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ORIGINAL ARTICLE

Efficacy of intra-arterial chemotherapy combined with intravesical chemotherapy in T1G3 bladder cancer when compared with intravesical chemotherapy alone after bladder-sparing surgery: a retrospective study

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Abstract

Purpose To assess the efficacy of intra-arterial chemotherapy (IAC) combined with intravesical chemotherapy (IVC) in T1G3 bladder cancer (Bca) after transurethral resection of bladder tumor (TURBT).

Methods Our study retrospectively reviewed 200 patients with T1G3 BCa who had all undergone TURBT. The patients' medical records were divided into two groups, one group only had IVC with pirarubicin after surgery, and the other group had IAC (cisplatin and epirubicin) combined with IVC after surgery. The patients were monitored regularly by urine cytology and cystoscopy. Survival and recurrence curves were calculated using the Kaplan–Meier method. Tumor recurrence, progression and tumor-specific death rate were compared with Chi-square test. A multivariate analysis was carried out to find out potential confounders.

Results A total of 200 medical record was analyzed, 131 patients received IVC, 69 IAC + IVC treatment, tumor-specific death rate between the combined IAC and IVC compared to IVC alone was 7.25 and 17.6%, respectively ($p < 0.05$); the tumor recurrence rate between the two groups was 31.8% (22/69) and 44.3%, respectively (58/131) ($p < 0.05$), and tumor recurred later in the IAC + IVC group ($p < 0.05$), tumor progression rate was 18.8% (13/69) and 28.2% (37/131), respectively, with $p < 0.05$. Overall survival was longer in IAC + IVC group ($p < 0.05$). Using the multivariable regression model, IAC was significantly related to disease recurrence ($p < 0.05$) and overall survival ($p < 0.05$).

Conclusion T1G3 BCa post-TURBT surgery patients who underwent IAC combined with IVC had a longer overall survival and increased time interval to first recurrence, lower tumor recurrence rate, progression rate and tumor-specific death rate than compared with those who only underwent IVC alone.

Keywords Bladder cancer · T1G3 · Intra-arterial chemotherapy · Intravesical chemotherapy

Introduction

Non-muscle invasive bladder cancer (NIMBC) is a common but costly disease with various treatment methods, with each their advantages and shortcomings. Stage 1 Grade 3 (T1G3) bladder cancer (BCa) is one of the most aggressive

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amongst the different classification of NIMBC and is associated with a high risk of recurrence and disease progression despite undergoing transurethral resection (TUR), 40–80% of tumors recur in spite of complete TUR and 20–50% of disease progresses [1, 2]. For T1G3 BCa, immediate radical cystectomy upon diagnosis of disease is usually seen as overtreatment and because radical cystectomy requires urinary diversion which adversely affects the patients' quality of life [3], hence many prefer not to choose to accept radical cystectomy as first-line treatment in T1G3 BCa [4, 5].

Residual tumors were found in 25–40% T1G3 BCa patients after TUR, which shows the importance of adjuvant chemotherapeutic measures after TUR [6]. The most common prophylactic treatment of T1G3 BCa is intravesical chemotherapy with either thio-tepa mitomycin C(MMC), doxorubicin (adriamycin;ADM), pirarubicin (THP) and epirubicin (EPI) [7–9]. However, all those chemotherapy agents have been only able to reduce recurrence but not progression, except immunotherapy with BCG which has shown some ability to delay tumor progression, however, BCG has not been approved by Chinese FDA until late 2015 and is still difficult to acquire in most of Chinese Medical institutions due to low production and consummation, thus most medical institutions still uses the other instillations after TUR, therefore, to lower the risk of progression in T1G3 bladder cancer, new alternative treatment methods are required [10, 11].

Intra-arterial chemotherapy (IAC) directly into the arteries that supply the bladder is being increasingly used after bladder-sparing therapy in T1G3 BCa, which could provide an effective way to decrease recurrence and progression rate after surgery, since IAC causes less adverse effect than adjuvant chemotherapy [11–13]. Several studies have already shown the effectiveness of IAC, our medical center itself has already showed that IAC could delay recurrence and progression of BCa in a study of 60 patients over a period of 2 years [12].

