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Original Article

Transurethral resection combined with gemcitabine intravesical instillation in the treatment of non-muscle invasive bladder cancer in the elderly

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Abstract: Objective: To observe the curative effect of transurethral resection combined with gemcitabine intravesical in the treatment of elderly patients with non-muscle invasive bladder cancer and its influence on the quality of life of patients. Methods: A prospective randomized controlled study was conducted on 85 patients with bladder cancer. Among them, 43 patients in the observation group were treated with transurethral resection of bladder tumor (TURBT) combined with gemcitabine (GEM) intravesical instillation; and another 42 patients in the control group were treated with TURBT combined with pirarubicin. The recurrence, progression-free survival and overall survival were observed, tumor-related factors were detected, adverse reactions and quality of life were recorded. Results: The recurrence rate at 3 years in the observation group was lower than that in the control group (P=0.033). The progression-free survival time and overall survival time in the observation group were longer than that in the control group (P<0.05). The level of IGFBP-3 in the observation group was higher than that in the control group, while VEGF was lower than that in the control group (P<0.05). The scores of mental health, physiological function and social function in the observation group were better than those in the control group (P<0.001). Conclusion: Transurethral resection combined with gemcitabine intravesical instillation for the treatment of elderly patients with non-muscle invasive bladder cancer can increase the progression-free survival time and the total survival time of the patients, and the side effects of postoperative chemotherapy are reduced and the quality of life of the patients is improved.

Keywords: Bladder cancer, transurethral resection, gemcitabine, curative effect, quality of life

Introduction

Bladder cancer is a common urological disease. The incidence of bladder cancer increases with age, especially in the elderly population, over 45 years old. Bladder cancer rates increase by 470,000 cases worldwide every year [1, 2]. Bladder cancer is characterized by easy recurrence and metastasis to myometrial invasion, which seriously endangers both life and health [3]. Bladder cancer can be divided clinically into non-muscle invasive bladder cancer (NMIBC), and muscle invasive bladder cancer (MIBC) according to the depth of disease invasion; with NMIBC accounting for about 70%-75% and MIBC accounting for about 25%-30% [4, 5]. Because of the distinct biological characteristics, fairly different clinical treatment options are chosen [6, 7]. For NMIBC, transurethral resection of the bladder tumor (TURBT) is recommended in the guidelines, but the postoperative recurrence rate is 60-70%, and about 20% of patients have disease progression [8]. Therefore, BCG or anthracyclines are recommended for adjuvant chemotherapy after surgery to improve the prognosis of patients [9, 10]. However, clinical studies have found that BCG is effective in bladder intravesical chemotherapy after operation, but it requires good physical condition of patients and has many side effects [11]. Anthracyclines, such as pirarubicin, can effectively inhibit tumor cells and have less cardiac toxicity. We found that intravesical instillation of pirarubicin can inhibit tumor cells and tumor angiogenesis, and has no difference in survival time compared with BCG, but has fewer side effects [12]. Therefore, pirarubicin is often used to replace BCG for postoperative intravesical chemotherapy in the clinic. Gemcitabine (GEM) has recently been

used as postoperative chemotherapy for bladder cancer. Studies have found that there is no difference in disease-free survival between GEM and BCG postoperative infusion chemotherapy. The incidence of side effects after GEM is significantly lower than BCG. Therefore, some studies believe that GEM and pirarubicin have the same curative effect [13]. In recent years, studies have shown that NMIBC patients are randomly divided into two groups after TURBT and injected with GEM or pirarubicin, respectively. The results have shown that the total recurrence rate of bladder cancer after GEM and pirarubicin infusion is 15.5% and 35.5%, respectively [14]. Therefore, the best postoperative chemotherapy for bladder cancer with GEM and pirarubicin has not been determined yet. Based on this, our study applied transurethral resection combined with gemcitabine and pirarubicin intravesical instillation in elderly patients with non-muscle invasive bladder cancer, and investigated postoperative recurrence rates and long-term quality of life in patients to compare the advantages and disadvantages of the two treatment methods. Results are reported as follows.

Materials and methods

General data

Altogether, 86 cases of bladder cancer patients admitted to The Affiliated Hospital of Southwest Medical University Urology Department from July 2014 to January 2017 were prospectively studied. The patients were divided into an observation group and a control group by a random number grouping method. One of the patients in the control group had sudden death during postoperative chemotherapy, and as such was excluded. The observation group received transurethral resection of bladder tumor (TURBT) combined with gemcitabine (GEM) intravesical instillation in 43 cases, and the control group received TURBT combined with pirarubicin in 43 cases. A long-term follow-up was carried out after the operation. All the above patients signed an informed consent and the study was approved by the Ethics Committee of The Affiliated Hospital of Southwest Medical University.

