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ORIGINAL ARTICLE

Efficacy of bladder perfusion of alternating hydroxycamptothecin and gemcitabine combined with low-dose tuberculin in the treatment of non-muscle invasive bladder cancer after TURBT

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Summary

Purpose: *To evaluate the clinical efficacy and safety of alternating sequential bladder perfusion of hydroxycamptothecin (HCPT) combined with low-dose tuberculin (BCG), and gemcitabine (GEM) combined with low-dose BCG in the treatment of non-muscle invasive bladder cancer (NMIBC) after transurethral resection of bladder tumor (TURBT).*

Methods: *A total of 170 patients with primary NMIB urothelial carcinoma were retrospectively collected from October 2014 to December 2016 and randomly divided into two groups with 85 cases in each group, in which 85 cases were given alternating bladder perfusion of HCPT combined with low-dose BCG (HCPT group), and 85 cases received alternating bladder perfusion of GEM combined with low-dose BCG (GEM group). The follow-up period was 24 months. The tumor recurrence rate, progression rate, time to recurrence and adverse reactions of therapy were observed and recorded, and the risk factors for tumor recurrence were analyzed.*

Results: *The general clinical features of the two groups of patients were comparable, and no patients died during the follow-up period. The 2-year tumor recurrence rate was 18.75% (15/80) in the HCPT group and 13.58% (11/81) in the GEM group, and the tumor progression rate was 5% (4/80) in the HCPT group and 1.23% (1/80) in the GEM group, without statistical significance (p>0.05). The log-rank test showed no statistically significant difference between the two groups in the 2-year survival without recurrence (p>0.05). The progression rate of bladder cancer was 2.5% in the HCPT group and 1.7 % in the GEM group, with no statistically significant difference (p>0.05). Multivariate logistic regression analysis showed that TNM stage, tumor size and tumor pathological grade were independent risk factors for tumor recurrence (p=0.0021, p=0.032, p<0.001, respectively). No significant differences were found in the incidence rates of adverse reactions such as dysuria, fever, rash and gastrointestinal reactions between the two groups, but patients in the HCPT group were more likely to have bladder irritation symptoms and hematuria (p=0.046, p=0.037, respectively).*

Conclusions: *For NMIBC patients after TURBT, alternating bladder perfusion chemotherapies of HCPT and GEM combined with low-dose tuberculin have equal efficacy. The incidence rates of bladder irritation and hematuria symptoms in the GEM group were lower than those in the HCPT group, and the overall tolerance was better in the former, so GEM can be considered as an ideal bladder perfusion chemotherapy drug.*

Key words: *hydroxycamptothecin, gemcitabine, tuberculin, non-muscle invasive bladder cancer, transurethral resection of bladder tumor, bladder perfusion*

Introduction

Bladder cancer is one of the most common malignant tumors of the urinary system in China, and more than 90% belong to urothelial cell carcinoma, and about 70% of the patients diagnosed with urothelial cell carcinoma are with non-muscle invasive bladder cancer (NMIBC) [1]. Transure-

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thral resection of bladder tumor (TURBT) is the first choice for the treatment of NMIBC. It has the characteristics of small trauma and quick recovery after operation. However, the recurrence rate after NMIBC operation is reported to be as high as 50-70%, and the tumor grade of malignancy in a few recurrence cases is increased, which is still a big problem at present in the treatment of bladder tumor [2]. Bladder perfusion therapy is an effective means to prevent bladder cancer recurrence, which can effectively prolong the time to recurrence, reduce the recurrence rate and greatly improve the prognosis of bladder cancer [3]. There are many kinds of drugs clinically used for bladder perfusion chemotherapy, but there is no clear consensus on which drug has more advantages.

Hydroxycamptothecin (HCPT) is an early drug used for postoperative perfusion chemotherapy of bladder tumor, showing good efficacy. Gemcitabine (GEM) intravenous chemotherapy has a good control effect on bladder urothelial carcinoma, and it has been reported that bladder perfusion is also effective, but the authoritative and accurate clinical data confirming its efficacy and safety in perfusion are not enough [4,5]. There are few studies on the comparison between GEM and HCPT perfusion. Recent studies have found that the non-specific immunopotentiator tuberculin (BCG) can act on the detrusor muscle of the bladder, reduce the invasive progression of superficial cancer and promote tumor cell shedding and necrosis. However, there are many toxic and side effects with the conventional dose, and some patients are forced to stop treatment due to intolerance [6-9]. In this study, three commonly used perfusion drugs, HCPT and GEM alternatively combined with low-dose BCG were applied to perform bladder perfusion treatment after TURBT in NMIBC patients, and to compare and analyze the recurrence rate of bladder tumor within 2 years after drug application and the adverse reactions of patients in the course of perfusion treatment. This study aimed to evaluate the feasibility and safety of clinical application of different drugs, thus providing a comprehensive reference for selecting a safer and more effective perfusion scheme in the clinical treatment of NMIBC patients.

