RESEARCH ARTICLE

Results of Intravesical Chemo-Hyperthermia in High-risk Non-muscle Invasive Bladder Cancer

Rahmi Gokhan Ekin[1]*, Ilker Akarken[2], Ozgur Cakmak[1], Huseyin Tarhan[1], Orcun Celik[1], Yusuf Ozlem Ilbey[1], Rauf Taner Divrik[3], Ferruh Zorlu[1]

Abstract

Purpose: To examine the effectiveness of mitomycin-C and chemo-hyperthermia in combination for patients with high-risk non-muscle-invasive bladder cancer. Materials and Methods: Between November 2011-September 2013, 43 patients with high-risk non-muscle-invasive bladder cancer undergoing adjuvant chemo-hyperthermia in two centers were evaluated retrospectively. Treatment consisted of 6 weekly sessions, followed by 6 sessions. Recurrence and progression rate, recurrence-free interval and side effects were examined. Analyzed factors included age, gender, smoking status, AB0 blood group, body mass index, T stage and grade, concominant CIS assets. The associations between predictors and recurrence were assessed using multivariate Cox proportional hazard analyses. Results: A total of 40 patients completed induction therapy. Thirteen (32.5%) were diagnosed with tumor recurrence. Median follow-up was 30 months (range 9-39). Median recurrence-free survival was 23 months (range 6-36). The Kaplan-Meier-estimated recurrence-free rates for the entire group at 12 and 24 months were 82% and 61%. There was no statistically significant difference between patient subgroups. Cox hazard analyses showed that an A blood type (OR=6.23, p=0.031) was an independent predictor of recurrence-free. Adverse effects were seen in 53% of patients and these were frequently grades 1 and 2. Conclusions: Intravesical therapy with combination of mitomycin-C and chemohyperthermia seems to be appropriate in high-risk patients with non-muscle-invasive bladder cancer who cannot tolerate or have contraindications for standard BCG therapy.

Keywords: Chemohyperthermia - recurrence - mitomycin C - thermochemotherapy - non muscle-invasive bladder cancer

Asian Pac J Cancer Prev, **16 (8)**, 3241-3245

Introduction

The lifetime risk of getting bladder cancer is 2.4% and bladder cancer is the fourth most common cancer in American men (Eser et al., 2009; Basiri et al., 2014). Approximately, 75% of new diagnosed cases of bladder cancer is non-muscle-invasive bladder cancer (NMIBC) and half of them show recurrence and/or progression after transurethral resection (TURBT) (Wang and Wang, 2012; Burger et al., 2013; Babjuk et al., 2013). Although the basis of treatment consists of complete TURBT, the main aim of treatment is to reduce the recurrence and prevent the progression. Therefore, after TURBT, in patient with high-risk NMIBC, intravesical therapy is needed and bacillus Calmette-Guerin (BCG) is the most effective therapy that requires special care in production, transport and installation (Wang and Wang, 2012; Babjuk et al., 2013).

New treatment approaches are being investigated to increase the effectiveness of adjuvant intravesical therapy. The use of hyperthermia in cancer treatment is not a new approach and based on this hypothesis, the outcome of adding hyperthermia in intravesical chemotherapy is being investigated (Colombo et al.,1995). The combination of chemotherapy and thermal energy's anticancer activity is higher than chemotherapy instillation and this combination prevents or delays tumor progression and recurrence (Lammers et al., 2011). Intravesical chemotherapy and hyperthermia combination is mainly treatment option in patients with BCG-resistance and they show promising results as the first treatment option (Lammers et al., 2011).

The aim of this retrospective two-center study is to evaluate the recurrence rate in the BCG-naive patients with high-risk of NMIBC who underwent adjuvant chemohyperthermia (C-HT) treatment.

Materials and Methods

Between November 2011-September 2013, according to the European Association of Urology (EAU) criteria, patients with high-risk of NMIBC underwent adjuvant C-HT in two centers were retrospectively evaluated (Babjuk et al., 2013). Exclusion criterias were patients who treated with intravesical treatment in last one year, above 1 cm diverticulum in bladder, histopathology nonurothelial

*[1]Department of Urology, Tepecik Teaching and Research Hospital, [2]Urology Clinic, Kemalpasa State Hospital, [3]Department of Urology, Sifa University, Faculty of Medicine, Izmir, Turkey *For correspondence: gokhanekin@gmail.com*

carcinoma, concomitant urothelial carcinoma in urethra or upper urinary tract, low bladder capacity (≤150 ml), high post-voided residual urine (≥100 ml), patients whose lifetime expectancy shorter than 24 months, urethral stricture and presence of false urethral. The study protocol was approved by the local ethics committee.

