A comparative study of gemcitabine and epirubicin in adjuvant chemotherapy of non muscle invasive bladder cancer

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Abstract

BACKGROUND: To compare the efficacy and safety of gemcitabine and epirubicin curing for patients with non muscle invasive bladder cancer (NMIBC).

METHODS: from October 2014 to October 2017, 86 patients with non muscle invasive bladder cancer diagnosed by transurethral resection of bladder tumor (TURBT), in urology department of Wenling Hospital Affiliated to Wenzhou Medical University were analyzed retrospectively. Among them, 42 were treated with gemcitabine and the other 44 with epirubicin. The two groups were treated with epirubicin or gemcitabine within 24 hours after operation, and bladder perfusion once a week was performed continuously after the first week of operation, a total of 8 times, and after that once a month till one year after operation. The clinical efficacy and adverse reactions of the two groups were compared. Kaplan-Meier was used to compare the recurrence free survival time of tumor after operation and Cox proportional risk model was used to analyze various factors affecting the prognosis.

RESULTS: 1. There was no significant difference between the two groups (P > 0.05). 2. The adverse reactions of the two groups were mainly bladder irritation, gross hematuria, fever, nausea and vomiting. The incidence of bladder irritation and gross hematuria in epirubicin group was significantly higher than those in gemcitabine group (P < 0.05), which meant it had statistical significance. There was no significant difference on the other side-effects between the two groups (P > 0.05). 3. The results of Kaplan-Meier survival analysis showed that the median tumor recurrence free survival time of gemcitabine group was 29.7 months, the one-year tumor recurrence free survival rate was 81%, and the two-year tumor recurrence free survival rate was 57%; while the median tumor recurrence free survival time of epirubicin group was 28.8 months, the one-year tumor recurrence free survival rate was 72%, and the two-year tumor recurrence free survival rate was 50%. Multivariate Cox analysis also showed that age, as well as tumor grade was independent risk factors for prognosis.

CONCLUSION: Gemcitabine assisted with intravesical instillation chemotherapy is more effective with fewer side-effects, which is worthy of further study. Age and tumor grade are independent risk factors for prognosis.
Background
Transurethral resection of bladder tumor combined with postoperative bladder perfusion is the standard treatment for NMIBC[1]. The main measure to prevent recurrence of NMIBC is to infuse chemotherapy drugs into bladder after TURBT. In this study, we will compare the efficacy, toxicity and survival rate of patients treated with gemcitabine and epirubicin after TURBT, which provides reference for therapy.

Methods
1 General information
This study included 86 patients with NMIBC from October 2014 to October 2017 in Wenling Hospital Affiliated to Wenzhou Medical University. Specific conditions of patients as follows: 73 males and 13 females with a median age of 65; 61 with single tumor, 25 with multiple tumor; 71 with tumor diameter less than 3 cm, 15 with tumor diameter greater than 3 cm; 58 with tumor stage of Ta, 28 with tumor stage of T1; 28 with high-grade tumor and 58 with low-grade tumor. Among them, gemcitabine was used in 42 cases and epirubicin was used in 44 cases. Inclusion criteria: postoperative pathology was in line with the NMIBC diagnostic criteria, without any treatments before; Patients and their families has signed informed consent; With detailed medical records and follow-up information; Patients were treated by the same surgeon during the whole therapy. Exclusion criteria: Patients with urinary tract infection, severe liver and kidney dysfunction or congenital heart disease or any other cardiac dysfunction and other important organ dysfunctions, along with those who are allergic to the drugs used.

2 Treatment plans
86 patients confirmed with NMIBC diagnosis after TURBT were given intravesical chemotherapy. 42 of them were given gemcitabine solution (Jiangsu Haosen Pharmaceutical Co., Ltd., GJZ h20030105). Mixing 1000 mg of gemcitabine with 50 ml of normal saline, and patients were required to empty urine before the program. Then infusing gemcitabine mixture liquid into the bladder through a disposable catheter under strict aseptic precautions. Body position (recumbent position, left recumbent position, right recumbent position and prone position) was changed once every 30
minutes to make the gemcitabine mixture liquid fully touch with the bladder walls, and finally the gemcitabine mixture liquid was kept in the bladder for 2 hours. While the other 44 cases were treated with epirubicin scheme (Haizheng Pfizer Pharmaceutical Co., Ltd., GJZ h19990280)50 mg epirubicin was mixed and dissolved in 50 ml normal saline, and as the perfusion time, body position, duration and treatment processing were the same as those of gemcitabine solution. Both of the two groups were treated with epirubicin or gemcitabine chemotherapy within 24 hours after operation, and bladder perfusion once a week was performed continuously after the first week of operation,a total of 8 times; and after that, once a month till one year after operation. If any chemotherapy-related adverse reactions happened during perfusion, the patients would be treated based on symptoms.

