

REVIEW ARTICLE

Research Progress in Neoadjuvant Chemotherapy for Bladder Cancer

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Abstract: Neoadjuvant chemotherapy is a systemic pre-operative treatment which can eliminate microscopic lesion of bladder cancer including metastatic lesion. It significantly improves 5-year survival rate of bladder cancer. For patients with non-organ-confined bladder cancer, neoadjuvant chemotherapy combined with radical cystectomy can be a better treatment option. This article covers the current status of bladder treatment and the rise of neoadjuvant chemotherapy, advantages and disadvantages of neoadjuvant chemotherapy, prediction of efficacy of neoadjuvant chemotherapy, the choices for neoadjuvant chemotherapy patient, improvement of neoadjuvant chemotherapy, and large-scale clinical trial of neoadjuvant chemotherapy for bladder cancer.

Keywords: Bladder cancer, Neoadjuvant chemotherapy, Treatment, Non-muscle-invasive bladder cancer, Muscle-invasive bladder cancer

1. Introduction

By characteristics of tumor occurrence and biological behavior, bladder cancer can be divided into muscle-invasive bladder cancer (MIBC) and non-MIBC (NMIBC); proportion in bladder cancer is approximately 30% and 70%, respectively^[1]. MIBC has greater invasiveness and metastasis capacity with almost half of the patients having fatal metastasis. NMIBC has high recurrence rate with 70% of post-operative patients having relapse conditions. Radical cystectomy is the first choice of treatment for bladder cancer. For the organ-confined bladder cancer, it has reliable efficacy of surgical treatment and can significantly prolong the survival of patients. When the organ-confined bladder cancer patient with negative lymph node biopsy result undergoes simple surgery, the 5-year survival rate can go up to 80%. On the other hand, simple surgery has limited efficacy on non-organ-confined bladder cancer patients, with a 5-year survival rate of only between 40% and 50%. When the lymph node metastasis is involved, the 5-year survival rate can be as low as 15% to 35%. Studies have shown that distant recurrence rate of bladder cancer (20–50%) was significantly higher than local recurrence rate (5–15%). In particular, MIBC had high risk of post-operative distant recurrence^[1].

2. Current status of bladder cancer treatment and the rise of neoadjuvant chemotherapy

2.1. Treatment for NMIBC

NMIBC, formerly known as superficial bladder cancer, includes carcinoma *in situ*, stage Ta and T1 bladder cancer. Its first-choice treatment is surgery^[1]. Due to the high recurrence rate in patients with NMIBC, intravesical chemotherapy/immunotherapy is often given after surgery. Intravesical instillation chemotherapy after transurethral resection of bladder tumor can effectively remove residual tumor cells after electrical

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resection. This significantly reduces the recurrence risk of NMIBC. The commonly used drugs include pirarubicin, epirubicin, doxorubicin, mitomycin, and gemcitabine^[2]. Studies have shown that instillation chemotherapy after bladder tumor resection can reduce the overall mortality and improve the overall survival^[3]. Bladder instillation immunotherapy mainly uses *Bacillus Calmette-Guérin* (BCG) to increase cytokine expression in bladder wall and urine through induction of local immune response, thereby to prevent tumor recurrence and control tumor progression. Post-operative BCG instillation can reduce the 5-year recurrence rate from 59% to 45%, and it is more effective than epirubicin for patients who are older than 70 years^[4].

2.2. Treatment and neoadjuvant chemotherapy for MIBC

For the treatment of invasive bladder cancer, radical cystectomy combined with pelvic lymphadenectomy has been the standard surgical procedure^[5]. For patients with high-grade bladder cancer, cisplatin-based adjuvant chemotherapy is often required after surgery to further destruct the lesions. Immediate intravesical chemotherapy and delayed treatment did not show to have a significant difference in survival improvement but immediate bladder infusion significantly prolonged progression-free survival of patient^[6].

After surgical treatment, prognoses of patients with MIBC were improved. Nevertheless, 50% of the patients died from multiple metastases within 2 years after surgery. This is because simple surgery could not eradicate micrometastases, which could lead to distant recurrence and metastasis of bladder cancer. Distant recurrence rates in stage pT2 and pT3/pT4 bladder cancer patients could go up to 10–27% and 19–35% respectively, whereas the local recurrence rates stage in stage pT2 and pT3/pT4 bladder cancer patients were 3–4% and 11–16% respectively^[7]. Therefore, restriction and eradication of microscopic lesion are keys to good post-operative prognosis. In 1988, Raghavan and Seher first gave pre-operative chemotherapy to the patients with invasive bladder cancer; this treatment was named neoadjuvant chemotherapy. Its significance lies on its role as pre-operative adjuvant chemotherapy to kill tumor cell, eradicate existing micrometastasis, reduce tumor volume, improve prognosis, and accomplish therapeutic goal in improving the survival rate of patients. Commonly used regimens for neoadjuvant chemotherapy include: MVAC regimen (methotrexate + vinblastine + doxorubicin + cisplatin), carboplatin + paclitaxel regimen, and GC regimen (gemcitabine + cisplatin). MVAC regimen is the conventional standard chemotherapy regimen for urothelial carcinoma of bladder, but GC regimen is also often used because it has the similar efficacy to MVAC regimen with fewer side effects. Neoadjuvant chemotherapy is suitable for bladder cancer patients with stage T2–T4a.

