42	100 %

BCG – Bacillus Calmette Guerin

Tumor recurrence was recorded during the 5 years follow-up. For Pharmorubicin, the recurrence rate was 22.8% in the first year and at 5 years there was a recurrence of 36.1%. For the group of patients treated with BCG recurrent rate was 14.2% in the first year and 33.3% at 5 years (Table 3).

TABLE 3. *Tumor recurrence = recurrence rate*

Recurrence	Total patients		Pharmorubicin		BCG	
1 year	25/125	20%	19/83	22,8%	6/42	14,2%
3 years	30/125	24%	21/83	25,3%	9/42	21,4%
5 years	44/125	35,2%	30/83	36,1%	14/42	33,3%

BCG – Bacillus Calmette Guerin

Disease-free survival (DFS) was calculated for the two studied groups. Thus, one-year DSF for the entire patient group was 80% and 64% at 5 years. Comparing the two series of patients treated we found a DSF of 77% for Pharmorubicin in the first year and 85.7% for BCG in the same period. At 5 years follow-up DSF was 63% respectively 66%. Our study showed a superior, but not significant, 5 year DFS (66.6% vs. 63.8%) for BCG arm compared with those of Pharmorubicin arm (Table 4).

TABLE 4. *Disease-free survival (DFS) up to 5 years*

DFS – NMIBC	Total patients		Pharmorubicin		BCG	
1year	100	80%	64	77%	36	85,7%
3 years	95	76%	62	74,6%	33	78,5%
5 years	81	64%	53	63,8%	28	66,6%

BCG – Bacillus Calmette Guerin

Our data showed tumor progression for the whole group of patients at 2.4% at one year and 9.6% at 5 years. For the Pharmorubicin group, the progression was 2.4% compared with 2,3% tumor progression in the BCG-treated group (Table 5).

TABLE 5. *Tumor progression*

Progression	Total patients		Pharmorubicin		BCG	
1year	3/125	2,4%	2/83	2,4%	1/42	2,3%
3 years	5/125	4%	4/83	4,8%	1/42	2,3%
5 years	12/125	9,6%	8/83	9,6%	4/42	9,5%

BCG – Bacillus Calmette Guerin

There is no significant difference in disease-free rates at 5 years (66% for BCG arm vs. 63% for Pharmorubicin) and no difference in progression rates.

Patients with tumor progression have required radical surgery, systemic chemotherapy or/and radiotherapy.

DISCUSSIONS

Intravesical BCG has been the standard of care for the prevention of NMIBC recurrence and progress in following resection. BCG is a live attenuated strain of Mycobacterium bovis, originally developed as a vaccine for tuberculosis. The mechanism of action is incompletely understood but it is postulated to work via a local immune response characterised by induced expression of cytokines in the urine and bladder wall (9). Before starting BCG in new patients, it is important to adequately debulk all visible tumour and re-resect T1 high grade tumours to reduce understaging.

The high recurrence and progression rate of pT1 bladder tumors is the reason to use intravesical therapy after TURB. BCG strain may have an impact on treatment outcome in NMIBC immunotherapy and Pharmorubicin as chemotherapy. Pharmorubicin as adjuvant intravesical therapy has also been shown to reduce the risk of recurrence in intermediate and high-risk NMIBC.

Studies have confirmed the that BCG after TURB is superior to TURB alone or TURB and intravesical chemotherapy for the prevention of recurrence of NMIBC in patients with Ta and T1 tumours (10,11). Although BCG is a very effective treatment, there is a consensus that not all patients with NMIBC should be treated with BCG due to the risk of toxicity (12,13). Despite this, around 30-45% of patients receiving adjuvant intravesical therapy develop recurrence of their cancer (14,15).

Trials of intravesical Pharmorubicin versus BCG can be difficult to interpret due to heterogeneous treatment groups and variable intervention schedules. Studies reported a significant difference in disease-free rates at 5 years but no difference in progression rates (24). Our study showed a superior, but nor significant, 5 year DFS (disease-free survival) and equal 5-year tumor progression (9.5% vs. 9.6%) for BCG arm compared with those of Pharmorubicin arm.

Our data showed no significant difference in recurrence rate (66.6% Pharmorubicin arm vs. 63.8% BCG arm) and progression-free survival among patients with intravesical adjuvant therapy with BCG compare with Pharmorubicin, after transurethral tumor T1 resection. DFS at 5 years was 64% for the study group, comparable to literature data. We found an equal 5-year tumor progression (9.5% vs. 9.6%) for BCG arm compared with those of Pharmorubicin arm.

