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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Evaluation of the effects of intra-arterial chemotherapy combined with intravesical chemotherapy against intravesical chemotherapy alone after transurethral resection of bladder tumor in T1-staged Grade 3 bladder cancer

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Abstract

Objective Comparing intra-arterial chemotherapy combined with intravesical chemotherapy against intravesical chemotherapy alone in the treatment of T1-staged Grade 3 (T1G3) bladder cancer after transurethral resection of bladder tumor (TURBT).

Materials and methods From January 2007 to December 2012, 203 patients diagnosed with NMIBC were randomly assigned into either intra-arterial chemotherapy combined with intravesical chemotherapy group (Group A, $n=68$) or intravesical chemotherapy alone group (Group B, $n=135$) after TURBT. Four cycles of intra-arterial chemotherapy were administered after initial TURBT with 1-month interval between each. Intravesical chemotherapy was administered in both groups including an immediate 50 mg epirubicin instillation after TURBT and weekly maintenance for 8 weeks, and then followed by monthly maintenance for 1 year. The primary endpoint was recurrence-free survival.

Results Out of 203 patients, 53 were in Group A and 98 in Group B, and they were evaluated for recurrence and progression rate where recurrence rate was 35.8% (19/53) in group A and 41.8% (41/98) in group B with a significant difference ($P<0.05$) and progression rate was 20.7% (11/53) in group A and 23.5% (23/98) in group B with a significant difference ($P<0.05$). Univariate and multivariate logistic regression analysis suggested that intra-arterial chemotherapy could be an independent risk factors related to both overall survival and time to first recurrence.

Conclusions Intra-arterial chemotherapy combined with intravesical chemotherapy could reduce the risk of recurrence and progression compared to intravesical chemotherapy alone in T1G3 bladder cancer.

Keywords Bladder cancer · T1G3 · Intra-arterial chemotherapy · Intravesical chemotherapy · Transurethral resection of bladder tumor

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Introduction

Bladder cancer is the fourth most common cancer incidence in men and the eighth leading cause of cancer death in men, it occurs four times more frequently in men than in women and the average age at diagnosis is around 70 years in both men and women (Roupret et al. 2018). Bladder cancer is subdivided into different categories according to the WHO classification system according to the anatomical and histological characteristic of the primary tumor and whether there are any local or distant metastasis. Non-muscle invasive bladder cancer (NIMBC) comprises a heterogeneous group of tumors with various biologic potential confined to the bladder urothelium or to the lamina propria and accounts for 75% of all cases of bladder cancer. 25% of all NIMBC are T1-staged Grade 3 (T1G3) bladder cancer and they have the worst prognosis amongst the non-muscle invasive bladder cancer, with a 5 year-recurrence and progression of 41.8% and 20.7%, respectively (Martin-Doyle et al. 2015; Sylvester et al. 2010).

Due to its prognosis, the treatment protocol for T1G3 bladder cancer remains highly controversial: radical cystectomy (RC) upon diagnosis is an option but is undesirable to the patient in most cases due to the urinary deviation and loss of normal urinary function associated with RC. On the other hand, transurethral resection of bladder tumor (TURBT) followed by intravesical instillations is more conservative, the patient preserves his bladder and urinary function, but has to undergo costly adjuvant therapy with vesical instillations and lifelong surveillance due to possible risk of recurrence or progression. In the EORTC 30911 trial by Sylvester et al., TURBT in Bca followed by intravesical chemotherapy (IVC) with epirubicin had a recurrence rate of 52.7% and progression rate of 24%, whereas TURBT followed by BCG immunotherapy resulted in a recurrence rate of 36.7% and progression rate of 6.8% and distant metastasis rate of 5.7% (Sylvester et al. 2010), which implies that patients undergoing IVC alone after TURBT are exposed to a high risk of recurrence and progression. Hence a novel method using intra-arterial chemotherapy (IAC) in combination with IVC could reduce disease recurrence and progression. Furthermore, in China, BCG was only approved by the Chinese Food and Drug Administration (CFDA) in late 2015, and has not yet gained widespread usage due to lack of supply and high cost of intravesical BCG therapy in China.