In this retrospective study, confirmed T1G3 BCa patients were studied, where all the patients had undergone transurethral resection of bladder tumor (TURBT). Patients who had received intra-arterial chemotherapy combined with intravesical chemotherapy were grouped together, and patients who only received intravesical chemotherapy post-operatively were grouped together, and patient characteristics between both groups were analyzed.

Materials and methods

In total, the medical records of 200 patients with histologically confirmed stage 1 grade 3 bladder cancer were reviewed, all those patients underwent transurethral resection of bladder tumor(TURBT) followed by standard intravesical chemotherapy with pirarubicin, and among them 69 patients further underwent intra-arterial chemotherapy alongside their IVC. The detailed treatment protocol in each group is described below. All treatment protocol involved in this retrospective study were already approved by the Ethics committee of the First Affiliated hospital of Sun Yat-Sen university and have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Intravesical chemotherapy (IVC) treatment protocol

A total of 200 patients underwent TURBT in this study. After their surgeries all 200 patients received intravesical chemotherapy: where an immediate prophylactic instillation of intravesical chemotherapy was administered within the first 24 h followed by a maintenance dose every week for the next 8 weeks and once a month for the next 10 months. The instillation drug used in all the IVC was pirarubicin(INN), which was left inside the bladder for a time period of 30 min each time, all procedures were carried out according to the AUA guidelines for the treatment of bladder cancer [14].

Intra-arterial chemotherapy (IAC) treatment protocol

Among those 200 patients, 69 patients subsequently started intra-arterial chemotherapy concomitantly to their intravesical chemotherapy. Intra-arterial chemotherapy started a week after bladder-sparing surgery, the patients were referred to the interventional department of our medical institution, where under an angiographic catheter was superselectively inserted using Seldinger's percutaneous technique under fluoroscopy into the vesical arteries, and cisplatin (60 mg/m^2) and epirubicin (50 mg/m^2) was administered each time for a total of 4 times, with an interval of 1 month between each IAC. If during catheter insertion, the catheter tips could not pass through the superior gluteal arteries, those arteries were embolized. In our study, we only reviewed patients who successfully completed all 4 schedules regimen of intra-arterial chemotherapy.

Before IAC all patients underwent preconditioning for 2 days to ensure urine output was greater than 2500 ml so as to reduce renal toxicity. A routine blood test, liver and renal function tests were performed before and after each chemotherapy to evaluate the status of the patient and whether they were safe to undergo further IAC. All patients were also prescribed 5-HT3 receptor antagonist to prevent and treat gastrointestinal distress, and if white blood cell count fell below 3.0×10^9, G-CSF was used to increase white blood cells.

Detailed IAC procedure

Angiographic catheters were inserted into the femoral arteries using Seldinger's percutaneous method, then a guidewire was guided under fluoroscopy into the branching point of the abdominal aorta in two patients, into the bilateral internal iliac arteries in five patients, the unilateral internal iliac artery in 60 patients, and the unilateral internal iliac artery and common iliac artery on the contra-lateral side in two patients. A 5F angiographic catheter was inserted and was connected to a transfusion port that was buried under the skin of the thigh or thighs (when catheters were inserted bilaterally). Every time the patient came for their IAC, cisplatin and epirubicin was separately dissolved into 50 ml of saline, then injected into the transfusion port, with each injection lasting about 10 min. If the catheters were inserted bilaterally, the chemotherapy drugs were equally divided in volume and injected bilaterally into their respective transfusion port. For patients whose catheter tips were placed into either the common iliac artery or the abdominal artery, during injection of the chemotherapy drugs, pressure was applied to the femoral artery to reduce the amount of drug leaking into the lower extremities.