Intravesical chemotherapy instillation was administered for all patients within 24 hours after TURBT. After 2-6 weeks, all the patients except primary carcinoma in situ (CIS) was performed second-TURBT as described previously (Divrik et al., 2010). 3-6 weeks after second-TURBT, induction of C-HT and mitomycin-C (MMC) combination therapy were performed as one session weekly for 6 consecutive weeks. Three weekly instillation at months 3 and 6 were planned for all the patients.

C-HT was performed with bladder wall thermochemotherapy (BWT, Elmedical, Hod-Hasharon, Israel) unit and 18-French flexible UniThermia catheter (Elmedical, Hod-Hasharon, Israel). Each session consists of 40 mg MMC in 50 ml saline solution and bladder wall hyperthermia to 42.5-450C during 60 minutes. No prophylactic anticholinergic or analgesic drugs were used.

After one month induction treatment, patients underwent cystoscopic examination and urinary cytology. Suspicious areas were sampled. On follow-up period, in the first 2 years every 3 months, cystoscopic examination and urinary cytology were performed. Upper urinary tract was evaluated with CT-urography each year.

Patient age, gender, smoking status, AB0 blood group, body mass index, TURBT pathology (T stage and grade), concomitant CIS assets, second TURBT pathology result, side effects after each instillation were examined. Tumor localization in TURBT, size and multiplicity were evaluated. In multiple tumors, tumor size was assessed largest tumor diameter. The Common Terminology Criteria for Adverse Events were used to evaluate local or systemic toxicity (Institute, 2010). Signs and symptoms were recorded at follow-up visits. Recurrence-free interval and presence of recurrence and progression were evaluated. Time was measured from the first C-HT treatment until presence of the disease recurrence or the end of follow-up.

Kaplan-Meier curves were used to estimate the probability of local recurrence. The curves were compared with the log rank test for differences in time to failure between subgroups. A multivariate Cox proportional hazard model was used to assess the independent association between age, sex, smoking status, blood type, tumor characteristics. $p < 0.05$ was considered statistical significance. Statistical analyses were performed by SPSS version 19.0 for Windows (IBM, NY, USA).

Results

Forty-three patients were involved in the study. Patients demographic and bladder carcinoma related characteristics are shown in Table 1. Three patients did not complete the induction treatment due to adverse effects, therefore patients excluded in outcome analysis. Patients that did not complete induction treatment were directed to other intravesical treatments.

All 40 patients were taken into recurrence analysis. Thirteen patients (32.5%) were diagnosed with tumor recurrence. Median follow-up for all patients was 30 months (mean 26, range 9-39). Median recurrence-free survival was 23 months (mean 23, range 6-36 months) following first C-HT instillation. Median follow-up for tumor-free patients was 30 months (mean 26, range 9-36 months). At third month, there were no recurrence detected. In 6th month, recurrence and progression determined in one patient who did not accept early radical cystectomy which was recommended as a result of high grade and T1 tumor. The patient was taken into bladder-sparing treatment protocol after T2 tumor was detected. During follow-up period, among 13 patients, 6 patients were detected with low grade Ta, 1 with CIS+Ta, 1 with only CIS, 3 with high grade T1 and 2 with T2 recurrence.

Table 1. Patients Demographic and Bladder Cancer Related Features (n=43)

	n	(%)
Age (years)		
Mean ± SD (min-max)	68±9.7 (47-85)	
Median	68	
Gender		
Male	39	(90.7)
Female	4	(9.3)
Smoking status		
Current smokers	23	(53.5)
Ever smoker	12	(27.9)
Non-smokers	8	(18.6)
Blood type		
A	23	(53.5)
B	3	(7.0)
AB	1	(2.3)
0	16	(37.2)
BMI (kg/m^2)		
Mean±SD (min-max)	26.1±4,0 (17.7-32.8)	
Median	26.70	
Bladder tumor history		
First episode	27	(62.8)
Recurrent	16	(37.2)
Tumor site		
Anterior wall	2	(4.7)
Right wall	15	(34.9)
Left wall	14	(32.6)
Base	8	(18.6)
Dome	4	(9.3)
Tumor T stage		
Ta	12	(27.9)
T1	29	(67.4)
Pure CIS	2	(4.7)
Tumor grade		
Low grade	18	(41.9)
High grade	25	(58.1)
Concomitant CIS		
Yes	8	(18.6)
No	35	(81.4)
Tumour diameter		
<3 cm	17	(39.5)
≥3 cm	26	(60.5)
Multifocality		
Yes	30	(69.8)
No	13	(30.2)

BMI: body mass index, CIS: carcinoma in situ

Patients that had CIS+Ta, only CIS and high grade T1 were undergoing intravesical BCG treatment. Also, upper urinary tract urothelial cell carcinoma detected in patient with CIS+Ta recurrence. The Kaplan-Meier-estimated recurrence-free rate for entire group at 12 and 24 months was 82% and 61% (Figure 1). There was no statistically significant difference in terms of Kaplan-Meier recurrence-free interval when patients subgroups that Ta/T1, high/low grade, CIS were examined. There could not perform statistical analysis as the number of patients that had progression were low.