3. Advantages and disadvantages of neoadjuvant chemotherapy

3.1. Advantages of neoadjuvant chemotherapy

Neoadjuvant chemotherapy has unique advantages. First, neoadjuvant chemotherapy is administered preoperatively. During the pre-operative stage, the patients who have not undergone surgery have better physical condition and can better tolerate adequate dose of chemotherapy compared to post-operative chemotherapy. Second, the effectiveness of chemotherapy for primary tumor can be efficiently evaluated. This provides prognostic information of patients and guidance for subsequent treatment. Most importantly, neoadjuvant chemotherapy can downstage primary tumor, some patients can accomplish complete pathological remission after receiving neoadjuvant chemotherapy, or the tumor is downstaged to pT1N0, underscoring the best timing for surgery.

3.2. Disadvantages of neoadjuvant chemotherapy

The European Association of Urology guideline recommends cisplatin-based neoadjuvant chemotherapy for T2–T4a bladder cancer patients without lymph node metastasis and distant metastasis. For bladder cancer patients who cannot tolerate cisplatin-based combination chemotherapy, neoadjuvant chemotherapy is not recommended unless the objective is to downstage tumor that cannot be removed surgically^[8]. However, overtreatment in patients with no obvious response to neoadjuvant chemotherapy or in patients without micrometastasis is not effective at all, and therefore, this sort of excessive medical intervention is unnecessary. Studies have shown that only 33.3% of bladder cancer patients benefited from neoadjuvant chemotherapy combined with surgical treatment^[9]. Pre-operative chemotherapy for drug-resistant bladder cancer patients delays surgery and reduces quality of life; it is likely to pose negative impacts for prognosis of patient and heavier medical burden. Unfortunately, there is no distinct molecular expression profile of bladder cancer for the identification of patients who respond to neoadjuvant chemotherapy, and conventional imaging techniques cannot provide definitive conclusion on the effectiveness of drug use in the patients^[10].

In addition, neoadjuvant chemotherapy has a limitation in staging bladder cancer patients (T2–T4), whereby its accuracy in clinical staging is 70%. The grading errors tend to occur in staging cT2 tumor than in the cT3–4 tumors. Despite the concerns in clinical staging, neoadjuvant chemotherapy does not negatively affect tumor resection^[8].

4. Prediction of efficacy of neoadjuvant chemotherapy

Neoadjuvant chemotherapy combined with radical

cystectomy is considered the standard treatment protocol for bladder cancer^[11]. The neoadjuvant chemotherapy with ideal efficacy can give rise to pathologic complete remission in patients with bladder cancer. However, distinguishing between responsive and unresponsive patients before neoadjuvant chemotherapy is challenging. At present, researchers are searching for the suitable markers which can be applied in the screening of patients who are responsive to neoadjuvant chemotherapy. With the new screening tool, the neoadjuvant chemotherapy-sensitive patients can be accurately identified, while the treatment on those who are chemotherapy-resistant will not be delayed^[12].

Assessment based on a single molecular marker may pose significant inaccuracy in the prediction of sensitivity to neoadjuvant chemotherapy in bladder cancer patients. Thus, molecular marker panel associated with bladder cancer that can detect multiple molecular markers (mutant gene or abnormal expression of protein) can be considered, to improve the accuracy of the prediction of neoadjuvant chemotherapy sensitivity in patients with bladder cancer.

5. Choices for neoadjuvant chemotherapy patients

Neoadjuvant chemotherapy is undoubtedly a good treatment for patients with MIBC, but it is not suitable for all patients.

In view of the definition of precision medicine, there is no well-defined standard for the application of neoadjuvant chemotherapy on individual bladder cancer patient. As mentioned above, current studies in this area focus on the discovery of bladder cancer-associated molecular marker for predicting the efficacy of neoadjuvant chemotherapy. Nevertheless, the molecular markers which purportedly predict neoadjuvant chemotherapy efficacy require corroboration of a large number of evidence-based studies before they can be applied in the clinical setting^[12].