3. Evaluation of efficacy and adverse reactions
The patients were re-examined once every 3 months in the first year, B-ultrasound, CT or MRI in the urinary system to evaluate whether there was recurrence of bladder tumor. After that re-examination should be once every 6 months in the second year, and then once a year later. The clinical and follow-up data of the patients was recorded. Moreover, the regular follow-up was conducted by outpatient or telephone. The latest follow-up time was on October 31st, 2019. Patients with recurrence during follow-up were reevaluated and excluded from the group immediately before the recurrence time would be recorded together with operation rearranged. The recurrence-free survival rate and adverse reactions were compared between the two groups during the follow-up time.

4. Statistical methods
All statistical analyses were carried out on SPSS 22 software. X2 test was used to compare the counting data; Fisher exact probability method of four grid table data was used when 1 ≤ T < 5 or T < 1; Rank sum test was used for rank data; Kaplan-Meier and log rank test were used for postoperative survival analysis; Cox proportional risk model was used for multivariate analysis. And when P < 0.05, it was statistically significant.

Results
1. Comparison of general conditions between the two groups of patients
There was no significant difference between the two groups on general conditions (including age,
gender, tumor number, tumor diameter, tumor stage, tumor grade) (P > 0.05), as shown in Table 1.

| group | Age (years) | Gender | Tumor number | Tumor diameter (CM) | Tumor stage | Tumor grade |
|-------|-------------|--------|--------------|---------------------|-------------|-------------|
|       | 60 | 60 | male | female | Single | Multiple | 3 | 3 | Ta | T1 | High grade | Low grade |
| Gemcitabine | 24 | 18 | 37 | 5 | 30 | 12 | 35 | 7 | 28 | 14 | 13 | 29 |
| Epirubicin | 31 | 13 | 36 | 8 | 31 | 13 | 36 | 8 | 30 | 14 | 15 | 29 |

X² | 1.652 | 0.660 | 0.010 | 0.034 | 0.022 | 0.096 |
P | 0.199 | 0.417 | 0.921 | 0.853 | 0.881 | 0.756 |

### 2. Comparison of main adverse reactions and side-effects between the two groups

The adverse reactions of the two groups were mainly bladder irritation, gross hematuria, fever, nausea and vomiting. The incidence of bladder irritation and gross hematuria in the epirubicin group was significantly higher than those in the gemcitabine group (P < 0.05). There was no significant difference on the other side-effects between the two groups (P > 0.05), as shown in Table 2.

| group | cases | Bladder irritation | Gross hematuria | urethral stricture | fever | nausea | vomiting |
|-------|-------|-------------------|-----------------|-------------------|-------|--------|----------|
| Gemcitabine | 42 | 3 | 1 | 0 | 0 | 1 |
| Epirubicin | 44 | 11 | 8 | 0 | 3 | 4 |

X² | — | — | — | — | — | — |
P | — | 0.039a | 0.030a | — | 0.242a | 0.361a |

Note: a Fisher exact test is used

### 3. Prognosis analysis

The two groups were followed up by telephone and outpatient, and Kaplan-Meier survival analysis was used. The results were shown in Fig. 1: the median tumor recurrence-free survival time of the gemcitabine group was 29.7 months, the one-year tumor recurrence-free survival rate was 81%, and the two-year tumor recurrence-free survival rate was 57%; While the median tumor recurrence-free survival time of epirubicin group was 28.8 months, the one-year tumor recurrence-free survival rate was 72%, and the two-year tumor recurrence-free survival rate was 50%. However, there came a obvious crossover on the nearly 30th month of follow up for the two group of patients. Considering possible confounding factors, the patients' age, gender, tumor number, tumor diameter, tumor stage, tumor grade and bladder perfusion scheme were included in the multivariate Cox proportional risk model analysis. The results showed that age and tumor grade were independent risk factors affecting the prognosis of patients, as shown in Table 3.
### Table 3 multivariate COX analysis of prognostic factors of patients

|         | B   | SE  | Wald  | df | P     | Exp(B) | CI 95.0% Lower limit | CI 95.0% Upper limit |
|---------|-----|-----|-------|----|-------|--------|----------------------|---------------------|
| age     | 0.070 | 0.019 | 14.028 | 1  | .000  | 1.073  | 1.034                | 1.113               |
| Tumor grade | 2.500 | 0.381 | 43.137 | 1  | .000  | 12.180 | 5.776                | 25.680              |

**Discussion**

The patients with NMIBC account for 70% of the primary bladder urothelial cell carcinoma [2]. At present, TURBT is the main treatment method. About 10% ~ 67% of the patients recur within 12 months after operation, and about 24% ~ 84% of the patients recur within 5 years after operation [3]. Intravesical instillation of TURBT is the main measure to prevent the recurrence of NMIBC, which can reduce the recurrence rate, improving the survival rate of the patients as well as preventing the tumor for higher level processing. Therefore, bladder perfusion after TURBT is advocated to prevent bladder tumor recurrence.

