RESEARCH ARTICLE

Efficacy of Postoperative Bladder Irrigation with Water for Injection in Reducing Recurrence Rates of Non Muscle Invasive Bladder Cancer

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Abstract

The aim of the study was to investigate the results of bladder irrigation with Water for Injection (WFI) after transurethral resection of bladder tumours for comparison with those for adjuvant use of BCG. A total of 239 patients (158 with single tumours, group A, and 81 with multiple tumours, group B) received continuous intravesical postoperative irrigation with WFI. Some 128 patients received intravesical irrigation with WFI, followed by weekly instillations of BCG (group C). Recurrence-free rate (RFR) and recurrence-free intervals (RFI) were recorded. RFR for those patients who received only intravesical irrigation with WFI (groups A and B) was 75.8%, 66.2% and 63.2% at the 1st, 2nd and 3rd year of follow up, respectively. Corresponding rates for group C were 61.7%, 55.4% and 49%. Median RFI in group B were 18, 11, 15, 15 and 12 months for Ta, T1, grade 1, grade 2 and grade 3 tumours, respectively. In group C corresponding intervals were 20, 33, 8, 20 and 42 months. BCG improved RFR only in T1 (p=0.014) and grade 3 tumours (p=0.007). In conclusion, postoperative bladder irrigation with WFI could increase RFR during the first and second year of follow up.

Keywords: Bladder tumors - BCG - tumor recurrence - bladder irrigation

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Introduction

Transurethral resection (TUR) remains the gold standard for the treatment of non muscle invasive bladder tumors (NMIBC). Although state-of-the-art TUR by itself can eradicate Ta, T1 tumours completely, these tumours commonly recur and can progress to muscle invasive (MIBC) (Witjes, 2009). 85% of patients will relapse, mainly during the first postoperative year (Heney et al., 1982; Dalesio et al., 1983; Torti et al., 1987; Gkritsios et al., 2013). Many recurrences are probably new tumors derived from urothelial dysplastic areas, but a significant proportion can be derived from tumour cells released during resection and eventually implanted in the injured areas (McDonald et al., 1956; Weldon et al., 1975; Page et al., 1978; Soloway et al., 1980; Hyacinthe et al., 1995; Selman et al., 2011).

There are controversial results from studies evaluating the adjuvant role of a single, postoperative intravesical instillation of chemotherapy regimens such as epirubicin, mitomycin C and gemcitabin within 24 hours after transurethral resection (Tolley et al., 1988; Oosterlinck et al., 1993; Hall, 1997; Brocks et al., 2005). Guidelines of the European Association of Urology for the treatment of NMIBC recommend that all patients receive one immediate instillation of chemotherapy after TUR. In patients at low risk of recurrence and progression, no further treatment is recommended prior to a subsequent recurrence. In patients with high-grade tumors or carcinoma in situ (CIS), bacillus Calmette-Guerin (BCG) immunotherapy is recommended (Babjuk et al., 2013).

Other studies suggested the use of continuous bladder irrigation with saline or glycine, both considered to have an ablative effect (chemoresection) on residual tumour cells (Whelan et al., 2001; Onishi et al., 2011). After the first report of Price in 1905, water for injection has been widely used for the irrigation of peritoneal cavity in order to destroy released cancer cells after surgery for several types of cancers including colorectal, gastric and hepatocellurar cancer as well as for bladder irrigation after transurethral resection of bladder tumours (Price 1905; Moskovitz et al., 1987; Chen et al., 2001; Brundell et al., 2002; Huguet et al., 2004; Lin et al., 2006; Chang et al., 2013). Water for injection has been shown to destroy bladder cancer cells in vitro through osmotic lysis (cytolysis) while some studies suggest that it may be more effective than BCG (Bolkier et al., 1991; Nargund et al., 2012).

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In this retrospective study we investigated the efficacy of continuous bladder irrigation with water for injection immediately after TUR both in single and multiple bladder tumours of all stages and grades, while patients with multiple tumours were compared to those who had multiple tumours and received intravesical instillations of BCG.

Materials and Methods

During the last 16 years, 789 bladder cancer patients were treated in our department with 1476 transurethral resections. All patients underwent a standard transurethral resection while random biopsies were obtained from abnormal looking urothelium or when bladder CIS or high-grade tumour was suspected (e.g positive cytology, recurrent tumour with previous history of a high-grade lesion). 367 patients with primary or recurrent non muscle-invasive bladder cancer were retrospectively studied. Patients with primary or concomitant carcinoma in situ or pT2 disease were excluded from the study. During surgery bladder was irrigated with a solution of mannitol and sorbitol. All patients received continuous bladder irrigation with water for injection immediately after surgery for a mean time of 18 hours.