Methods

General data

The medical records of patients treated in the Urology Department from October 2014 to December 2016 and finally diagnosed with bladder cancer were collected and analyzed. Inclusion criteria were as follows: 1) patients who received TURBT for the first time after admission; 2) patients with NMIB urothelial carcinoma confirmed by postoperative pathological results; and 3) patients undergoing urography and plain or enhanced computed tomographic urography (CTU) examination before operation, with no tumor invasion or pelvic lymph node enlargement. Exclusion criteria: 1) patients with previous tumor history; 2) patients with other systemic refractory diseases, such as bleeding disorders that cannot be corrected, serious heart or lung dysfunction; or 3) patients who were not treated in accordance with the doctor's advice.

The comparison of general clinical data between the two groups is shown in Table 1. There were no statistically significant differences between the two groups in

Table 1. Baseline demographic and clinical characteristics of the studied patients

Characteristics	*HCPT group (n=85) n (%)*	*GEM group (n=85) n (%)*	*p value*
Age, years (mean±SD)	45.48±10.44	48.52±12.81	0.092
Gender			0.528
Male	55 (64.7)	50 (58.8)	
Female	30 (35.3)	35 (41.2)	
TNM stage			0.534
Ta	47 (55.3)	52 (61.2)	
T1	38 (44.7)	33 (38.8)	
Pathologic grade			0.588
Low	63 (74.1)	67 (78.9)	
High	22 (25.9)	18 (21.2)	
Tumor size (cm) (mean±SD)	3.01±1.31	2.95±1.14	0.751
Number of tumors			0.349
1	54 (63.5)	47 (55.3)	
≥2	31 (36.5)	38 (44.7)	

HCPT: hydroxycamptothecin; GEM: gemcitabine; TNM: tumor, lymph node, metastasis

clinical data such as gender, age, tumor number, tumor size, pathological type and pathological stage after operation, which were comparable. All the selected patients complied with the Helsinki Declaration, they were informed accordingly and signed the informed consent. This study was approved by the ethics committee of the Central Hospital of Wuhan.

Treatments performed

A total of 170 patients were treated with TURBT, and then they were randomly divided into the HCPT and low-dose BCG perfusion group (HCPT group, n=85) and the GEM and low-dose BCG perfusion group (GEM group, n=85) according to the different perfusion drugs used. The HCPT group and GEM group were given 40 mL 0.9% sodium chloride solution+30 mg HCPT and 50 mL 0.9% sodium chloride solution+1000 mg GEM, respectively, for the first time to start perfusion therapy within 24 h after TURBT. In order to prevent the wound and the blood from absorbing too much drug, the drug was kept for 30 min after the first perfusion and then emptied, and the position was selected according to the tumor location so as to make the drug fully contact with the tumor margin as far as possible.

HCPT group: The bladder was perfused with 10 mg HCPT + 20 mL 0.9% NaCl solution on the 7th day after operation and 10 mg BCG + 40 mL 0.9% NaCl solution on the 14th day after operation. After that, HCPT and BCG were perfused alternately every 3 days, that is HCPT was perfused on the 17th day after operation, BCG was perfused on the 20th day, and so on to the 56th day after operation. From day 63 after operation, HCPT and BCG were perfused alternately once every other week, 8 times each. At 183 days after operation, the two drugs were injected alternately every 15 days, 8 times each. From day 438 after operation, the two drugs were alternately infused every other month for 2 years after operation. The perfusion dose of the two drugs was the same as that in the first perfusion after operation.

GEM group: The bladder was perfused with 300 mg GEM + 20 mL 0.9% sodium chloride solution on the 7th day after operation and with 10 mg BCG + 40 mL 0.9% sodium NaCl on the 14th day after operation. Subsequently, GEM and BCG were perfused alternately at the same intervals as those in HCPT group, and the two drugs were perfused at the same dose as that in the first time after operation.