Inclusion and exclusion criteria

Inclusion criteria: ① The study conformed to the diagnostic criteria for non-muscle invasive bladder cancer (NMIBC) in the 2014 Chinese Guidelines for Diagnosis and Treatment of Urological Diseases [15]; ② All patients were aged over 18 years.

Exclusion criteria: ① Patients who were unable to tolerate surgery or chemotherapy drugs; ② Patients with serious heart, liver, kidney and other diseases; ③ Patients with mental disorders or cerebrovascular diseases leading to a decline in quality of life; ④ Patients with other malignant tumors; ⑤ Patients with severe coagulation disorders; ⑥ Patients who were difficult or inconvenient during the follow-up and patients were not suitable for surgery; ⑦ Patients with an expected survival time of less than 1 year.

Methods

All included patients were treated with TURBT. About 30 min after the operation, if there was no obvious gross hematuria, bladder intravesical chemotherapy was performed. Immediately after the operation, the observation group was treated with GEM bladder irrigation. GEM (H20030105, Jiangsu Haosen Pharmaceutical Group Co., Ltd., China) of which 1 g was added into 50 mL of 0.9% normal saline to prepare an infusion solution. Bladder syringe was used for bladder infusion and retention. During the retention period, the body position was changed once every 15 min, the retention time was 1 h, once per week, for a total of 8 weeks, and once a month for a completion of 8 weeks of treatment.

The control group was treated with pirarubicin (H10930105, Main Luck Pharmaceutical Inc, Shenzhen, China) where 30 mg of pirarubicin was added into 50 mL of 0.9% normal saline to prepare the infusion solution. The infusion method and course of treatment were the same as those in the observation group.

Outcome measures

Main outcome measures: All patients were followed up after the operation to observe the postoperative recurrence, progression, and progression time. The progression-free survival (PFS) of patients (in review with cystoscopy after treatment, the observation of whether the tumor recurred *in situ* or progressed to other body parts) was observed to record the recurrence time. The total survival time referred to

Table 1. Comparison of complications during treatment (n, ($\overline{x}$ ± sd))

Items	Observation group (n=43)	Control group (n=42)	χ^2/t	P
Gender (male:female)	33:10	34:8	0.225	0.635
Age	64.2±9.1	66.3±10.9	0.965	0.337
BMI (kg/m^2)	21.60±7.96	22.61±7.48	0.603	0.548
Tumor grade (case)			0.132	0.176
High-level	26	27		
Low level	17	15		
cTMN stage (case)			0.336	0.845
Tis	2	2		
Ta	7	5		
T1	34	35		
Number of tumors occurring			0.112	0.738
Single tumors	36	34		
Multiple tumors	7	8		

Note: BMI: body mass index; cTNM: tumor lymph node metastasis.

the time from the beginning of chemotherapy to death. The final follow-up point was February 2020. The OS of patients whose relapse or progression date or survival date exceeded the follow-up deadline finished according to the follow-up deadline. Recurrence rate (%) = recurrence cases/total number of cases * 100.

One year after receiving preoperative and postoperative chemotherapy, 5 mL of venous blood from the elbow was collected at 8 o'clock in the morning on an empty stomach. The blood samples were placed in an ethylene diamine tetraacetic acid sterile tubes. After being placed in a refrigerator at 4°C for 15 minutes, the serum was separated by centrifuge. The centrifugation speed was 3,300 rpm, and the separated serum was placed in a freezer at -80°C. The concentration of serum insulin-like growth factor-I (IGF-I), serum insulin-like growth factor binding protein-3 (IGFBP-3) and vascular endothelial growth factor (VEGF) were determined by enzyme-linked immunosorbent assay.

Secondary outcome measures: Adverse reactions: The incidence of bladder irritation, hematuria, nausea and vomiting, liver and kidney dysfunction, and drug allergies were recorded. The incidence of complications (%) = the number of complications/total number of cases * 100.

Before and 6 months after chemotherapy, SF-36 quality of life survey was conducted for patients through outpatient follow-up, including general health (GH), mental health (MH), physical functioning (PF), role-physical (RP), social function (SF), role-emotional (RE), physical pain (BP) and vitality (VT).