Follow-up and outcomes

Each patient was followed individually and contacted by phone regularly, cystoscopy, blood routine, biochemical test and urine cytology were performed every 3 months during the first 2 years, subsequently cystoscopy was performed every year after the first 2 years until the end of the follow-up period. Bladder biopsy was performed when necessary during cystoscopy when a new tumor was found or a suspected carcinoma in situ was observed. Outcomes of this study were biopsy-proven and histologically confirmed tumor recurrence (Ta or T1), tumor progression (recurrence with stage T2 or worse), and tumor-specific survival. Adverse reactions to IAC was also recorded according to the CTCAE v4.0 grading system published by the United States Department of Health and Human Services: March 28, 2009), where the severity of each adverse effect resulting from the IAC was graded ascendingly from 1 to 5 where grade 1 represented a mild adverse effect (AE) and grade 5 implied death of the patient resulting to AE. In patients with recurrence or progression, the patient's next treatment was also reviewed in our study.

Statistical analysis

The overall survival rate, tumor-specific death rate, recurrence rate, progression rate and time to first recurrence were assessed. Survival and recurrence curves were calculated using the Kaplan–Meier method. Patient characteristics between IAC + IVC and IVC alone was compared using independent sample Student *t* test for continuous parameters and Chi-square test for categorical parameters. Multivariable proportional hazards model was used to test prognostic factors with $p < 0.05$ in univariate analysis. All analyses were performed with SPSS 22.0 statistical software where all statistical tests were two sided, and p values < 0.05 was considered statistically significant.

Result

Patient characteristics

A total of 200 patient were reviewed in this study, of which 172 were male patients and 28 were female patients, their age was between 29 and 83 years old with a mean age of 64.43 ± 12.446 years. Original tumor size at first diagnosis varied between 1.0 and 6.0 cm with an average of tumor size of 2.68 ± 1.40 cm (Detailed patient characteristics in Table 1). Among those 200 patients, 131 patients only received IVC where they were followed after for 82 months (median) with an IQR of 119; 58 patients had one or more recurrence of BCa, with the tumor recurrence occurring 10 months (median and IQR: 18 months) after the initial TURBT. Among the 58 patients with tumor recurrences, 23 patients passed away due to the disease progression; 14 patients underwent radical cystectomy after tumor recurrence was observed; 21 patients had a downstaging of their recurrent tumor biopsy stage and were able to undergo repeat TURBT and continued with their original treatment modality but with a modified drug regimen.

Table 1 The association between tumor characteristics

Characteristics	IAC + IVC	IVC	*p* value
Age medium (range years)	62 (30–80)	64 (29–83)	0.191
Sex			
Male (%)	62 (88.7%)	110 (84.0%)	0.070
Female (%)	7 (11.3%)	21 (16.0%)	
ECOG performance status			
0	24 (34.5%)	38 (29.0%)	0.763
1	36 (51.7%)	60 (45.8%)	0.786
2	9 (13.8%)	33 (25.2%)	0.338
Tumor size *n* (%)[a]			
< 3 cm	31 (55.2%)	69 (52.7%)	0.093
≥ 3 cm	38 (44.8%)	62 (47.3%)	
Median	2.5	2.0	
Multifocal			
Single	43 (62.3%)	73 (55.7%)	0.226
Multifocal	26 (37.7%)	58 (44.3%)	

[a]Maximum size of largest tumor resected

Among the 69 patients in the IAC + IVC treatment group, the follow-up period was 98 months(median) with an IQR of 73 months; among them 22 patients had one or more tumor recurrence where the tumor recurred 11.5 months(median) with an IQR of 13.5 after the initial resection; five patients passed away due to the disease progression; eight patients underwent radical cystectomy after tumor recurrence was observed; nine patients underwent TURBT again because the pathological staging of the tumor was lower than the initial tumor, those patient were then switched to IVC treatment only after their second surgery.

