Review

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The Current Strategies for Neoadjuvant Chemotherapy in Muscle Invasive Bladder Cancer: The Place of Immunotherapy in Future

Özlem Ercelep

Marmara University Pendik Training and Research Hospital, Clinic of Medical Oncology, İstanbul, Turkey

Abstract

Muscle invasion is present in approximately thirty percent of bladder cancers. Radical cystectomy and bilateral pelvic lymph node dissection following neoadjuvant chemotherapy is the recommended treatment for muscle invasive bladder cancer. Local and distant relapses are seen in a significant proportion of patients with surgery alone. Micrometastases at the time of diagnosis that cannot be detected by imaging may be responsible for these relapses. The aim of neoadjuvant and adjuvant therapies is to eliminate these micrometastases. Several randomized trials have shown that platinum-based combination neoadjuvant chemotherapy can improve survival outcomes, compared with locoregional treatment alone. Although the proportion of patients receiving treatment has increased compared to previous years, it is still low. Immunotherapies in neoadjuvant treatment are promising in the appropriate patient group. In this article, we aimed to review current neoadjuvant treatment strategies in muscle invasive bladder cancer in the literature.

Keywords: Bladder cancer, chemotherapy, neoadjuvant therapy

Introduction

Although the gold standard treatment in bladder cancer is surgical, the rate of cure varies between 50-65% by surgery alone (1). It is seen that systemic treatment applications are of great importance considering the low chance of obtaining a cure and low survival rates in patients treated with surgery alone in case of the tumor invades the muscle layer. Urothelial (transitional cell) carcinoma accounts for about ninety percent of bladder cancers in Europe and North America. In other parts of the world, non-urothelial bladder cancers are more common. Although neoadjuvant cisplatin-based chemotherapies provide a survival benefit compared to local treatments alone, only twenty percent of patients receive neoadjuvant chemotherapy before radical cystectomy (2,3,4,5). The reasons such as physicians not believing in the benefit of the treatment, fear of the side effects of the treatment, not guiding the patients for chemotherapy due to the concerns of delay in curative treatment, and impaired renal function and poor performance prevent patients from receiving treatment.

All patients should be clinically staged prior to treatment in bladder cancer. It is necessary to start treatment as soon as possible after the diagnosis and staging. In an observational study, it was shown that delay of 8 weeks or more in neoadjuvant therapy was associated with the increase in stage in 2,200 patients (6).

The survival benefit of cisplatin-based chemotherapies before surgery has been demonstrated in the meta-analyses of 11 randomized studies (7). Compared with local therapy alone, neoadjuvant cisplatin-based treatments improve 5-year survival from 45% to 50%, while improve disease-free survival by 9%. However, there are no randomized studies comparing neoadjuvant chemotherapy regimens. A clear difference between regimens was not shown in retrospective studies (8,9). In the largest one of those retrospective studies, the data of 935 patients with node negative (N0) muscle invasive bladder cancer (T2-T4a), from 19 centers from North America and Europe were analyzed. In that study, 64% of patients received cisplatin gemcitabine, 20% methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) and 15% other regimens. There was no difference between the chemotherapy regimens in terms of pathological complete response rates (9).

In the intergroup-0080 trial, surgery alone was compared with neoadjuvant classical MVAC regimen (every 3 days for 28 days) followed by surgery in 307 patients with T2-4N0M0 disease. In the study with a median follow-up time of 8.7 years, median survival in the neoadjuvant therapy arm was 77 months,

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Address for Correspondence: Özlem Ercelep, Marmara University Pendik Training and Research Hospital, Clinic of Medical Oncology, İstanbul, Turkey
Phone: +90 216 657 06 06 **E-mail:** ozlembalvan@yahoo.com **ORCID-ID:** orcid.org/0000-0001-5892-3519
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whereas it was 46 months in the surgery alone arm (p=0.06). While the 5-year overall survival benefit in the study was 5%, it was seen that this benefit was more pronounced in T3-4 tumors with 20%. In this study, the 5-year survival rate of patients with complete pathological response (pT0) was 85%. In the study, the pathological complete response (15% versus 38%, p<0.001) was found better in the arm receiving neoadjuvant chemotherapy compared to surgery alone. In summary, in that study, patients who received neoadjuvant therapy had a higher pathological complete response rate, and this was associated with increased survival (10).

The dose-dense MVAC treatment used in conjunction with the granulocyte colony stimulating factor every two weeks showed superiority in survival compared to classical MVAC treatment in locally advanced and metastatic disease (11,12). After these studies, single arm, two-phase 2 studies were conducted to investigate the neoadjuvant use of dose-dense MVAC (filgrastim every 14 days, 3 or 4 cycles depending on toxicity). In the first study, the pathological full response rate was 26% (43% of the patients were clinically node positive patients in this study), whereas in the other study, the pathological full response rate was 38% (in this study, 7% of the patients were clinically node positive patients) (13,14). The dose-dense MVAC treatment regimen is considered an alternative treatment regimen, especially in patients who have short duration until surgery and are clinically N0 patients.