The patients were not allowed to drink water 4 h before perfusion, and the bladder was emptied. After the injection of the drug into the bladder through urinary catheter, the patients were asked to lie in supine, prone, left lateral and right lateral positions for 15 min, respectively, so that the drug could fully contact the bladder wall and the drug could be left in the bladder for 1 h before emptying.

Observational indices

Patients enrolled were followed up monthly with blood and urine routine tests and renal function examinations, and they were asked about any adverse reactions after treatment. Cystoscopy was performed every 3 months during 2 years, color ultrasound of the urinary system was conducted every 6 months, and chest X-ray, upper urinary tract B-ultrasound and pelvic computed tomography (CT) were carried out once a year. The recurrence rate, progression rate and drug adverse reactions of the two groups were followed up and compared during 2 years. During the follow-up period, if tumor recurrence was found, the time to recurrence was recorded. A new lesion shown in cystoscopy or biopsy but without muscle infiltration found by pathological examination was regarded as tumor recurrence. If the patients showed no recurrence by cystoscopy or color ultrasound, this was regarded as no tumor recurrence.

Statistics

SPSS 22.0 software package (IBM, Armonk, NY, USA) was used for statistical analysis. Measurement data were expressed as mean ± standard deviation (x±s), and the comparison between two groups was tested by the t-test or log-rank test. Count data were expressed as percentage (%), and assessed with x^2 test. The Kaplan-Meier method was used to plot survival curves. $P<0.05$ denoted that the difference was statistically significant.

Results

Preoperative general data

In this study, 170 patients with NMIBC were selected, including 105 males (61.8%) and 65 females (38.2%) aged 41-70 years (average 47.02±11.18). In the HCPT group, there were 54 cases (63.5%) with single tumor and 31 cases (36.5%) with multiple tumors, with average tumor diameter 3.01±1.31 cm. In the GEM group, there were 47 cases (55.3%) with single tumor and 38 cases (44.7%) with multiple tumors with average tumor diameter 2.95±1.14 cm. After operation 63 cases (74.1%) had low grade and 22 cases (25.9%) high grade in the HCPT group. In the GEM group, 67 cases (78.9%) had low grade and 18 cases (21.2%) high grade. In terms of TNM stage, 47 cases (55.3%) had TA stage and 38 cases (44.7%) T1 stage in the HCPT group. In the GEM group, 52 cases (61.2%) had TA stage and 33 cases (38.8%) T1 stage. There was no significant difference in the basic data between the two groups of patients ($p>0.05$) (Table 1).

Comparison of the clinical efficacy between the two groups

The patients were followed up for 24 months, and no patient died during the follow-up period. In the HCPT group, 5 cases were lost to follow-up, and 80 cases were followed-up completely, including 15 cases of tumor recurrence with a recurrence rate of 18.75% and 4 cases of tumor progression with a progression rate of 5%. In the GEM group, 4 cases were lost to follow-up, and a total of 81 cases were

followed-up completely, including 11 cases of tumor recurrence, with a recurrence rate of 13.58%, and 1 case of tumor progression, with a progression rate of 1.23%. There were no significant differences in the recurrence rate and progression rate between the two groups (p=0.399 and p=0.210, respectively) (Figure 1). The survival time without recurrence in each group within 2 years was compared (Figure 2) and the log-rank test revealed no statistically significant difference between the two groups (p>0.05).

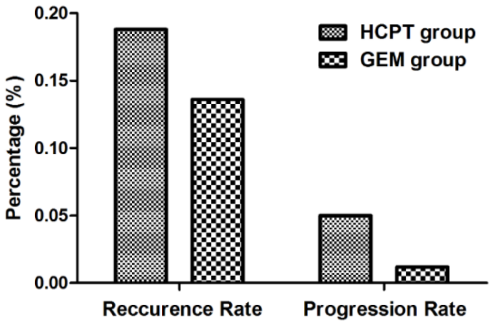

Figure 1. The recurrence rate and progression rate of nonmuscle-invasive bladder cancer after transurethral resection of bladder cancer of the patients in the two groups. The recurrence rate was 18.75% and 13.58% (p=0.399) in the HCPT group and GEM group respectively, and progression rate was 5% and 1.23% (p=0.210), respectively.