A multivariable Cox-regression subgroup analysis was performed to assess the effect of different parameters. Significant differences were noted in the likelihood of ABO blood type and patients with A blood type were more likely to be recurrence-free than patients with nonA blood type (OR=6.23, 95% CI 1.18-32.87, p=0.031). Age, sex, smoking status, recurrence history, tumor T stage, grade, concomitant CIS, multifocality were found to have a statistically insignificant effect on the recurrence-free interval, probably owing to small number of patients in each subgroup.

Table 2 lists the signs and symptoms of toxicity. Grading of side effects was based on common toxicity criteria (Institute,2010). The most frequent adverse events are noninfective cystitis (37.2%) and frequency (25.2%). Three patients (6.9%) dropped out from treatment due to grade 2 (n=2) and grade 3 (n=1) pelvic pain. Bladder spasms were associated with decreased bladder capacity and treatment session was delayed in 4 patients (9.3%). Temporary rash was seen in two patients after fourth session and elongated rash was seen in a patient after eight sessions. One patient was diagnosed with bladder perforation on posterior wall after ninth session upon the development of abdominal pain and bladder repair performed but patient died in intensive care unit. Adverse effects were seen in 53% (n=23) of patients and these were frequently grade 1 and 2. Except for one patient stated, adverse effects were subsided with conservative treatments.

Table 2. Patients Chemohypertermia Adverse Event Rate (n=43)

Adverse event	Any Grade (%)	Specific grade (%)				
		1	2	3	4	5
Bladder/pelvic pain	23.2	9.3	6.9	6.9	x	x
Bladder spasm	20.9	2.3	18.6	-	x	x
Frequency	25.2	16.2	9.3	X	x	x
Noninfective cystitis	37.2	27.9	9.3	-	-	-
Hematuria	9.2	6.9	2.3	-	-	-
Urinary incontinence	2.3	2.3	-	-	x	x
Allergic reaction	6.9	4.6	-	2.3	-	-
Bladder perforation	2.3	-	-	-	-	2.3

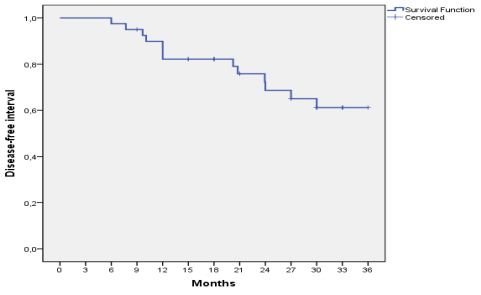

Figure 1. Kaplan-Meier Curve of Recurrence-free Survival

Discussion

Due to recurrence and progression, follow-up tests, repetitive-TURBT and other additional treatments are performed patients with NMIBC (Wang and Wang,2012). Bladder carcinoma is one of the high cost cancers and National Health Service spent 55.39 million UK pounds for bladder carcinoma treatment in 2002 (Sangar et al., 2005). Majority of expenditures constitute follow-up of patients with NMIBC (Sangar et al., 2005; Eser et al., 2009; Basiri et al., 2014). Recurrence rate of Ta/T1 bladder carcinoma in five years after TURBT is 31-78% and progression occurs among 5-20% of them (Divrik et al., 2010; Okamura et al., 2012; Wang and Wang, 2012; Richards et al., 2014; Grivas et al., 2014). BCG is recommended as a standard treatment for high-risk patients to reduce recurrence and progression in NMIBC (Okamura et al., 2010; Okamura et al., 2012; Babjuk et al., 2013; Grivas et al., 2014). In addition to decreases on life quality and additional complication risks, NMIBC recurrence and progression also brings the financial burden. Because of this, new treatment ways and optimization of current treatments are needed.