6. Improvement of neoadjuvant chemotherapy

As one of the standard treatments for MIBC, neoadjuvant chemotherapy is associated with considerable toxicity which limits its widespread application to some extent. Conventional MVAC regimen with granulocyte colony-stimulating factor given 4 weeks before surgery significantly increases the toxic effects, including hand and foot skin reactions, mucositis, hypokalemia, and neutropenia. These severe adverse reactions affect treatment progress, leading to delayed or early termination of chemotherapy. In an intergroup study in the United States, 108 (72%) of 150 patients experienced chemotherapy-related toxicity of Grade 3 and above; this explains why only a small percentage of patients received neoadjuvant chemotherapy. Therefore, the conventional MVAC warrants an improvement.

In a study, 65 MIBC patients received a sequential neoadjuvant chemotherapy consisting of three cycles of IAG regimen (isosfamide, doxorubicin, and gemcitabine) followed by four cycles of GCI regimen (GC regimen combines with ifosfamide)^[13]. The patients who were followed for 85.3 months in the study were high-risk patients with lymphovascular invasion, hydronephrosis, micropapillary tumor, or upper urinary tract disease. The study showed that 5-year overall survival rate and disease-specific survival rate were 63% and 68%, respectively, which are comparable to the results of an MVAC scheme. There was no significant improvement in downstaging rate before and after the sequential GCI regimen. Only two patients who failed IAG therapy were downstaged to pT0 following the sequential GCI treatment regimen. If the regimen before sequential treatment is effective to the patients, the treatment regimen should be continued. If it is not effective, treatment with other regimens should be implemented early, which can better improve the long-term survival rate of patients.

7. Large-scale clinical trial of neoadjuvant chemotherapy for bladder cancer

Although many studies recommend neoadjuvant chemotherapy for invasive bladder cancer, it has not been widely used^[14]. In Europe, approximately 5,000 bladder cancer patients undergo cystectomy annually; a feasibility survey on this group of patients showed that only about 12% of the patients received neoadjuvant chemotherapy^[15]. A study involving 5,692 patients with MIBC has been carried out to determine the trend of neoadjuvant chemotherapy application for the locally advanced MIBC^[16]. From 2006 to 2010, the number of patient receiving neoadjuvant chemotherapy increased from 10.1% to 20.8% ($P = 0.005$), indicating that neoadjuvant chemotherapy is gaining consideration. However, the usage rate of 20.8% was apparently far being considered as “widely accepted” because the usage rate of adjuvant chemotherapy was higher than that of neoadjuvant chemotherapy. This is because neoadjuvant chemotherapy causes heart and kidney function disorders due to its toxic properties and delaying surgery may lead to cancer progression, and thus, neoadjuvant chemotherapy was replaced with post-operative adjuvant chemotherapy.

Literature reported that pre-operative chemotherapy may lead to increased morbidity and mortality^[17]. The researchers recruited 3760 bladder cancer patients in their study, 416 (11.1%) of which received neoadjuvant chemotherapy before surgery. The complication rate, readmission rate, and mortality of the patient group were 66.0%, 32.2%, and 5.3%, respectively, on the 30th day after the surgery. The complication rate, readmission rate, and mortality were 72.5%, 46.6%, and 8.2%, respectively, on the 90th day after surgery. When the patients were stratified by neoadjuvant chemotherapy, there was no significant

difference in complication rate, blood transfusion rate, prolonged hospitalization rate, rehospitalization rate, and mortality between two groups ($P > 0.1$). The study showed that the pre-operative neoadjuvant chemotherapy is not associated with increased post-operative morbidity and mortality in patients with MIBC. Therefore, neoadjuvant chemotherapy can be considered a safe treatment.

8. Conclusion

Neoadjuvant chemotherapy can improve the overall survival rate of patients with MIBC, but it has noticeable drawbacks as well. Regimens developed earlier have undesirable side effects. Although the newly developed regimens could resolve the side effect problem to some extent, neoadjuvant chemotherapy is still not widely in use. From the perspective of precision medicine, it is necessary to conceive and define a strong research direction in the exploration of new markers for the prediction of distant metastasis of bladder cancer and patients sensitivity to neoadjuvant chemotherapy^[18], in addition to optimizing systemic treatment and efficacy evaluation of bladder cancer. The current research direction places much emphasis on designing the molecular marker panel related to bladder cancer that employs the use of multiple molecular markers to improve the accuracy of prediction of neoadjuvant chemotherapy for bladder cancer patients through cross-prediction. We believe that neoadjuvant chemotherapy for bladder cancer will be more widely used after these problems are resolved.

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Conflict of interest

The author declares no potential conflicts of interest.

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