Intra-arterial chemotherapy was first introduced by Japanese investigator Kubota et al. (1986); the idea behind IAC is localized injection of chemotherapeutic agents into the major blood vessels leading to the tumor to increase concentration at tumor site, thus increasing efficacy and reducing systemic toxicity (Hoshi et al. 1997). It has already been shown useful in reducing disease recurrence and progression in muscle-invasive bladder cancer when used perioperatively (Liang et al. 2015), and also in high-risk T1 bladder cancer studies (Sun et al. 2017; Zhang et al. 2016). In this randomized controlled single-institution trial, we aim to study the effect of IAC when combined with IVC when compared with IVC alone in T1G3 BCa after TURBT.

Materials and methods

Patient selection

This study was approved by the Ethics Committee of our hospital the first affiliated hospital of Sun Yat-Sen university, and conformed to ethical guidelines of the 1975 Declaration of Helsinki. All patients were properly informed of all procedures, risk and possible outcomes of each types of treatment, and a signed consent form was obtained from each patient signifying agreement to participate in this study.

Between January 2007 to December 2012, 203 patients with suspected or known as solitary NMIBC were recruited into this study. Patient inclusion criteria were: first time visit patient without any prior treatment, complete tumor resection by TURBT, pathologically confirmed high-grade T1 bladder transitional cell carcinoma (WHO 2004/1973) from their TURBT, no evidence of distant metastasis, age at least 18 years, and provision of written informed consent. Exclusion criteria were as follows: patient aged 85 years old or older, Ta or low-grade T1 tumor, carcinoma in situ, stage T2 or higher neoplasm (muscle invasive), recurrent or metastatic tumor, Eastern Cooperative Oncology Group (ECOG) performance status score > 2, previous treatment with any kind of instillation therapy (including chemotherapy of BCG), and any other concomitant malignancy.

Treatment protocol

Patients were recruited into the study after their first TURBT and a T1G3 bladder cancer was confirmed by post-operative histopathological report. Before further treatment, a signed consent form was obtained from each patient, the consent form indicated that they would be randomly allocated to either treatment with both IVC and intra-arterial chemotherapy (IAC + IVC group) or with intravesical chemotherapy (IVC alone: control group), the consent form informed the patient of possible difference in risk of recurrence and progression, and details on possible additional adverse effects associated with intra-arterial chemotherapy. Once they signed the consent form, they were immediately allocated into 2 groups; allocation was carried out using a computer-generated randomized list. Treatment group (Group A)

received IAC concomitantly with their IVC, and group B (control) only underwent IVC after TURBT.

All patients (both group A and group B) in this study underwent a first TURBT and a second TURBT (re-TURB) around 4 weeks after the first TURBT where final post-op combined histology result confirmed T1G3 bladder cancer. Biopsy specimens were collected from susceptible areas; muscle tissues were present in all samples. After the first initial TURBT, all patients underwent immediate prophylactic intravesical chemotherapy with anthracycline drug: pirarubicin within the first 24 h, followed by an induction intravesical chemotherapy with weekly chemotherapy with for 8 weeks and maintenance intravesical chemotherapy monthly for 10 months, all according to Chinese treatment guidelines.

Unlike group B, patients in group A subsequently started intra-arterial chemotherapy concomitantly to their IVC 4 weeks after their TURBT, the patients were referred to the interventional medicine department of our medical center where an infusion port with an angiographic catheter was placed super selectively into the arteries leading into the bladder. Angiographic catheter was inserted percutaneously using Seldinger's technique where a guide wire was inserted and guided under fluoroscopy into the vesicle arteries and then a 5F angiographic catheter was passed over the guide wire to reach the targeted artery that leads to the bladder. Once the catheter was placed successfully, an infusion port was connected to the distal end of the catheter and buried underneath the skin next of the thigh.