Hypethermia shows direct cytotoxic effect through inhibiting DNA, RNA and protein synthesis in cell's S-phase (Hildebrandt et al., 2002). As C-HT not only has cytotoxic effect but also rises the effectivity of mitomycin C, it was first used by Colombo et al. on 44 patients with NMIBC and 70% complete response reported (Colombo et al.,1995). During mean 35.3 months follow-up period of 24 patients that were given MMC and C-HT combination due to high grade tumor, recurrence-free determined in 62.5% of them (Lammers et al., 2011). In other similar study, Van der Heijden et al. applied C-HT treatment on 90 patients with intermediate and high risk and at the end of first and second year, recurrence determined 14.3% and 24.6% of patients (Lammers et al., 2011). Nevertheless detailed tumor characteristics of patients were not given. Almost 55% of patients were high-risk and there weren't high-risk patients as much as our study. Moskovitz et al. found recurrence-free rate 91% in 289 days of follow-up period on 47 intermediate and high risk patients after giving C-HT treatment (Moskovitz et al., 2012). In another study by same group's single centered 10-years experiences, estimated recurrence rate at 2 years was 32.8% (Moskovitz et al., 2012). In randomized controlled study that compared C-HT and MMC, estimated recurrence rates at 2 years were 19% and 62% (Lammers et al., 2011). Same study's 10 years later Kaplan-Meier estimated recurrence rates were 47% and 85% for C-HT and MMC alone (Colombo et al., 2011). In the systematic review published by Lammers et al. C-HT treatment alone caused 59% less recurrence rate in comparison with MMC alone (Lammers et al., 2011). There are publications that reports C-HT success low. In 2002, Volpe et al. published C-HT results of 30 patients

that took previously intravesical treatment history and recurrence-free survival rates of 16 patients that were given prophylactic treatment (no tumor in bladder) were 87% and 58% at first and second year (Volpe et al., 2012). In our study, our results about 43 C-HT treated patients were similar to the results of Volpe et al. recurrence identified in 16.3% (7/43) and estimated recurrence rate was 51% at 24 months. Cheng et al. reported 44.4% recurrence rate with intravesical BCG in T1G3 NMIBC, 10-years estimated recurrence-free survival was 48% (Cheng et al., 2004; Okamura et al., 2010; Okamura et al., 2012). Nevertheless, there is no study that directly compares C-HT and BCG, results of publications that report C-HT recurrence rates are resembling or better than BCG. But in our patient group, similar results were not observed. In our study, although follow-up period was shorter, there determined worse recurrence-free survival than study of Cheng et al., which was observed through BCG treatment. Divrik et al. found recurrence-free survival rates of MMC patients that were/weren't underwent second TURBT as 82% and 57% in first year, 65% and 37% in third year (Divrik et al., 2010). As there is no effective intravesical treatment like second TURBT in recurrence-free survival, avoidance of microscopic tumors is still the most important treatment method in NMIBC.

There is not much systematic information about adverse effects of C-HT in literature (Lammers et al., 2011). In some studies, as prophylactic anticholinergic and analgesic were used, the real adverse effect rate is not reported. For evaluation of C-HT adverse effects, Common Toxicity Criteria for Adverse Effects was used in new publications. According to Lammers et al.'s systematic review, the most frequent adverse effects during sessions are bladder spasms (21.6%) and bladder pain (17.5%) (Lammers et al., 2011). Storage lower urinary tract symptoms (25.6%) and hematuria (6%) are frequent in the first days after treatment (Lammers et al., 2011). Most of the adverse effects are reported as mild (grade 1) (Lammers et al., 2011). Adverse effect rates are in harmony with literature in our study too and can be cured with conservative treatment. Less seen adverse effects which are reported are non-specific rash (7.5%) and urethral strictures (3.5%) (Lammers et al., 2011). We have not determined urethral strictures in any of our patients. As there is no publication that used BWT (Elmedical, Hod-Hasharon, Israel) device in literature, difference of our C-HT device or small patient number may be a reason for this. Posterior wall thermal reaction (PWTR) is and expected side effect and it was the most prominent phenomenon found by cystoscopy. PWTR is not related with symptoms and it is little, superficial color change that occurs due to heating device's contact with bladder mucosa during session and there haven't reported any serious burnt (Lammers et al., 2011). We reported bladder perforation and death after C-HT application. As PWTR rate is 40%, these patients should be followed carefully. PWTR may not be an innocent lesion. Briefly, we found C-HT related adverse effect 53%. No matter this rate is high when compared to literature, these are frequently grade 1-2 adverse effects.

Limitations of our study are; there is no control group, small number of patients, short follow-up period, small number of patients with progression and inability to evaluate this progression. Strong side of this study is all patients took C-HT with adjuvant purpose. C-HT studies are frequently carried out on BCG-failed patient group. As our recurrence-free survival results are lower than C-HT and BCG datas in literature, we recommend BCG for primer intravesical treatment on patients that can be tolerated. Prospective studies that compare whether BCG or C-HT is more effective for primer intravesical treatment need to be completed.