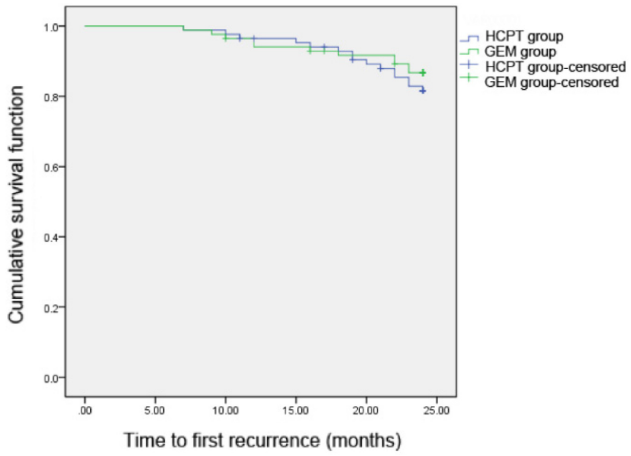

Figure 2. Kaplan-Meier analysis for recurrence-free survival of the patients in the two groups. Log-rank test indicated no statistically significant difference in recurrence-free survival rate of patients in the two groups (p>0.05).

A total of 26 patients with tumor recurrence within 2 years were analyzed, including 17 patients aged >65 years old and 9 patients aged <65 years old. There were 14 males and 12 females. In terms of TNM stage, there were 7 cases with TA stage and 19 cases with T1 stage. The average tumor size was >3 cm in 18 cases and <3 cm in 8 cases. The tumor pathological grade was high in 19 cases and low in 7 cases. There were 15 cases with multiple tumors and 11 cases with single tumor. The disease recurred in 15 cases in the HCPT group and in 11 cases in the GEM group. Multivariate logistic regression analysis showed that TNM stage, tumor size and tumor pathological grade were independent risk factors for tumor recurrence (p=0.0021, p=0.032, p<0.001, respectively) (Table 2).

Comparison of adverse reactions

After performing the related perfusion drugs, the adverse reactions in each group of patients were followed-up, mainly including whether there were symptoms such as bladder irritation, hematuria, dysuria, fever and rash. After symptomatic treatment according to different symptoms and delayed perfusion time, the adverse reactions could be relieved and the patients continued receiving their perfusion treatment.

Both groups of patients had no dysuria after perfusion. After the operation, bladder irritation occurred in 16 cases (20.0%) in the HCPT group and 6 cases (7.4%) in the GEM group, and the difference between the two groups was statistically significant (p=0.046). Hematuria occurred in 9 cases (11.3%) in the HCPT group and 2 cases (2.5%) in the GEM group, showing a statistically significant difference (p=0.037). The incidence rates of bladder irritation and hematuria in the GEM group were evidently lower than those in the HCPT group. The incidence rates of rash, fever and gastrointestinal

Table 2. Multivariate analysis of risk factors of tumor recurrence

Risk factors	*OR*	*95% CI*	*p value*
Age, years (>65)	2.296	0.960~5.491	0.087
Gender (male)	1.472	0.634~3.416	0.387
Tumor stage	4.802	1.893~12.182	0.021
Tumor size (>3cm)	3.641	1.483~8.938	0.032
Pathologic tumor grade	9.937	3.949~25.005	0.001
Multifocal tumor	1.087	0.466~2.535	0.832
HCPT+BCG instillation	0.694	0.298~1.613	0.523

OR: odds ratio; CI: confidence interval; HCPT: hydroxycamptothecin; BCG: bacillus Calmette Guerin

Table 3. Comparison of adverse reaction in the two studied groups

Adverse reactions	*HCPT group* *n (%)*	*GEM group* *n (%)*	*p value*
Bladder irritation symptoms	16 (20.0)	6 (7.4)	0.046
Hematuria	9 (11.3)	2 (2.5)	0.037
Rash	4 (5.0)	1 (1.2)	0.367
Fever	13 (16.3)	6 (4.9)	0.143
Gastrointestinal AR	3 (3.8%)	1 (1.2)	0.742

HCPT: hydroxycamptothecin; GEM: gemcitabine; AR: adverse reaction

reactions in the two groups were not statistically significant (p>0.05). The incidence rate of various adverse reactions in the two groups are summarized in Table 3.

Discussion

Transitional cell bladder tumors are the most common tumors in the urinary system, and their recurrence rate can reach 80% after surgical resection. Bladder perfusion of drugs can eliminate residual lesions or carcinoma *in situ*, reduce or delay tumor recurrence, prevent tumor infiltration and improve survival and quality of life of patients [9]. Commonly used drugs for bladder perfusion after operation are chemotherapeutic drugs and immune agents.