239 patients received only continuous intravesical irrigation with water for injection; 158 patients had a single tumor (group A) while 81 had multiple tumours (group B). Patients in group A were compared with 128 patients (group C) with multiple tumors treated with continuous bladder irrigation with water for injection followed by 6-8 weekly intravesical instillations of BCG, beginning two weeks after transurethral resection. Written informed consent regarding possible complications was obtained from each patient submitted to BCG instillations. Recurrence-free rate (RFR) and recurrence-free intervals were recorded for patients in all groups.

Follow-up cystoscopies were scheduled at least at 3 and 6 months, postoperatively and every 6 months thereafter. Every histological proven tumor was regarded as relapse. RFR was recorded at the 1st, 2nd and 3rd year of monitoring for all groups. The distribution of RFR was estimated using the Kaplan-Meier method the comparisons were performed with log-rank test. Subgroup analyses were done, for patients with and without concomitant BCG treatment and with low-grade (G1/2) and high-grade (G3) NMIBC. Values were considered statistically significant at $p<0.05$.

Results

Histological characteristics of patients in each group are shown in Table 1. RFR for the patients who received only intravesical irrigation with water for injection (groups A and B) was 75.8%, 66.2% and 63.2%, for the first, second and third year of follow up, respectively. The corresponding rates according to stage and grade are shown in Table 2.

RFR for the patients with solitary tumours (group A) who received only intravesical instillation with water for injection were 84.2%, 77.3% and 74.1%, for the first, second and third year, respectively. Corresponding rates according to stage and grade are shown in Table 3.

Table 1. Histolological Characteristics of Patients in Groups A, B and C

Characteristics		Group A	Group B	Group C
Stage	Ta	183	57	53
	T1`	56	24	75
Grade	Grade 1	69	17	10
	Grade 2	125	49	58
	Grade 3	45	15	60

Table 2. RFR for Patients Receiving only Water for Injection According to Stage and Grade

		RFR (%)		
		1 Year	2 Year	3Year
Stage	Ta	80.4	69	66.2
	T1	60.8	57.2	53.6
Grade	Grade 1	87	76.9	74
	Grade 2	75.2	65.6	62.4
	Grade 3	60	51	46.7

Table 3. RFR According to Stage and Grade for Patients with Single tumor Receiving Only Water for Injection

		RFR (%)		
		1 Year	2 Year	3Year
Stage	Ta	88	79	76
	T1	72	72	69
Grade	Grade 1	93	89	85
	Grade 2	87	78	75
	Grade 3	64	57	54

Table 4. Median Relapse free Intervals for Groups B and C According to Stage and Grade

		Months (95% CI)	
		Group B	Group C
Stage	Ta	18 (11.4-24.6)	20 (8.8-31.2)
	T1	11 (6.9-15.1)	33 (9.3-56.7)
Grade	Grade 1	15 (9.2-20.7)	8 (0-19.3)
	Grade 2	15 (1.7-28.3)	20 (7.5-32.5)
	Grade 3	12 (1.8-22.1)	42 (19.4-64.5)

For group B RFR was 59.3%, 44.5%, 42% for the first, second and third year while corresponding rates for group C were 61.7%, 55.4% and 49%. For the first and second year of follow up RFR for groups B and C, without grade 3 tumors, was 61%, 46% and 58%, 46%, respectively. The median relapse-free interval for groups B and C according to stage and grade are shown in Table 4.

Intravesical BCG instillations did not provide an extension of the relapse-free interval in Ta, grade 1 and grade 2 tumours (p=0.926, p=0.871, p=0.788). However there was prolonged relapse-free interval in T1 (p=0.014) and grade 3 tumours (p=0.07) treated with BCG (Figures 1-2).

Among the 128 patients with solitary G1/G2 tumors, one patient (0.8%) showed tumor progression to invasive stage T2 at a median interval of 14 months. Among the 81 patients with multiple Ta/T1, G1/G2/G3 tumors treated only with continuous injection of water for injection, four (4,9%) experienced disease progression to muscle invasive

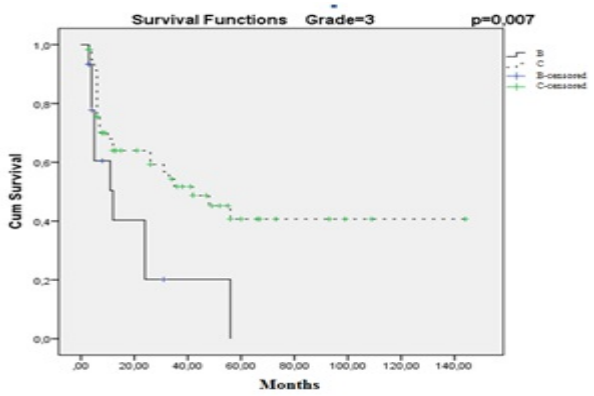

Figure 1. Patients with Grade 3 Tumours Treated with BCG had Better RFR (Kaplan Meier log rank test,p=0.007)