After successful insertion, cisplatin (60 mg/m^2) and pirarubicin (50 mg/m^2) were dissolved into 50 ml of saline solution, then administered over 10 min each time for four times with 1-month interval between each injection. During injection of chemotherapy drug, pressure was applied onto the femoral artery to prevent leakage of drugs into the lower limbs, all patients in this group complied with all 4 cycles of intra-arterial chemotherapy.

Before each IAC, patient underwent 2 days of preconditioning where each patient had to have a minimum of 2500 ml of daily urine output to reduce renal toxicity. Before and after each IAC, blood tests were drawn to monitor liver and kidney function, a full blood count and a urine routine test was also carried out. During their IAC treatment patients were routinely given 5-HT3 receptor antagonist to reduce gastrointestinal distress, granulocyte colony-stimulating factor (G-CSF) to increase white blood cell (WBC) count when WBC $< 3.0 \times 10^9$.

Patient assessment

Each patient was followed up individually by our department's research assistants, they were phoned regularly to keep track of their health status and to remind them of their treatment schedule to increase compliance. Cystoscopy, urine cytology and blood test were carried out every 3 months during the first 2 years. Afterwards cystoscopy was performed every year till the end of follow-up. A biopsy was done if there were susceptible lesions under cystoscopy. Observed factors in this study were histologically shown recurrence of bladder cancer (CIS, Ta or T1), progression of bladder cancer (T2 or higher), and tumor-specific survival. Adverse effect resulting from IAC was also recorded and graded according to Common Terminology Criteria for Adverse Effect (CTCAE) v4.0 grading system published by the United States Department of Health and Human Services, where each grade represents the severity of the adverse effect (AE): Grade 1 meant mild AE lasting less than 24 h without requiring medical intervention, Grade 2 implied moderate AE requiring non-invasive treatment, Grade 3 signified severe AE requiring hospitalization, Grade 4 was life-threatening AE and Grade 5 meant death caused by AE.

Statistical analysis

All data were analyzed using the statistical analysis software SPSS22.0, where p values below 0.05 were considered statistically relevant, and all tests were two-sided. Outcomes observed in this study were overall survival rate, tumor-specific death rate, recurrence rate, progression rate and time to first recurrence. Survival and recurrence curves were calculated using the Kaplan–Meier method. Patient characteristics between both groups were compared using independent sample Student's t test for continuous parameters and χ^2 test for categorical parameters.

Results

Patient characteristics

A total of 203 patients were preoperatively selected for this study, according to our criteria 52 patients were excluded. The reasons are the following: lack of malignancy ($n = 13$), multiple cancers ($n = 3$), Ta or low-grade T1 cancer ($n = 6$), CIS or muscle invasive cancer ($n = 8$), withdrawal of informed consent ($n = 3$), loss to follow-up ($n = 12$), near perforation ($n = 4$), or other reasons ($n = 3$) (Fig. 1).

At the end there was 53 patients in group A and 98 patients in group B. Patient characteristics of the two groups are listed in Table 1. There is no statistical significance in baseline characteristics between the two groups.