Kaplan–Meier curves for overall survival and time to first recurrence are as shown in Fig. 1, where IAC + IVC was associated with a higher overall survival and longer time to first recurrence ($p < 0.05$). Overall survival between the combined IAC and IVC compared to IVC alone was 85.5% (59/69) and 73.3% (96/131), respectively ($p < 0.05$), the tumor-specific death rate between the two groups was 7.25% (5/69) and 17.6% (23/131), respectively ($p < 0.05$), the tumor recurrence rate between the two groups was 31.8% (22/69) and 44.3% (58/131), respectively ($p < 0.05$), tumor progression rate was 18.8% (13/69) and 28.2% (37/131), respectively, with $p < 0.05$, where all the above differences were statistically significant. Furthermore, the tumor recurrence interval between the two groups was 11.5 and 10 months, respectively ($p < 0.05$, statistically significant), those results are summarized in Table 2. In terms of adverse effect in patient undergoing IAC, 40 patients experienced nausea and vomiting, seven patients experienced leukocytopenia, 12 patient experienced impaired hepatic function, two patients experienced impaired renal function, all impaired function was light and reversible (details in Table 3).

Table 2 Clinical outcome of high risk patients in IAC + IVC and IVC group

Variable	IAC + IVC	IVC	*P* value
3-year overall survival	86.9% (60/69)	82.4% (108/131)	0.013
5-year overall survival	86.9% (60/69)	78.6% (103/131)	0.002
Tumor-specific death rate	7.25% (5/69)	17.6% (23/131)	0.047
Tumor recurrence rate	31.8% (22/69)	44.3% (58/131)	0.025
Tumor recurrence interval	11.5 (months)	10 (months)	0.041
Tumor progression rate	18.8% (13/69)	28.2% (37/131)	0.016

After univariate analysis where p value was set at 0.05, we then entered significant factors into a multivariate proportional hazards model (Tables 4 and 5).Intra-arterial chemotherapy proved to be independent risk factors related to both overall survival (HR = 0.27, 95% CI 0.13–0.53, $p = 0.001$) and time to first recurrence (HR = 11.418, 95% CI 9.486–13.350, $p = 0.001$), and patient age and ECOG score were independent risk factors for overall survival (HR = 2.29, 95% CI 1.03–5.10, $p = 0.042$ and HR = 0.59, 95% 0.36–0.96, $p = 0.032$, respectively.)

Discussion

The treatment guidelines for T1G3 bladder cancer states that both radical cystectomy and bladder-sparing therapy are acceptable [15]; However, opting for bladder-sparing therapy puts the patient at a high risk of recurrence or disease