Statistical methods

SPSS 17.0 was applied. The continuous variables in accordance with normal distribution were expressed by the mean ± standard deviation ($\overline{x}$ ± sd), and the t test was applied to the consistency of the normal distribution and variance. Paired t test was applied to the comparison before and after the treatment. The intra-group comparison adopted t test of independent samples, which was expressed by t. Rank sum test was used for non-conforming normal distribution and variance homogeneity, which was expressed by χ^2. The counting data were tested by Pearson chi-square test, which was expressed by chi-square. Survival analysis was conducted by Kaplan-Meier method and Log-rank test. P<0.05 indicates a statistically significant difference.

Results

Comparison of general data and baseline data

One of the patients in the control group had sudden death during postoperative chemotherapy, and as such was excluded. After comparing the general data and baseline data of the two groups, it was found that there was no significant statistical difference in gender, age, BMI, tumor grade, cTMN stage and the number of tumors occurring between the two groups (P>0.05). See **Table 1**.

Comparison of recurrence rates within 3 years

There was no statistical difference in recurrence rate between the two groups within 6 months, 1 year and 2 years. The recurrence rate in the observation group within 3 years was significantly lower than that in the control group (P<0.05), as shown in **Table 2**.

Table 2. Comparison of general data and baseline data (n, %)

Items	Observation group (n=43)	Control group (n=42)	χ^2/t	P
Recurrence within 6 months	0 (0.00)	1 (2.38)	1.036	0.309
Recurrence within 1 months	6 (14.00)	5 (11.90)	0.079	0.778
Recurrence within 2 months	8 (18.60)	12 (28.57)	0.972	0.336
Recurrence within 3 months	10 (23.26)	19 (45.24)	4.568	0.033

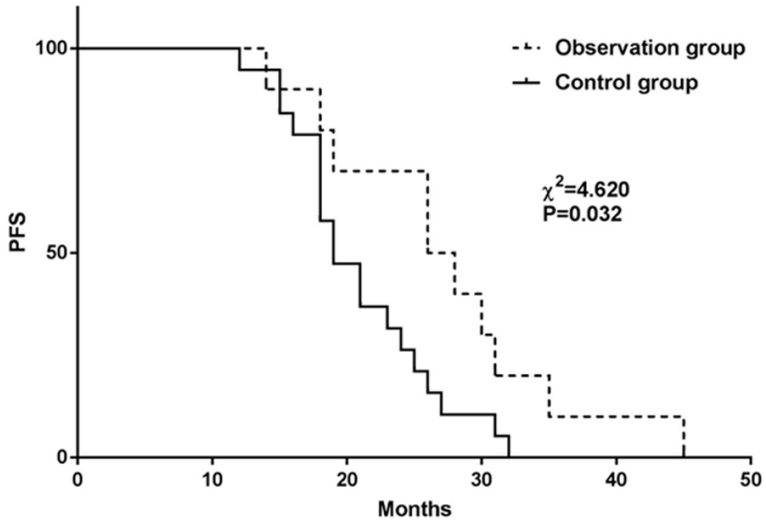

Figure 1. Comparison the PFS survival curves. PFS: progression-free survival.

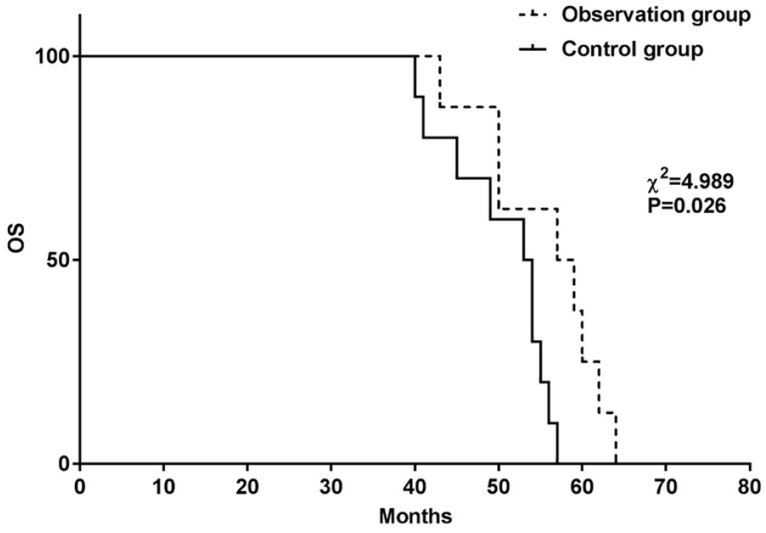

Figure 2. Comparison the OS survival curves. OS: Overall survival.