HCPT is a new anticancer molecule extracted from the Chinese herbal plant Camptotheca acuminata, and it is the only anticancer drug that can selectively inhibit Topol I. HCPT has a molecular weight of 364.34 kD and is basically not absorbed by bladder mucosa, so its systemic effects are very mild or absent. HCPT controls DNA replication, blocks DNA synthesis, interferes with the cell cycle, causes DNA breaks and degrade by inhibiting the normal function of Topol I rejoining DNA broken ends and further causing DNA damage, resulting in apoptosis of cancer cells under the synergistic effect of various regulatory proteins in the body [10,11]. GEM is a deoxycytidine analogue, which belongs to cell cycle-specific drugs. It mainly acts on tumor cells in DNA synthesis phase and can prevent tumor cells in G1 phase to enter the S phase under certain conditions [12]. Some studies have also shown that GEM can also act on RNA of tumor cells and affect its synthesis, thus inhibiting the proliferation of tumor cells [13]. Besides, GEM has a large molecular weight and is not easily absorbed by bladder mucosa, it has good fat solubility which is also conducive to its clinical promotion and application [14].

BCG is a non-specific immunopotentiator, which can penetrate deeply into the detrusor muscle of bladder and act on them. It is the only perfusion drug that can reduce the invasive progression of superficial cancer. BCG can accelerate the induction of immune responses, increase the body's immune function, enhance macrophage function, activate T and B lymphocytes, and improve humoral and cellular immune functions [15]. In addition, BCG can cause local inflammatory reaction and make a large number of lymphocytic infiltrate under the mucosa. In particular, a large number of T cells proliferate rapidly. The lymphatic factors secreted by BCG (such as IL-2 and TNF) enter the lesions in large quantities, destroying the tumor growth environment and promoting falling off and necrosis of tumor cells [16]. Therefore, BCG can reduce the total cystectomy rate and improve the long-term survival rate and quality of life of patients [17]. In the past, bladder perfusion with conventional dose (75-120 mg/perfusion) has achieved good results, but with many side effects, such as granuloma of posterior urethra, tuberculosis of epididymis and prostate, BCG hepatitis and acute renal failure, so some patients were forced to stop perfusion treatment [18].

The different mechanisms of action and possible adverse reactions of various drugs should be fully taken into account in clinical single drug bladder perfusion to find a more appropriate treatment scheme [19]. At the same time, based on the different action characteristics of various drugs, many authors are currently exploring different application methods of bladder perfusion chemotherapy drugs, such as combined perfusion chemotherapy and sequential perfusion chemotherapy [20]. Some studies have revealed that combined perfusion chemotherapy and sequential perfusion chemotherapy can produce synergistic effects between drugs and better prevent bladder tumor recurrence, and the adverse reactions produced during perfusion do not significantly increase compared with single drug therapy [21].

In this study, two groups of drugs combined with low-dose BCG were used to prevent tumor recurrence after TURBT in patients with NMIBC. The

results demonstrated that there were no significant differences in tumor recurrence rate and progression rate between the two groups within 2 years. It can be considered that HCPT and GEM combined with low-dose BCG, respectively, have the same efficacy in preventing bladder tumor recurrence and progression. In terms of adverse reactions and safety during combined perfusion, no significant differences were found in the incidence rates of adverse reactions such as dysuria, fever, rash and gastrointestinal reactions between the two groups, but patients in the HCPT group were more likely to have bladder irritation and hematuria. The overall tolerance in the GEM group was good, and GEM could be considered as an ideal chemotherapy drug for bladder perfusion.

In this study, bladder perfusion of HCPT and GEM combined with low-dose BCG, respectively, were compared, so as to provide a reference for clinical formulation of bladder perfusion chemotherapy. Due to the limitation of the study sample size, the 2-year recurrence rate, progression rate and incidence of adverse reactions in this study were analyzed, so as to compare the efficacy and safety of each group of drugs, and during the follow-up period the description of clinical symptoms of patients inevitably had some subjectivity, thus affecting the final results. At the same time, the number of samples was small, which inevitably led to certain one-sidedness in the final result. There is still a need for more rigorous research and discussion with large-sample data.

Conclusion

For NMIBC patients after TURBT, bladder perfusion chemotherapy of HCPT combined with low-dose BCG and GEM combined with low-dose BCG have equal efficacy. The incidence rates of bladder irritation and hematuria symptoms in the GEM group are lower than those in the HCPT group, and the overall tolerance is better in the former, so GEM can be considered as an ideal bladder perfusion chemotherapy drug.

Conflict of interests

The authors declare no conflict of interests.

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