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Original Research Article

Effect of sequential gemcitabine and epirubicin therapy on high-risk non-muscle invasive bladder cancer following transurethral bladder tumour resection

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Abstract

Purpose: *To investigate the efficacy of sequential gemcitabine and epirubicin therapy on high-risk non-muscle invasive bladder cancer (NMIBC) after transurethral resection of bladder tumour (TURBT).*
Methods: *The records of 100 high-risk NMIBC patients, who underwent TURBT at the Tongling People's Hospital, Tongling City, China between January 2020 and March 2023 were retrospectively analyzed. A total of 46 patients, treated with epirubicin after operation, were assigned to control group, while 54 patients, treated with both gemcitabine and epirubicin, were included in the study group. DKK-1 and YKL-4 levels were assayed by immunomagnetic bead-based liquid chip technology and enzyme-linked immunosorbent assay, respectively. Furthermore, treatment efficacy was determined and compared between the two groups.*
Results: *There were no significant differences in the pre-treatment DKK-1 and YKL-40 levels between the two groups ($p > 0.05$). However, both groups experienced a significant drop in post-treatment levels, with significantly lower post-treatment levels in the study group ($p < 0.05$). There were no significant differences in catheter retention time and hospitalization time between the two groups ($p > 0.05$). The study group achieved a significantly better overall response rate than the control group. The pre-treatment SF-36 scores of the two groups were similar, while their post-treatment SF-36 scores increased significantly ($p < 0.05$).*
Conclusion: *Sequential therapy with gemcitabine and epirubicin is effective in the therapy of high-risk NMIBC after TURBT. It significantly lowers DKK-1 and YKL-40 levels, improves postoperative quality of life and reduces the postoperative recurrence rate without increasing adverse reactions and affecting the catheter retention and hospitalization times. A more comprehensive analysis is required to obtain improved outcomes.*

Keywords: *Gemcitabine, Epirubicin, Transurethral Resection of Bladder Tumor, High-risk non-muscle invasive bladder cancer, Efficacy*

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INTRODUCTION

Bladder cancer (BC) is a common malignant tumour of the urinary system [1]. It is classified into non-muscle invasive bladder cancer (NMIBC) and muscle- invasive bladder cancer (MIBC) [2]. Cancer cells that have breached the mucosal layer but have not reached the muscular layer are referred to as NMIBC [3-5]. Transurethral resection of bladder tumour (TURBT) is a frequently used treatment for early

BC [6]. However, for high-risk NMIBC, transurethral resection alone may not achieve a complete cure. Thus, adjuvant therapy such as chemotherapy or radiotherapy may be required [7]. Nowadays, postoperative chemotherapy drugs used for high-risk NMIBC include gemcitabine, epirubicin, doxorubicin and cisplatin [8].

Gemcitabine is a novel type of anti-tumour drug that blocks the proliferation of tumour cells and lowers tumour recurrence rate. It demonstrates few toxic side effects and a low incidence of adverse reactions. In addition, it also contributes to good tolerance of patients [9]. After entering the nucleus and binding to DNA, epirubicin inhibits DNA polymerase, thereby hindering DNA replication and transcription, which effectively prevents tumour recurrence with low side effects and high safety [10].

Cao *et al* revealed that gemcitabine is effective and well tolerated in postoperative chemotherapy of BC [11]. However, the impact of sequential gemcitabine and epirubicin therapy on high-risk NMIBC after TURBT have been under-reported. Accordingly, this study aims to analyse the impact of sequential gemcitabine and epirubicin therapy on high-risk NMIBC after TURBT, providing a reliable reference for the therapy of high-risk NMIBC after TURBT.

METHODS

Patient data

This retrospective analysis focused on the recorded data of 100 patients with high-risk NMIBC who underwent TURBT at the Tongling People's Hospital, Tongling, China between January 2020 and March 2023. Among these patients, 46 patients treated with epirubicin after operation were assigned to control group, while the remaining 54 patients, treated with both gemcitabine and epirubicin, were included in study group. The study was approved by the Medical Ethics Committee of Tongling People's Hospital, China (approval no. 202406) and met the Declaration of Helsinki criteria [12].