CONCLUSIONS

The risk of recurrence and progression associated with conservative treatment of pT1G3 NMIBC indicates there is an absolute necessity to associate instillation therapy with TURB.

Intravesical instilling treatment after TURB reduce the recurrence rate and tumor progresion. In our series there are no major differences between efficacity of intravesical immunotherapy (BCG) vs. chemotherapy (Pharmorubicin). Disease-free survival and progression-free survival are comparable to the two studied lots.

ACKNOWLEDGEMENTS: *This study, being a retrospective one, did not require a written consent from the patients involved. The authors declare no conflict of interests and no sponsorship was provided in this study. All authors have read and approved this publication and had equal scientific contribution in publishing this material.*

REFERENCES

1. **Ferlay J., Shin H.R., Bray F., Forman D., Mathers C., Parkin D.M.** Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 10 International Agency for Research on Cancer. 2010. (Last accessed on 2017 Feb 16). Available from: http://globocan.iarc.fr/
2. **Babjuk M., Burger M., Zigeuner R., Shariat S.F., van Rhijn B.W., Compérat E. et al.** EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: Update 2013. *Eur Urol.* 2013; 64:639–53.
3. **Sylvester R.J., van der Meijden A.P., Oosterlinck W. et al.** Predicting recurrence and progression in individual patients with stage Ta, T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol.* 2006; 49(3):466–5. doi: 10.1016/j.eururo.2005.12.031.
4. **Nargund V.H., Tanabalan C.K., Kabir M.N.** Management of non-muscle-invasive (superficial) bladder cancer. *Semin Oncol.* 2012; 39:559–72.
5. **Böhle A., Bock P.R.** Intravesical bacillus Calmette-Guérin versus mitomycin C in superficial bladder cancer: Formal meta-analysis of comparative studies on tumor progression. *Urology.* 2004;63:682–6.
6. **Shelley M.D., Mason M.D., Kynaston H.** Intravesical therapy for superficial bladder cancer: A systematic review of randomised trials and meta-analyses. *Cancer Treat Rev.* 2010;36:195–205.
7. **Fuge O., Vasdev N., Allchorne P., Green J.S.** Immunotherapy for bladder cancer. *Res Rep Urol.* 2015;7:65–79.
8. **Shouki N. Bazarbashi, Haya J. Azouz, Amal H. Abu Sabaa, Ali H. Aljubran, Ahmad M. Alzahrani, Mohammed F. Alotaibi,** Recurrence and progression in nonmuscle invasive transitional cell carcinoma of urinary bladder treated with intravesical bacillus Calmette-Guerin: A single center experience and analysis of prognostic factors, *Urol Ann.* 2016 Jul-Sep; 8(3): 333–337. doi: 10.4103/0974-7796.184891
9. **Pan J., Liu M., Zhou X.** Can intravesical bacillus Calmette-Guérin reduce recurrence in patients with non-muscle invasive bladder cancer? An update and cumulative meta-analysis. *Front Med.* 2014; 8:241–9.
10. **Gandhi N.M., Morales A., Lamm D.L.** Bacillus Calmette-Guérin immunotherapy for genitourinary cancer. *BJU Int.* 2013; 112:288–97.
11. **Hudson M.A., Ratliff T.L., Gillen D.P., Haaff E.O., Dresner S.M., Catalona W.J.** Single course versus maintenance bacillus Calmette-Guerin therapy for superficial bladder tumors: A prospective, randomized trial. *J Urol.* 1987; 138:295–8.
12. **Palou J., Laguna P., Millán-Rodríguez F., Hall R.R., Salvador-Bayarri J., Vicente-Rodríguez J.** Control group and maintenance treatment with bacillus Calmette-Guerin for carcinoma *in situ* and/or high grade bladder tumors. *J Urol.* 2001; 165:1488–91.
13. **Böhle A., Jocham D., Bock P.R.** Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: A formal meta-analysis of comparative studies on recurrence and toxicity. *J Urol.* 2003; 169:90–5.
14. **Ali-El-Dein B., Sarhan O., Hinev A., Ibrahiem el-HI, Nabeeh A., Ghoneim M.A.** Superficial bladder tumours: Analysis of prognostic factors and construction of a predictive index. *BJU Int.* 2003; 92:393–9.
15. **Bazarbashi S., Soudy H., Abdelsalam M., Al-Jubran A., Akhtar S., Memon M. et al.** Co-administration of intravesical bacillus Calmette-Guérin and interferon a-2B as first line in treating superficial transitional cell carcinoma of the urinary bladder. *BJU Int.* 2011; 108:1115–8.