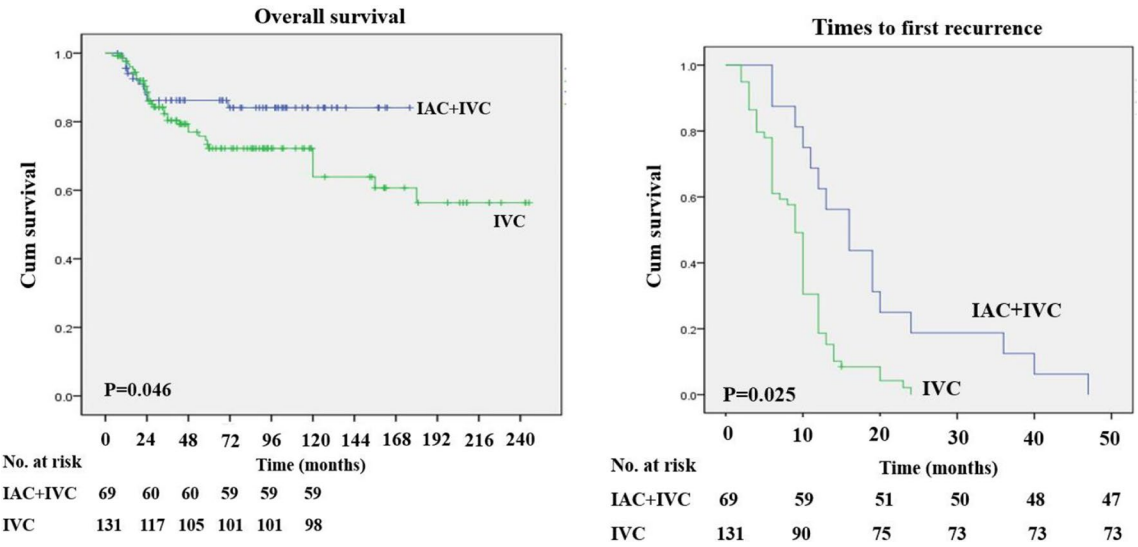

Fig. 1 Kaplan-Meier curves for overall survival and time to first recurrence

Table 3 Adverse reactions of intra-arterial chemotherapy

Adverse reactions	Grade0	Grade I	Grade II	Grade III	Grade IV	Incidence %
Nausea/vomiting	29	21	10	9	–	57.9
Hypo-leukemia	62	4	1	2	–	11.3
Neutropenia	62	3	3	–	1	11.3
Increase alanine aminotransferase	57	8	3	1	–	17.4
Increase creatinine	67	1	1	–	–	2.3

According to CTCAE v4.0 common terminology criteria for adverse events version 4.0

Table 4 Univariable and multivariable analyses according to overall survival

Factor	Univariable		Multivariable	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (years)				
<65 years, ≥65 years	120 (58.90–181.10)	0.001	2.29 (1.03–5.10)	0.042
Sex				
Male, female	187.01 (169.71–204.31)	0.282		
ECOG	182.16 (165.79–198.54)	0.001	0.59 (0.36–0.96)	0.032
Number of tumors				
Single, multiple	181.66 (158.24–205.10)	0.434		
Tumor size, cm				
< 3, ≥ 3	173.41 (149.10–197.72)	0.612		
Intravenous chemotherapy				
Yes, no	183.15 (166.78–199.53)	0.046	0.27 (0.13–0.53)	0.001

CI confidence interval, *HR* hazard ratio

Table 5 Univariable analyses according to times to first recurrence

Factor	HR (95% CI)	*p* value
Age (years)		
<65 years, ≥65 years	11.580 (9.097–14.063)	0.980
Sex		
Male, female	10.286 (7.700–12.872)	0.543
ECOG	10.000 (9.307–10.693)	0.938
Number of tumors		
Single, multiple	10.957 (8.268–13.645)	0.337
Tumor size, cm		
< 3, ≥ 3	11.399 (9.493–13.305)	0.589
Intravenous chemotherapy		
Yes, no	11.418 (9.486–13.350)	0.001

CI confidence interval, *HR* hazard ratio

progression that ultimately ends in the patient undergoing a radical cystectomy [3]. On the other hand, many patients are discouraged by the urinary diversion brought by radical cystectomy because it causes great discomfort and decreases the patient's quality of life [16]. Hence, if IAC combined with IVC can have a similar prognosis to radical cystectomy in T1G3 bladder cancer, then patients can avoid radical cystectomy and the decrease in quality of life linked to it.

Current recommended treatment after bladder-sparing surgery for T1G3 bladder cancer is intravesical instillations with BCG, but BCG has only been approved by the Chinese food and drug association in 2015 [10, 17]. Since it has been approved, there are only limited producers and suppliers of BCG in China, thus intravesical BCG instillations still remains highly unavailable in many institutions. Hence, many patients only have access to other intravesical chemotherapy drugs such as MMC, epirubicin and pirarubicin, of which we chose pirarubicin as control in our retrospective review because at the start of our study BCG was not yet allowed in China and pirarubicin was the next most recommended intravesical chemotherapy drug [18]. Additionally, several studies have already shown that only BCG instillations can decrease progression in T1G3 bladder cancer, while the other instillation drugs reduce recurrence rate [19], therefore, this new combination of IVC and IAC could bridge the gap between a risky prognosis of a bladder-sparing surgery followed by intravesical chemotherapy and the overtreatment and urine diversion associated with a radical cystectomy.