Inclusion criteria

The included patients were those who were confirmed to have high-risk NMIBC through pathological diagnosis; patients who successfully underwent TURBT; patients who had basically normal liver and kidney functions, blood routine results and could tolerate the drugs adopted; and patients who had detailed clinical records.

Exclusion criteria

The study excluded patients falling within the following categories: Patients with suspected or confirmed bladder perforation during operation, or exhibited obvious postoperative gross hematuria that was not suitable for immediate perfusion; patients who had urinary system infection, lymphatic or distant metastasis of tumour; patients with a history of urinary tract stricture, defect, filling or other serious bladder disease; patients with organ dysfunction; and patients who had a history of mental illness.

Therapeutic regimen

Patients in both groups underwent TURBT and received treatment with chemotherapeutic drugs within 1 week after operation. Control group was treated with epirubicin. Specifically, 50 mg of epirubicin (Zhejiang Hisun Pharmaceutical Co. Ltd, State Food and Drug Administration (SFDA), approval no. H19990279) was mixed with normal saline to prepare the perfusion solution.

The patient was instructed to empty the bladder and a urinary catheter was placed into the bladder. Then, the perfusion solution was infused and retained in the bladder for 2 h. The patient's posture was adjusted (prone position, left and right supine positions as well as supine position) every 30 min to ensure that the bladder wall fully contacted with the drug solution. The infusion was conducted once a week for 8 weeks followed by once a month for another 10 months. The total treatment lasted for 12 months. Study group was additionally treated with gemcitabine. The first intravesical instillation of epirubicin was conducted in the same way and with the same dosage as control group. For the second sequential treatment, gemcitabine (Huangshi Feiyun Pharmaceutical Co. Ltd, SFDA, approval no. H20133195) was used.

The perfusion solution was prepared by dissolving 1000 mg of gemcitabine in 30 mL of normal saline and the solution administered in the same way as control group. The two drugs were used alternately, once a week for 8 weeks followed by once a month, for another 10 months. The total treatment also lasted for 12 months.

Evaluation of parameters/indices

Serum DKK-1 and YKL-40 levels

Fasting venous blood was drawn from the patients before and 18 months after treatment. The blood samples were centrifuged in Eppel

tubes at low temperature to obtain the serum. The sera were stored in a refrigerator at – 80 ℃ for the determination of DKK-1 and YKL-40 levels. DKK-1 and YKL-4 levels were assayed by immunomagnetic bead-based liquid chip technology and enzyme-linked immunosorbent assay, respectively.

Efficacy

The chemotherapeutic effects of the two groups were compared with reference to the Radiologist's Guide to Response Evaluation Criteria in solid tumours (version 1.1) [13]. Complete remission (CR) was defined as the absence of target lesion; partial remission (PR) as a ≥ 30 % decrease in the sum of the longest diameters of baseline lesions; stable disease (SD) as a decrease that did not meet the criteria for partial remission; and disease progression (DP) as a ≥ 20 % increase in the sum of the longest diameters or the appearance of new lesions. The overall response (ORR) rate was calculated using Eq 1.

ORR = ((CR+PR)/TN)100 …… (1)

where TN is the total number of cases.

Postoperative recurrence rate

An 18-month follow-up was conducted on the patients after treatment and the postoperative recurrence rate within 18 months after treatment were recorded and analyzed for both groups.

Catheter retention time and hospitalization time

The catheter retention time and hospitalization time were recorded and compared between the two groups.

Quality of life (QoL) assessment

The MOS 36-Item Short-Form Health Survey (SF-36) was applied to evaluate the patients' QoL before and 18 months after treatment.

Adverse reactions

Adverse reactions in both groups were analysed.