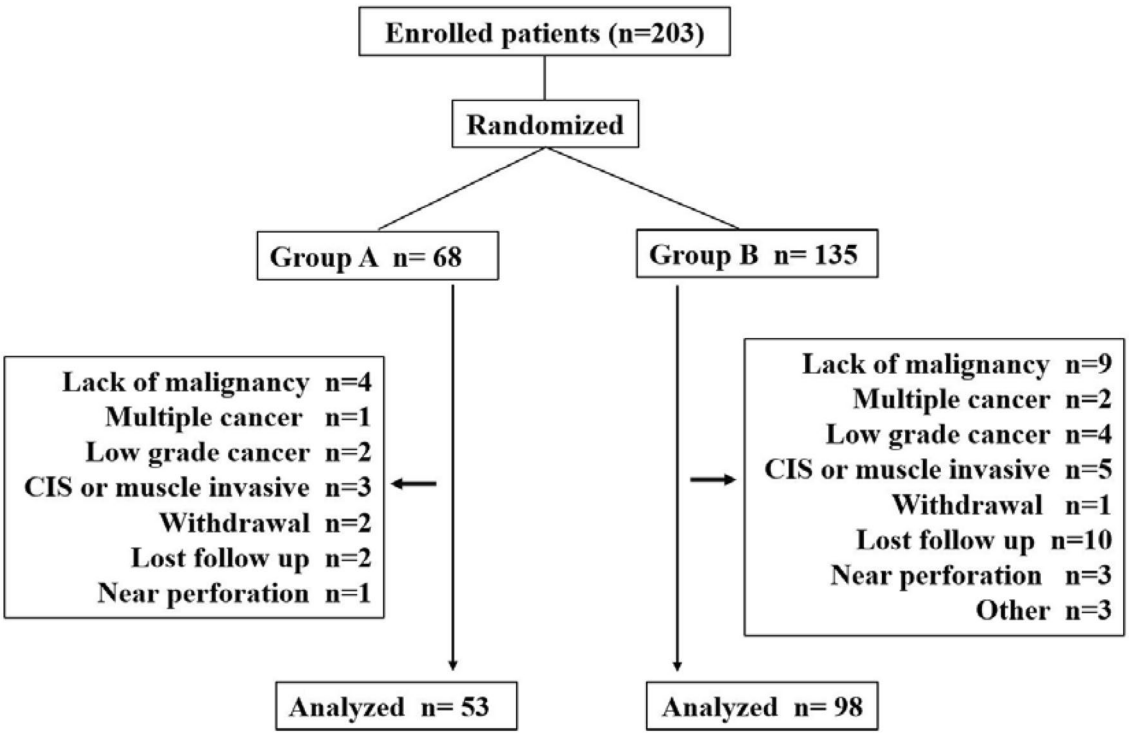

Fig. 1 CONSORT flow diagram of this study. Group A: intra-arterial chemotherapy combined with intravesical chemotherapy. Group B: intravesical chemotherapy alone

Table 1 Patient and tumor characteristics

	Group A	Group B	*P* value
Age medium (range years)	68 (30–84)	67 (29–82)	0.484
< 65	19 (35.8%)	40 (40.8%)	0.550
≥ 65	34 (64.2%)	58 (59.2%)	
Sex			0.986
Male (%)	47 (88.7%)	87 (88.8%)	
Female (%)	6 (11.3%)	11 (11.2%)	
Tumor size *n* (%)[a]			0.652
< 3 cm	25 (47.2%)	50 (51.0%)	
≥ 3 cm	28 (52.8%)	48 (49.0%)	
Multifocal			0.634
No	34 (64.2%)	59 (60.2%)	
Yes	19 (35.8%)	39 (39.8%)	

Group A: intra-arterial chemotherapy combined with intravesical chemotherapy; Group B: intravesical chemotherapy alone

[a]Maximum size of largest tumor resected

Treatment efficiency

A total of 53 patients were allocated into the group A, where the patients had intra-arterial chemotherapy concomitantly to intravesical chemotherapy after TURBT, those patients' follow-up period ranged from 7 to 131 months, median follow-up period was 79 months, during the follow-up period 19 patients experienced one or more tumor recurrence, time to first tumor recurrence ranged from 3 to 47 months, median time to tumor recurrence 13 months, among the patients with tumor recurrence, 3 patients died because the bladder cancer progressed and they could not or did not want to undergo further surgery, 8 patients chose to undergo radical cystectomy after tumor recurrence, 8 patients had a down-staged recurrent tumor and underwent further bladder-sparing surgery followed by intravesical chemotherapy only but with changed chemotherapy regimen.

98 patients were allocated into group B, where they only received intravesical chemotherapy after TURBT, those patients were followed up after for 7–127 months after their surgery, median follow-up period was 59 months, amongst them there were 41 patients who experienced one or more tumor recurrence, interval to recurrence ranged from 4 to 56 months, and median interval to recurrence was 10 months. Among those 41 patients with tumor recurrence: 15 patients died because their tumor progressed and refused further surgery or were unable to undergo further surgery; 8 patients opted for radical cystectomy after tumor recurrence; 18 patients had a down-staged recurrent tumor and underwent another bladder-sparing surgery followed by intravesical chemotherapy only, but with a changed regimen.