Comparison of progression-free survival time of patients

The follow-up time of the two groups of patients was 36-65 months on January 31, 2020, with an average follow-up time of 52.3±9.6 months. The median relapse time of the observation group was 26.0 months (95% CI: 16.703-35.297); while the median relapse time of the control group was 19.0 months (95% CI: 15.801-22.199). The relapse time was statistically different between the two groups (P<0.05). See **Figure 1**.

Comparison of total survival time

During the follow-up, 18 patients in both groups died, including 8 cases in the observation group and 10 cases in the control group. The median survival time of the observation group was 57.0 months (95% CI: 44.527-69.473), and the median survival time of the control group was 53.0 months (95% CI: 45.252-60.748). The recurrence time was statistically different between the two groups (P<0.05). See **Figure 2**.

Comparison of recurrence indexes before and after treatment

There was no statistical difference in IGF-I, IGF-BP-3 and VEGF between the two groups before treatment (P>0.05). After treatment, IGF-I and VEGF in the two groups were lower than before treatment, while IGF-BP-3 was higher than before treatment. The comparison between the two groups showed that IGF-BP-3 in the observation group was significantly higher than that in the control group, while VEGF was significantly lower than the control group (P< 0.05), as shown in **Table 3**.

Comparison of complications during treatment

The comparison of complications between the two groups showed that the total incidence rate of complications in the observation group (11.63%) was lower than that in the control group (21.43%), but there was no statistical dif-

Table 3. Comparison of recurrence rates within 3 years ($\bar{x} \pm sd$)

Items	IGF-I (ug/mL)	IGFBP-3 (ng/mL)	VEGF (ng/mL)
Observation group before treatment	4.86±0.52	128.65±13.02	97.69±11.23
Control group before treatment	4.81±0.49	130.261±3.26	95.14±11.63
t	0.456	0.778	1.028
P	0.650	0.439	0.307
Observation group after treatment	2.64±0.26*	188.26±20.23*	46.39±5.95*
Control group after treatment	2.71±0.31*	158.69±16.85*	67.39±7.03*
t	0.129	7.313	14.880
P	0.262	<0.001	<0.001

Note: Compared with before treatment in the same group, *P<0.05. IGF-I: insulin-like growth factor-I; IGFBP-3: serum insulin-like growth factor binding protein-3; VEGF: vascular endothelial growth factor.

Table 4. Comparison of recurrence indexes before and after treatment patients (n, %)

Complications	Observation group (n=43)	Control group (n=42)	χ^2	P
Bladder irritation	1 (2.33%)	4 (9.52%)	1.989	0.158
Hematuria	1 (2.33%)	2 (4.76%)	0.370	0.543
Feel sick and vomit	1 (2.33%)	0 (0.00%)	0.998	0.320
Impaired liver and kidney function	0 (0.00%)	1 (2.38%)	1.036	0.309
Leukopenia	2 (4.65%)	2 (4.76%)	0.001	0.981
Total number of cases	5 (11.63%)	9 (21.43%)	1.483	0.223

ference between the two groups (P>0.05), as shown in **Table 4**.

Quality of life scores of patients in both groups before and 6 months after operation

There was no difference in preoperative quality of life scores between the two groups (P>0.05). General health, mental health, physiological function, social function, physical pain and vitality of the two groups of patients were significantly improved 6 months after operation in relation to before treatment (P<0.05). The comparison of the quality of life scores of the two groups of patients at 6 months after operation showed that the scores of mental health, physiological function, role-physical and social function of the observation group were better than those of the control group (P<0.001), as shown in **Table 5**.

Discussion

About 70% of the patients with primary bladder cancer have non-muscle invasive bladder cancer (NMIBC) [16]. Previous studies have reported that the postoperative recurrence rate of patients with non-muscle invasive bladder cancer (NMIBC) after TURBT treatment is 60-70%, and about 20% of patients develop disease progression [17, 18]. There are many factors affecting postoperative recurrence, neoadjuvant chemotherapy is one of the influencing factors [19]. Gemcitabine (GEM) is recommended as the first-line chemotherapy drug for bladder cancer in the 2017 NCCN guidelines in the United States [20]. Previous studies also showed that GEM could effectively reduce the recurrence rate for high-risk and medium-risk NMIBC patients undergoing postoperative chemotherapy [21]. In this study, treatment with GEM was found to have significantly lower recurrence rates within 3 years than treatment of patients undergoing postoperative chemotherapy with pirarubicin; suggesting GEM has better effects in reducing the postoperative recurrence rate. Further research found that GEM can improve the patients' progression-free survival period and total survival time. Previous studies showed that GEM postoperative chemotherapy has a progression-free survival time of 19.6 months, which is better than BCG postoperative chemotherapy of 15 months [11], suggesting that GEM can prolong the patients' progression-free survival time.