In conclusion, high-risk non-muscle invasive bladder cancer as primary intravesical therapy with combination of mitomycin-C and chemohyperthermia seems to be appropriate in patients who cannot tolerate or have contraindication standard BCG therapy. Even though side effects of chemo hyperthermia are common, they generally can be tolerated. .

References

Babjuk M, Burger M, Zigeuner R, et al (2013). EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. *Eur Urol*, **64**, 639-53.

Basiri A, Shakhssalim N, Jalaly NY, et al (2014). Difference in the incidences of the most prevalent urologic cancers from 2003 to 2009 in Iran. *Asian Pac J Cancer Prev*, **15**, 1459-63.

Burger M, Catto JWF, Dalbagni G, et al (2013). Epidemiology and risk factors of urothelial bladder cancer. *Eur Urol*, **63**, 234-41.

Cheng CW, Chan SFP, Chan LW, et al (2004). 15-year experience on intravesical therapy of T1G3 urinary bladder cancer: a conservative approach. *Jpn J Clin Oncol*, **34**, 202-5.

Colombo R, Lev A, Da Pozzo LF, et al (1995). A new approach using local combined microwave hyperthermia and chemotherapy in superficial transitional bladder carcinoma treatment. *J Urol*, **153**, 959-63.

Colombo R, Salonia A, Leib Z, et al (2011). Long-term outcomes of a randomized controlled trial comparing thermochemotherapy with mitomycin-C alone as adjuvant treatment for non-muscle-invasive bladder cancer (NMIBC). *BJU Int*, **107**, 912-8.

Divrik RT, Sahin AF, Yildirim U, et al (2010). Impact of routine second transurethral resection on the long-term outcome of patients with newly diagnosed pT1 urothelial carcinoma with respect to recurrence, progression rate, and disease-specific survival: a prospective randomised clinical trial. *Eur Urol*, **58**, 185-90.

Eser S, Zorlu F, Divtik RT, et al (2009). Incidence and epidemiological features of cancers of the genitourinary tract in Izmir between 1993-2002. *Asian Pacific J Cancer Prev*, **10**, 491-6.

Grivas N, Hastazeris K, Kafarakis V, et al (2014). Efficacy of postoperative bladder irrigation with water for injection in reducing recurrence rates of non muscle invasive bladder cancer. *Asian Pac J Cancer Prev*, **15**, 2263-6.

Hildebrandt B, Wust P, Ahlers O, et al (2002). The cellular and molecular basis of hyperthermia. *Crit Rev Oncol Hematol*, **43**, 33-56.

Institute NC, (2010). Common terminology criteria for adverse events (CTCAE) Version 4.0. , 2009.

Lammers RJM, Witjes JA, Inman B a, et al (2011). The role of a combined regimen with intravesical chemotherapy and hyperthermia in the management of non-muscle-invasive bladder cancer: a systematic review. *Eur Urol*, **60**, 81-93.

Moskovitz B, Halachmi S, Moskovitz M, et al (2012). 10-year single-center experience of combined intravesical chemohyperthermia for nonmuscle invasive bladder cancer. *Future Oncol*, **8**, 1041-9.

Okamura T, Akita H, Ando R, et al (2010). Intravesical bacillus Calmette-Guérin (BCG) instillation for primary and recurring T1G3 bladder cancers. *Asian Pac J Cancer Prev*, **11**, 1107-10.

Okamura T, Ando R, Akita H, et al (2012). Are there time-period-related differences in the prophylactic effects of bacille calmette-guérin intravesical instillation therapy in Japan? *Asian Pacific J Cancer Prev*, **13**, 4357-61.

Richards KA, Smith ND, and Steinberg GD, (2014). The importance of transurethral resection of bladder tumor in the management of nonmuscle invasive bladder cancer: a systematic review of novel technologies. *J Urol*.

Sangar VK, Ragavan N, Matanhelia SS, et al (2005). The economic consequences of prostate and bladder cancer in the UK. *BJU Int*, **95**, 59-63.

Volpe A, Racioppi M, Bongiovanni L, et al (2012). Thermochemotherapy for non-muscle-invasive bladder cancer: is there a chance to avoid early cystectomy? *Urol Int*, **89**, 311-8.

Wang H-F, Wang J (2012). Research progress in potential urinary markers for the early detection, diagnosis and follow-up of human bladder cancer. *Asian Pac J Cancer Prev*, **13**, 1723-6.