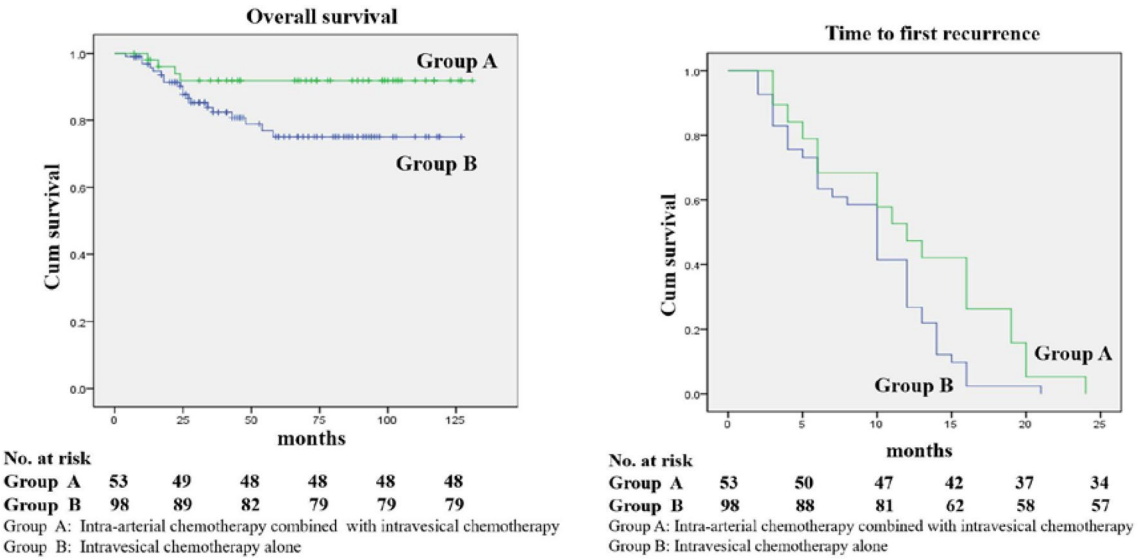

Fig. 2 Kaplan–Meier curves for overall survival and time to first recurrence are shown. Statistically significant difference in Kaplan–Meier curves for overall survival and time to first recurrence were identified between the two groups

Table 2 Univariable and multivariable analyses according to overall survival

Factor	Univariable		Multivariable	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)				
< 65 vs. ≥65	120 (58.90–181.10)	0.001	6.65 (3.16–14.00)	0.001
Sex				
Male vs. female	111.461 (103.87–119.06)	0.702		
Multifocal				
No vs. yes	111.964 (104.87–119.06)	0.646		
Tumor size, cm				
< 3 vs. ≥3	108.17 (98.92–117.43)	0.998		
Intravenous chemotherapy				
Yes vs. no	121.85 (113.25–130.45)	0.040	0.303 (0.10–0.87)	0.016

CI confidence interval, *HR* hazard ratio

In a total follow-up period of 7–131 months in this study, we noticed that overall survival between patients undergoing IAC + IVC and IVC alone was 90.5% (48/53) and 80.6% (79/98), tumor-specific death rate was 5.66% (3/53) and 15.3% (15/98), recurrence rate between the two groups was 35.8% (19/53) and 41.8% (41/98) and progression rate was 20.7% (11/53) and 23.5% (23/98), respectively, all the above differences were statistically significant ($P < 0.05$) (Fig. 2). Time interval to tumor recurrence was 13 months in the IAC + IVC group and 10 months in the IVC group alone.