Relevant recurrence markers were frequently detected in patients with NMIBC. Studies showed that insulin-like growth factor-I (IGF-I) plays a promoting role in the occurrence and development of tumors [22, 23]. Serum insulin-like growth factor binding protein-3 (IGF-BP-3) can competitively combine with IGF-I to block

Table 5. Quality of life scores of patients in both groups before and 6 months after operation (score, ($\bar{x}$ ± sd))

Items	Observation group before treatment	Control group before treatment	t	P	Observation group 6 months after operation	Control group 6 months after operation	t	P
General health (GH)	63.23±8.67	64.23±9.07	0.520	0.605	75.10±9.28***	75.19±9.29***	0.045	0.964
Mental health (MH)	68.23±8.78	67.82±8.92	0.214	0.831	81.50±10.34***	72.22±8.85**	4.441	<0.001
Physiological function (PF)	51.34±6.23	50.23±6.34	0.814	0.418	76.26±14.69***	56.23±13.69**	6.500	<0.001
Role-physical (RP)	43.78±5.23	42.83±4.78	0.874	0.385	67.69±10.26***	45.87±7.26	11.290	<0.001
Social function (SF)	56.46±6.34	55.56±6.49	0.647	0.520	75.35±9.27***	61.21±6.59*	8.088	<0.001
Role-emotional (RE)	50.23±5.93	50.56±6.12	0.252	0.801	56.29±8.17	53.69±8.03	1.479	0.143
Physical pain (BP)	70.23±8.67	70.78±8.32	0.298	0.766	75.98±9.27**	74.26±9.51**	0.844	0.401
Vitality (VT)	68.90±7.92	68.52±7.34	0.229	0.819	71.50±8.34*	70.22±8.85*	0.686	0.494

Note: Compared with before treatment in the same group, *P<0.05, **P<0.01, ***P<0.001.

the activation of IGF-I signaling pathway and play a cancer inhibiting role [24]. Vascular endothelial growth factor (VEGF) can inhibit antineoplastic drugs from entering tumor cells to avoid tumor cell necrosis and is also a cancer promoting factor. Previous studies have shown that gemcitabine reduces VEGF levels in patients with bladder cancer with positive human epidermal growth factor receptor 2 [25] and IGF-1 and VEGF levels in patients with bladder cancer treated with gemcitabine chemotherapy [26]. This study further detected the above three tumor markers. The results showed that IGF-I and VEGF after chemotherapy intervention were both lower than before treatment, while IGF-BP-3 was higher than before treatment. The decreased degree of VEGF and the increased degree of IGFBP-3 in the observation group treated with GEM chemotherapy were better than those in the control group; suggesting that the decreased recurrence rate with GEM chemotherapy may be related to the influence of relevant tumor factors.

In terms of postoperative complications, previous studies have shown that there is no difference in disease-free survival between GEM and BCG postoperative perfusion chemotherapy. The incidence of side effects after GEM was significantly lower than BCG [13], and the side effects of chemotherapy after GEM were lower, which may be related to more accurate identification of malignant tumor cells by GEM, better killing of tumor cells and less damage to other cells [27]. Previous studies have found that intravesical instillation of pirarubicin can inhibit tumor cells and tumor neovascularization. Compared with BCG, bladder instillation of pirarubicin had no difference in survival time, but had fewer side effects [12]. In this study, adverse reaction rates of chemotherapy after GEM were found to be lower than that of pirarubicin, but there was no statistical difference, which may be related to the small sample size in this study. The quality of life of GEM postoperative chemotherapy patients was improved due to their longer non-progressive survival time and lower side effects. In this study, it was found that the quality of life of GEM postoperative chemotherapy patients was better than that of the control group in mental health, physiological function, physiological function and social function scores. It was suggested that GEM postoperative chemotherapy in NMIBC patients could improve the quality of life of patients while improving the non-progressive survival time of patients and reduced postoperative complications.

Deficiencies and Prospects: This study is a single-center study. We can further carry out a multi-center randomized controlled study, and increase the follow-up time of patients to 5 years in order to observe the 5-year survival period of patients, so as to clarify the value of GEM postoperative chemotherapy for NMIBC patients.

To sum up, transurethral resection combined with gemcitabine bladder perfusion for the treatment of elderly patients with non-muscle invasive bladder cancer can increase the progression-free survival time and total survival time of patients, and postoperative chemotherapy has fewer side effects and can improve the quality of life of patients.

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Disclosure of conflict of interest

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