Statistical analyses

The SPSS 22 statistical software was used to process all data and GraphPad Prism 8 for data visualization. Count data were described as rate and inter-group comparisons were conducted using Chi-square test. Measurement data were described as mean ± standard deviation (SD) and comparisons between groups were made using the *t*-test. A *p*-value of less than 0.05 indicates statistically significant difference.

RESULTS

Patients' baseline data

There were no significant differences between the two groups with regard to gender, age, body mass index, multiple tumors, history of smoking, as well as place of residence ($p > 0.05$; Table 1).

Table 1: Baseline data of the two groups

Variable	Sub-factor	Study group	Control group	χ^2	*P*-value
Age					
	<55 years	25	22	0.023	0.879
	≥55 years	29	24		
Gender					
	Male	34	25	0.762	0.383
	Female	20	21		
BMI					
	≥23kg/m^2	21	19	0.060	0.806
	<23kg/m^2	33	27		
Multiple tumors					
	Yes	10	8	0.021	0.884
	No	44	38		
History of smoking					
	Yes	35	27	0.395	0.530
	No	19	19		
Place of residence					
	Rural area	38	26	2.068	0.151
	Urban area	16	20		

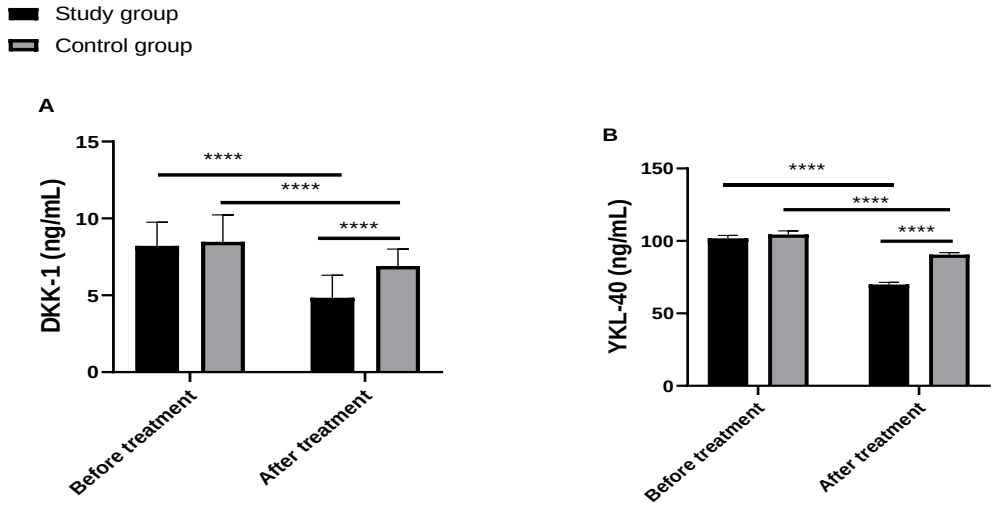

Figure 1: Changes in pre- and post-treatment DKK-1 and YKL-40 levels. (A) Pre- vs. post-treatment DKK-1 levels in both groups. (B) Prior- vs. post-treatment YKL-40 levels in both groups. ****$P < 0.0001$