After univariate analysis where P value was set at 0.05, significant factors were subjected to a multivariate analysis, and the following observations were made. Intra-arterial chemotherapy proved to be independent risk factors related to both overall survival (HR = 121.85, 95% CI 113.25–130.45, $P = 0.040$) and time to first recurrence

Table 3 Univariable analyses according to times to first recurrence

Factor	HR (95% CI)	*P* value
Age (years)		
< 65 vs. ≥ 65	10.250 (8.843–11.657)	0.766
Sex		
Male vs. female	10.580 (8.998–12.162)	0.170
Multifocal		
No vs. yes	10.526 (8.664–12.389)	0.475
Tumor size (cm)		
< 3 vs. ≥3	10.290 (8.276–12.305)	0.882
Intravenous chemotherapy		
Yes vs. no	12.263 (9.315–15.211)	0.028

CI confidence interval, *HR* hazard ratio

(HR = 12.263, 95% CI 9.315–15.211, $P = 0.028$), and patient age (cut-off value 65 years) was also an independent risk factors for overall survival (HR = 120 95% CI 58.90–181.10, $P = 0.001$) (Tables 2, 3). Hence we can derive from our study that intra-arterial chemotherapy influences both overall survival and time to first recurrence.

Toxicity

Toxicities associated with IAC were evaluated according to CTCAEv4.0. In patients who underwent IAC treatment, 35 patients experienced nausea and vomiting, 9 patients experience neutropenia, 7 patients experienced low leukocytes count, 12 patients experienced hepatic dysfunction and 3 patients experienced impaired renal function. Gastrointestinal toxicities are most common AEs. Most adverse effect were mild to moderate and were easily reversible (Table 4).

Discussion

According to AUA guidelines, both bladder-sparing therapy and early radical cystectomy are recommended for the treatment of T1G3 bladder cancer (Chang et al. 2016), but the loss of normal urinary route and creation of urinary diversion can be a cause of great discomfort to many patients, hence they usually opt for bladder-sparing therapy as their first choice of treatment. After bladder-sparing surgery, most worldwide guidelines recommend immunotherapy with BCG intravesical instillations to reduce risk of recurrence and progression in patients (Spiess and Cancer 2017), but it was not until late 2015 that BCG for vesical instillations was accepted by the Chinese Food and Drug Administration (CFDA), even today BCG for vesical instillations is not produced in great quantity and is therefore not readily available to patients. Hence, intravesical chemotherapy with either thio-tepa mitomycin C (MMC), pirarubicin and epirubicin is still the standard treatment according to local guidelines. According to a meta-analysis comparing 9 eligible clinical trial combining a total of 1277 patients by Bohle, intravesical chemotherapy had 27% higher risk of progression than with BCG (Sylvester and Lamm 2002), hence our study aimed at testing a novel treatment of using intra-arterial chemotherapy in T1G3 bladder cancer after bladder-sparing surgery that could reduce recurrence and progression when compared to current most available treatment using intravesical chemotherapy only. Moreover, due to a shortage in production and supply of BCG in China, this treatment could prove to be a much needed alternative. This alternative treatment could breach the gap in both treatments.

In our study, recurrence rate in IAC and IVC combined was 31.8% which was statistically lower than IAC (44.5%, $P < 0.05$) alone, and progression rate was also lower in the IAC + IVC group when compared to IVC group (18.8% vs 27.0%, $P < 0.05$). This result confirms the current trend where IAC combined with IVC has shown better prognosis (Sun et al. 2017; Liu et al. 2018). Moreover, cancer-specific death rate in IAC + IVC group was 7.25% compared to 16.8% in the IVC alone group, and the time to first recurrence was 11.5 months and 10 months (median values) in IAC + IVC and IVC group, respectively. This points to a better prognosis in patients undergoing intra-arterial chemotherapy concomitantly to intravesical chemotherapy, which as hypothesized could be due to a higher concentration of anti-tumor drugs in the tumor organ and a better distribution of the anti-tumor drugs (Hoshi et al. 1997): the intravesical chemotherapy attacking the tumor from the mucosal layer and the intra-arterial chemotherapy infiltrating the bladder and specially the tumor from the blood supply.