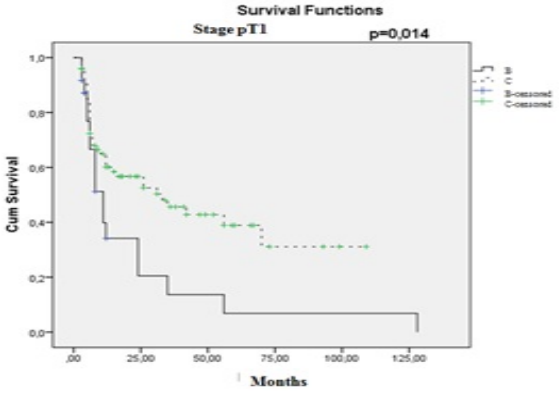

Figure 2. Patients with T1 Tumours Treated with BCG had Better RFR (Kaplan Meier log rank test, p=0.014)

disease (all with T1 tumor at initial diagnosis) after a median interval of 12 months. Among the 128 patients who received BCG, six (4,7%) progressed to muscle invasive disease (all with T1 tumor at initial diagnosis) at a median interval of 9 months.

Discussion

In this retrospective study regarding the prophylactic effect of continuous intravesical instillation with water for injection after transurethral resection of non muscle invasive bladder tumors, RFR during the first year of follow up was similar to that observed in the study of Bohle et al for intermediate-risk tumors (80% *vs* 78,8%) and even better for grade 3 (60% *vs* 42,4%) and single tumours (85% *vs* 81%), despite the highest proportion of grade 2 and grade 3 tumours in our sample (Bohle et al., 2009). In the same study authors concluded that the single administration of gemcitabine was not more effective than administration of saline.

Water for injection irrigation achieved very similar RFR to those observed in the study of Okamura et al. who included patients who received single intravesical chemotherapy (90% *vs* 92,4% in the first year, 83% *vs* 82,7% in the second year and 79% *vs* 78,8% in the third year) (Okamura et al., 2002). After a single postoperative intravesical instillation of mitomycin for low-risk tumors Solsona et al observed RFR of 98.2%, 84.2% and 80.7% in the first, second and third year respectively while our corresponding percentages were 90%, 83% and 79%, which indicates similar percentages in the second and third year of monitoring (Solsona et al., 1999). These observations imply that the continuous postoperatively intravesical instillation of water for injection in low risk tumors could have similar efficacy compared to a single intravesical cytostatic factor administration.

On the contrary distilled water and mitomycin had comparable in vitro effects in cultures of human bladder cancer cells (Fechner et al., 2006).

It also appears that the continuous irrigation with water for injection is more effective than active surveillance. Among 32 Ta, low grade tumors Soloway et al., recorded progression in muscle invasive disease in three patients (9%), while the corresponding percentage in our study was only 0.8% (Soloway et al., 2003).

Our results were better than those of Onishi et al who used normal saline postoperatively (Onishi et al., 2011). Although our intermediate-risk group of patients contains a much higher percentage of stage T1 tumors (23,4% *vs* 8,2%) it showed higher RFR in the first (80% *vs* 76,7%), second (70% *vs* 67.3%) and third year (67% *vs* 61,3%) of monitoring.

In another study RFR was recorded for 69 patients with primary, low-grade tumors (Shapiro Amos and Ofer Gofrit, 2012). 31 patients received continuous irrigation with water for injection for 24 hours while 38 patients did not received any adjuvant treatment. Relapse rates after 24 months were 25% for irrigation group and 58% for surveillance group. These results are consistent with those achieved with water foor injection (79% recurrence free survival at 3 years for single G1/G2 tumors). On the other hand Sakai et al did not observed difference in recurrence free rate in patients irrigated with distilled water for three hours after surgery (Sakai et al., 2006).

Our results showed that the addition of BCG instillations in multiple Ta G1/G2 tumors does not increase the RFR. Instead in T1 and G3 tumors BCG was superior to water for injection, achieving a significantly higher RFR (33 months vs 11 months and 42 months vs 12 months, respectively). In a metanalysis among 1476 low-intermediate risk patients, the recurrence rate of those who received a single intravesical chemotherapy was 36.7% while our corresponding rates were 24.2%, 33.8% and 36.8% for the first, second and third year of monitoring, respectively (Sylvester et al., 2004). In the same study among 111 patients with multiple tumors the recurrence rate was 81.5% for those treated only with transurethral resection and 65.2% for those who received immediate postoperative intravesical chemotherapy. In our study the relapse rate for patients who received only water for injection was 40.7%, 55.5%, 58% in the 1st, 2nd, 3rd year respectively while no superiority of BCG was observed. In the same meta-analysis it is also highlighted the ineffectiveness of single postoperative intravesical chemotherapy instillation in multiple tumors and the need for repeat doses which is also needed in BCG instillations.

In conclusion, continuous bladder irrigation with water for injection after transurethral resection seems to increase the RFR during the first and the second year of follow up for grade 1 and 2 tumors. Further prospective

clinical comparison with single intravesical chemotherapy is needed.

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