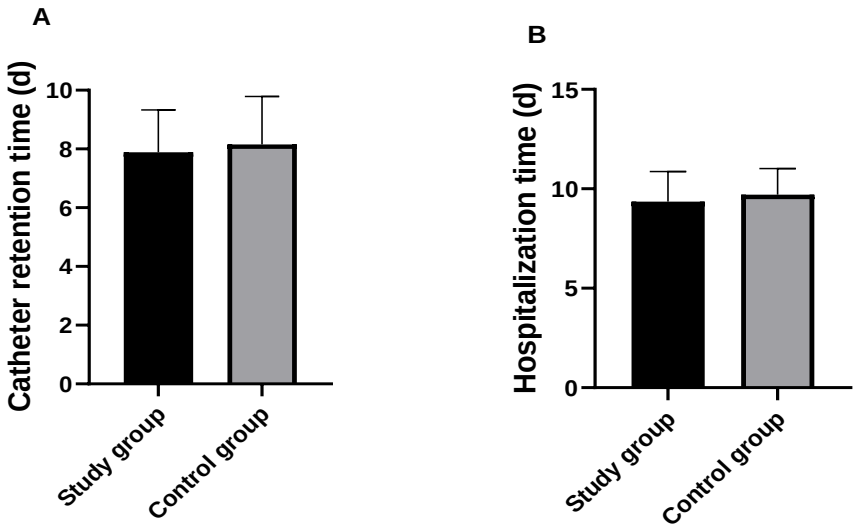

Figure 2: Catheter retention time and hospitalization time. (A) Comparison of catheter retention time between the two groups. (B) Comparison of hospitalization time between the two groups

DKK-1 and YKL-40 levels

The pre-treatment DKK-1 and YKL-40 levels of the two groups were not significantly different ($p > 0.05$), whereas the post-treatment levels in both groups dropped significantly ($p < 0.0001$), with even more significant drops in study group ($p < 0.0001$; Figure 1).

Catheter retention time and hospitalization time

The catheter retention time and hospitalization time were not significantly different between the control and study groups ($p > 0.05$; Figure 2).

Efficacy

In contrast to control group, study group yielded a significantly better overall response rate ($p = 0.012$; Table 2).

Quality of life (QoL)

The pre-treatment SF-36 scores of the two groups were not significantly different ($p > 0.05$), whereas their post-treatment SF-36 scores improved significantly ($p < 0.0001$), with higher scores in study group ($p < 0.0001$; Figure 3).

Table 2: Comparison of clinical efficacy between the groups

Group	Complete remission	Partial response	Stable disease	Progression of disease	Overall response
Study	20 (37.04)	25 (46.30)	8 (14.81)	1 (1.85)	45 (83.34)
Control	9 (19.57)	19 (41.30)	16 (34.78)	2 (4.35)	28 (60.87)
χ^2					6.360
P-value					0.012

Table 3: Incidence of adverse reactions

Group	Urinary tract irritation	Myelosuppression	Haematuria	Gastrointestinal adverse reactions	Total adverse reactions
Study	2 (3.70)	0 (0.00)	1 (1.85)	1 (1.85)	4 (7.40)
Control	5 (10.87)	1 (2.17)	2 (4.35)	3 (6.52)	11 (23.91)
χ^2					5.085
P-value					0.024

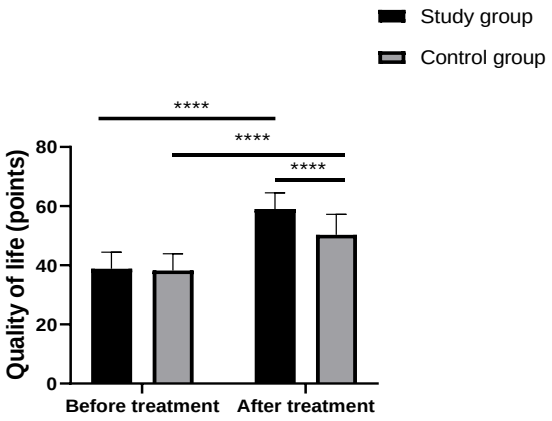

Figure 3: Pre- and post-treatment quality of life in the two groups. **** $P < 0.0001$

Incidence of adverse reactions

Study group displayed a significantly lower overall incidence of adverse reactions, including urinary tract stimulation, myelosuppression, haematuria and gastrointestinal adverse reactions, compared to control group ($p = 0.024$; Table 3).

Postoperative recurrence rate

The recurrence of NMIBC within 18 months after treatment were compared between the two. There were 4 cases (7.41 %) of recurrence in study group and 14 cases (30.43 %) of recurrence in control group. Study group presented a significantly lower postoperative recurrence rate compared to control group ($\chi^2 = 8.924$, $p = 0.003$).