In this study, there were fewer side-effects both in the two groups, mainly for bladder irritation, hematuria, fever, nausea and vomiting. Serious adverse reactions didn’t occur both in the two groups during the perfusion treatment process. However, the incidence of side-effects in gemcitabine group was far lower than that in epirubicin group, and the incidence of bladder irritation and hematuria in epirubicin group was significantly higher than that in gemcitabine group, which showed Statistical significance (P < 0.05). There was no significant difference on the other side-effects between the two groups (P > 0.05). The adverse reactions in both groups were tolerable and disappeared within 1–2 days after perfusion, on which showed that treatment with gemcitabine was more safer based.

In terms of tumor recurrence-free survival rate, the median tumor recurrence-free survival rate in gemcitabine group was 29.7 months, the one-year tumor recurrence-free survival rate was 81%, and the two-year tumor recurrence-free survival was 57%; While the median tumor recurrence-free survival rate in epirubicin group was 28.8 months, the one-year tumor recurrence-free survival rate was 72%, and the two-year tumor recurrence-free survival was 50%. In terms of tumor recurrence-free survival rate of two years, the gemcitabine group performed better than the epirubicin group. When the patients in the two groups were followed up for nearly 30 months, there came a crossover. Considering possible confounding factors, age, gender, tumor number, tumor diameter,
tumor stage, tumor grade and bladder perfusion scheme were included in the multivariate Cox proportional risk model analysis. The results showed that age and tumor grade were independent risk factors affecting the prognosis of patients.

BCG is recognized as the best bladder perfusion drug, but its side-effects are obvious, which resulted in delaying or even pausing perfusion among the 12.5% of BCG perfusion patients [4]. Comparing the efficacy of gemcitabine and BCG infusion in the treatment of NMIBC patients with ineffective BCG treatment by DI multicenter randomized controlled study, showing that the recurrence rate of gemcitabine group was significantly lower than that of BCG group, and also the 2-year recurrence-free survival rate was higher than that of BCG group, though the disease progression rate was no difference [5]. In this study, gemcitabine group performed better than epirubicin group in median tumor recurrence-free survival time for 1-year and 2-year tumor recurrence-free survival rate. Age may be a factor that was easy to be ignored by us. As the elderly may also have higher probability of suffering from obesity, hypertension, diabetes and other chronic metabolic diseases. Furthermore, lacking of exercise is common among the elderly, which has been proved to be related to the poor prognosis of urinary system tumors [6-8]. Kluth’s researech showed that the poor performance of the specific tumor survival rate were linked to obese patients[9]. A study of 27784 patients showed that exercise was a protective factor against bladder cancer [10]. The histopathological grade of tumor was obviously related to the recurrence of patients. The higher of the grade, the easier of recurrence would be [11], which was also verified in this study. Nevertheless, unlike the traditional view, tumor number, tumor diameter and tumor stage were not reflected in this study, which was also risk factors and different from some previous literature reports. Of course, the clinical experience of surgeons along with the active change of body position during perfusion also played a vital role in this study. Considering the regional differences of patients and the BMI index, smoking, obesity and blood pressure, diabetes factors were not included in the study. Other reasons like a small number of samples in this group, the single center study, and lack of follow-up time may also make a difference.

Conclusion
In conclusion, for patients with NMIBC diagnosis after TURBT, we suggest adopting gemcitabine assisted with intravesical instillation chemotherapy, which has definite curative effect, lowering incidence of adverse reactions, with higher safety and reliability. Age and tumor grade are independent risk factors affecting the prognosis of patients.

**Abbreviations**

NMIBC: non muscle invasive bladder cancer.

TURBT: transurethral resection of bladder tumor.

**Declarations**

**Authors’ contributions**

H-BY drafted the manuscript and revised the literature. J-WW reviewed the manuscript. J-WW helped in drafting the manuscript. All authors read and approved the final manuscript.

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**Availability of data and materials**

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

**Competing interests**

The authors declare that they have no competing interests.

**Consent for publication**

Written informed consent was obtained from the patients for publication of the case report and any accompanying images. A copy of the written consent is available for review by the editor in chief of this journal.

**Ethics approval and consent to participate**

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 was obtained from all individual participants included in the study. This article does not contain any studies with animals performed by any of the authors

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Figures
Figure 1

tumor recurrence-free survival curve of two groups