The recurrence rate with IVC alone after bladder-sparing surgery was 44.3% which substantial to a study by Bohle et al. [10] whose recurrence rate was 46.4%. A meta-analysis of 11 trials investigating the effect of intravesical

BCG including 2749 patients observed a recurrence rate of 38.6% with intravesical BCG [10]; in comparison, our study showed that with IVC and IAV combined after bladder-sparing surgery recurrence rate was 31.8% where most recurrence occurred at around 11.5 months, which occurred later than those who only received IVC. This observation, implies that IAC combined with IVC has a lower recurrence rate and higher time to first recurrence than IVC alone.

Tumor progression rate 18.8% in the intra-arterial chemotherapy combined with intravesical chemotherapy group versus 28.2% in the intravesical therapy group alone, this showed that IAC and IVC can effectively decrease progression rate after bladder-sparing surgery, this is consistent with the idea that in intra-arterial chemotherapy the chemotherapy drugs can directly infuse into the different muscle layers of the bladder thus acting onto any possible micrometastases arising from or infiltrated into the smooth muscle layer, and the chemotherapeutic drugs can also act onto the pelvic lymph nodes which are usually not treated adequately by intravesical therapy alone [20, 21].

Bladder urothelial carcinoma is considered a "chemosensitive" tumor, where perioperative chemotherapy regimen with cisplatin(CDDP) combinations such as gemcitabine with cisplatin or M-VAC(Methotrexate, vinblastine, doxorubicin(Adriamycin) and Cisplatin) regimens have shown response rate of up to 70% [22, 23], which is why they are both listed as first-line chemotherapy regimen of choice in the case of BCa, however, there is a high toxicity associated with intravenous injection of those drug combination, our study aimed at an effective combination with lower side-effect to increase the compliance of the patients. Several studies have shown that substituting ADR with epirubicin in intravenous chemotherapy, resulted in less toxicity than comparable ADR-based regimens [24, 25]. Hence, a combination of cisplatin and epirubicin was chosen to be injected intra-arterially into the vesicular arteries since they have both been proven to be safe and effective against BCa.

In our study, the main side-effects we observed from IAC was gastrointestinal distress, myelotoxicity, and hepatic and renal dysfunction, which were all slight adverse reactions which the patients quickly recovered from without major medical interventions. Those adverse effects are common in chemotherapy, but with localized injection of the chemotherapy drugs, we can reduce its concentration in the whole body and decrease the adverse effects of the drugs on the other organs of the body. Moreover, with a localized injection, we can ensure a higher concentration of medicine at the tumor site, thus increasing its efficiency [26, 27].

In terms of limitation, our study being a retrospective study decreases the strength of our evidence considerably due to possible biases prone to happen in a retrospective design. Moreover, the low number of cases and events that were reviewed further limits the strength of the conclusion we can draw from analyzing them. According to the AUA guidelines, BCG instillations are the golden standard treatment for patient with bladder cancer, and we do recommend BCG treatment to our patient since it has been available to us, yet we have failed to compare patients undergoing BCG immunotherapy in our study because there are currently too few cases and patient follow-up period is not long enough to draw conclusions. Ultimately, a prospective randomized control trial with both cohort from the same institution with similar attributes will provide a higher quality of data on whether BCG is better than IAC combined with IVC. This way, patients who are unfit for BCG instillations (hypersensitive to BCG, or who have serious adverse effects to BCG instillations), may have an alternative choice of treatment [28].

Conclusion

Intra-arterial chemotherapy combined with intravesical chemotherapy is more effective when compared with intravesical chemotherapy with pirarubicin alone after TURBT in terms of overall survival time and time interval to first recurrence, reduces recurrence rate, progression and tumor-specific death rate in T1G3 bladder cancer. Intra-arterial chemotherapy could provide an alternative bladder-preserving therapy with better results than intravesical chemotherapy alone.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

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