DISCUSSION

Bladder cancer is a common malignant tumour affecting the bladder mucosa, particularly in the middle-aged and elderly [2]. It mainly includes NMIBC, which manifests primarily as lower urinary tract irritation symptoms such as discomfort during urination, urgency and frequent urination. This condition not only significantly impacts patients' quality of life but also imposes a significant economic burden on patients and society [3]. Transurethral resection of bladder tumour (TURBT) is the preferred clinical treatment for NMIBC. While effective in removing the tumour and prolonging the survival time, it is associated with a high risk of recurrence. Recurrence not only prolong the treatment duration but also increases the risk of tumour malignancy [14].

Chemotherapy has been found to effectively prevent postoperative recurrence of cancer [15]. Gemcitabine, a chemotherapeutic agent that blocks the progression from G1 phase to S phase is now considered a first-line treatment for BC [16]. Epirubicin, an anthracycline antibiotic with anti-neoplastic properties, is less toxic than doxorubicin and is highly suitable for chemotherapy after TURBT. Previous research has characterized epirubicin as strong anticancer activity, broad anticancer spectrum, low drug resistance and rapid efficacy with high safety [17]. The combination use of drugs helps to enhance the efficacy of treatment, reduce side effects and lower drug resistance in patients with high-risk NMIBC after TURBT.

The DKK-1 has been identified as a primary regulator that negatively regulates the Wnt signal pathway [18], while KL-40, a novel glycosyl hydrolase, exerts a direct effect on tumour cell invasion and metastasis [19]. This study also analyzed pre- and post-treatment DKK-1 and YKL-40 levels. The two groups did not differ significantly in pre-treatment DKK-1 and YKL-40 levels. However, post-treatment levels in both

groups decreased significantly, with study group showing significantly lower levels.

The results implied that sequential treatment with gemcitabine and epirubicin lowered DKK-1 and YKL-40 levels in patients compared to epirubicin alone. Furthermore, the two groups had similar catheter indwelling and hospitalization time, indicating that the combined therapy did not extend these durations. This study reveals further a significantly lower overall response rate in control group than in the other. The findings suggest that the combined use of gemcitabine and epirubicin was more effective in the therapy of high-risk NMIBC after TURBT possibly because gemcitabine improves its activity through various mechanisms and is retained in tumour cells for a longer duration. When it combines with epirubicin, gemcitabine promotes tumour cell apoptosis to the greatest extent and prevents multidrug resistance. Similarly, Campone *et al* reported good tolerability and activity of gemcitabine combination with epirubicin in patients with metastatic breast cancer [20].

The SF-36 was applied for QoL evaluation. Prior to treatment, the two groups did not significantly differ in SF-36 scores. However, their post-treatment SF-36 scores increased significantly, with higher scores in study group. These findings suggested that in the aspect of chemotherapy for high-risk NMIBC after TURBT, combined chemotherapy improved the QoL of patients. Finally, control group showed a significantly higher incidence of adverse reactions than study group. The finding suggests that combined chemotherapy reduced adverse reactions in patients. Additionally, the results revealed a significantly lower postoperative recurrence rate within 18 months after treatment in study group than in control group, implying the positive effect of combined therapy in controlling the postoperative recurrence rate of patients.

Limitations of the study

The study has some limitations. Firstly, the limited sample size of this study may result in some biases in the conclusion of the study. In addition, the study lacks data on the long-term prognosis of patients, focusing solely on the short-term efficacy.

CONCLUSION

Sequential therapy with gemcitabine and epirubicin is effective in the treatment of high-risk NMIBC after TURBT. It substantially lowers DKK-1 and YKL-40 levels, improves postoperative QoL and reduces postoperative recurrence rate, without increasing adverse reactions and affecting the catheter retention and hospitalization times. The long-term effect of this combined therapy needs further exploration.

DECLARATIONS

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Ethical approval

The study was approved by the Medical Ethics Committee of Tongling People's Hospital, China (approval no. 202406).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Jinhai Zhu and Junjie Qian conceived and designed the study, and drafted the manuscript. Zeping Zuo and Hongtao Yu collected, analyzed and interpreted the experimental data. Junjie Qian revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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