Cisplatin-based intravenous chemotherapy has been reported previously to have a beneficial effect in the treatment of bladder cancer; Li et al. conducted a study on the effect of intravenous chemotherapy showing that it was as effective as radical cystectomy in muscle invasive bladder cancer (Li et al. 2017). According to EAU guidelines, the use of cisplatin-based chemotherapy regimen such as MVAC (methotrexate, vinblastine, adriamycin and cisplatin) or GC (gemcitabine and cisplatin) intravenous chemotherapy regimens are both recommended as first-line chemotherapy regimen in the treatment of bladder cancer (Woldu et al. 2017; Skarlos et al. 1997). On the other hand, pirarubicin is recommended anti-tumor agent in intravesical instillations since it is rapidly absorbed into tumor cells (Kunimoto et al. 1983) and it is also used in intravenous chemotherapy. Hence in our

Table 4 Adverse reactions of intra-arterial chemotherapy

Adverse reactions	Grade 0	Grade I	Grade II	Grade III	Grade IV	Incidence %
Nausea/vomiting	18	18	9	8	–	66.0
Hypo-leukemia	46	4	1	2	–	13.2
Neutropenia	44	6	1	2	–	16.9
Increase alanine aminotransferase	41	10	1	1	–	22.6
Increase creatinine	66	1	2	–	–	4.5

According to CTCAE v4.0, Common Terminology Criteria for Adverse Events, version 4.0

study, we have chosen a combination of cisplatin and pirarubicin as our chemotherapeutic agents in our intra-arterial chemotherapy treatment.

Intra-arterial chemotherapy has been introduced into the treatment of bladder cancer by Japanese researcher Kubota et al. 1986 (1986), where the idea behind IAC is that localized injection of chemotherapeutic drugs directly into the blood vessels leading to the neoplastic organ, in this way there is a higher concentration of anti-tumor drug in the neoplastic organ resulting in more effective distribution, and reduction of chemotherapeutic agent in the systemic circulation reducing toxicity, as shown by Hoshi et al. in an animal model, where anti-tumor agent were directly injected into the arteries leading to the bladder and the concentration of anti-tumor drug measured (Hoshi et al. 1997; Eapen et al. 2004). In our study, adverse effect related to IAC were recorded, where the most common adverse effects were gastrointestinal distress and neutropenia, and the most common grade was Grade 0, which implied that most adverse effect were mild and were easily reversible without extensive hospital intervention. Other morbidities related with IAC are usually puncture site infection, femoral artery hematoma, thrombosis, but in our study none of the patients undergoing IAC reported any puncture-related co-morbidities. This could be attributed to the highly experienced and trained interventional department of our medical center and the setting up and delivery of proper perioperative care.

It is widely accepted that CIS and tumor size directly affects patient prognosis (Sylvester et al. 2005): recurrence and progression, but at the start of our study, due to lack of homogeneity among different urologists in reporting the degree of CIS, we have decided to exclude patients with CIS from our study. To remedy this, our medical center is currently standardizing the reporting of CIS among all urologists. Secondly, even though this study was a randomized control clinical trial, it is a single-institution two-armed study, it still lacks the evidence power of a multicenter clinical trial, hence further studies involving multiple centers across different countries including patients of different ethnicities could provide more information on the effect of this treatment on different populations. This study could have also been improved by being a double-blind study, where the control group should also be undergoing intra-arterial injections of saline solution, but it would have been unethical to perform invasive procedures such as intra-arterial injections on patients in the control group.

Conclusion

The result of this study shows that intra-arterial combined with intravesical chemotherapy after TURBT is a safe and effective treatment method for patients with T1G3 bladder cancer, in comparison with the current first-line treatment used in China (TURBT followed by intravesical chemotherapy alone), IAC + IVC shows significantly lower rates of recurrence and progression, hence this study could provide insight in establishing a new alternative treatment for high-risk non-muscle invasive bladder cancer such as T1G3 bladder cancer.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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