Compared with MVAC treatment, gemcitabine cisplatin (GC) treatment in metastatic patients showed similar efficacy and less toxicity (15). There are no randomized studies in neoadjuvant use of this regimen. In a meta-analysis conducted in 2016, the data of 13 retrospective studies were analyzed. Although this meta-analysis showed similar response rates between GC/carboplatin treatment and MVAC treatment, survival results were found inferior in gemcitabine-platinum arm. In the analysis made by excluding carboplatin data, GC treatment was found inferior (16).

The effectiveness of neoadjuvant cisplatin, methotrexate, vinblastin therapy (methotrexate, vinblastin, cisplatin, leukoverine, 3 cycles every 28 days) was compared with local treatment in 976 high-grade patients in a phase 3 trial. In this study, 6% absolute survival benefit was shown at the end of 10 years of follow-up (36% vs 30%) (17).

In the Nordic Cystectomy 1 trial, 311 patients were enrolled in the T1-4N0M0 phase; one group underwent a combination regimen with neoadjuvant cisplatin (cisplatin and adriamycin) followed by radiotherapy and surgery, and the other group underwent surgery after radiotherapy without neoadjuvant therapy (18). While the 5-year overall survival benefit in the study was shown in T1-2 tumors, a 15% difference was found in favor of neaoadjuvant therapy in patients with T3-4 stage (p=0.03). The same study group performed Nordic cystectomy 2 trial and examined 317 patients by dividing them into neoadjuvant therapy (cisplatin and methotrexate) and surgery alone arm (19). There was no difference between the two arms in terms of survival. When Nordic 1 and 2 trials were analyzed together, it was observed that 5-year survival increased from 48% to 56% with neoadjuvant therapy (p=0.049).

In one of the studies conducted to investigate the effect of response obtained with neoadjuvant therapy on survival, the results of 449 patients with T2-4NxM0 tumor who were included in prospective Nordic cystectomy trials and had a pathological complete response with neoadjuvant therapy were retrospectively analyzed. The difference in 5 year survival between the group with and without pathological complete response was shown (57.1% versus 88.2%) (p=0.001) (20). As a result of the study, it was demonstrated that a significant advantage in 5-year survival in patients with complete pathological response with neoadjuvant therapy was gained.

Treatment in Patients with Kidney Failure

Urinary system obstruction should be investigated primarily in patients with bladder cancer presenting with kidney failure. If there is obstruction and if the kidney functions are normalized by placing a stent in the ureter or percutaneous nephrostomy, a standard dose of cisplatin can be given. If kidney failure is not caused by obstruction and if stent placement or nephrostomy does not improve kidney failure, carboplatin can be used instead of cisplatin (21). Data show that carboplatin is less effective than cisplatin in urothelial cancers (22,23,24,25). However, there are no randomized studies comparing cisplatin and carboplatin as neoadjuvant therapy.

Neoadjuvant Immunotherapy

With the demonstration of the effectiveness of immunotherapies in metastatic urothelial cancers, the use of immunotherapies in neoadjuvant therapy has also been investigated. In two different phase 2 studies, the place of atezolizumab and pembrolizumab in neoadjuvant therapy was investigated. In the PURE-01 study, the effectiveness of neoadjuvant pembrolizumab therapy was evaluated in 50 patients with muscle invasive bladder cancer. In this study, pathological complete response as the primary outcome was 42% and reduction in stage was 54%. In subgroup analysis, benefit was seen in patients with pdl1 ≥10% or with high tumor mutation. In the second study, the effectiveness of atezolizumab in neoadjuvant therapy was evaluated and similar results were obtained with pemborolizumab (26,27). If these results are confirmed by randomized phase 3 studies, immunotherapy in neoadjuvant therapy may be used in the near future.

In the light of this information, neoadjuvant therapy is recommended in clinical guidelines beginning from the T2N0M0 stage or in the disease with nodal involvement (TxN1-3M0). The contribution of neoadjuvant therapy to survival does not appear to be very high, since randomized studies and studies in meta-analysis included patients in the T2 stage. While MVAC systemic therapy is preferred in healthy individuals under the age of 70, cisplatin-gemcitabine therapy is the preferred chemotherapy regimen for individuals over 70 years of age or with comorbidity. However, in practice, cisplatin-gemcitabine therapy is applied in most centers for reasons such as treatment toxicity and difficulty of administration.

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Ethics

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