

The Combination of Gemcitabine and Carboplatin in Neoadjuvant Treatment of Bladder Cancer: A Pilot Study

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ABSTRACT

The toxicity of cisplatin precludes its use in patients with bladder cancer with abnormal renal function tests or poor performance status, thus carboplatin may be used as a substitute. In this study, we evaluated retrospectively the patients treated with neoadjuvant gemcitabine-carboplatin (GCb) in our clinic to assess the efficacy and toxicity of this regimen. Patients with localized muscle invasive bladder cancer were treated with 3 cycles of gemcitabine (1000 mg/m² days 1, 8 q3w) and carboplatin (AUC= 4 according to the Calvert formula, day 1, q3w) combination and were subsequently operated. Response rates in terms of pathological complete response (pCR) and safety issues were assessed. Fourteen patients were evaluated. Median age of the patients was 62 (range 55-79) and all were males. Median creatinine clearance was 51 ml/min (range 29-72 ml/min). Nine patients completed 3 cycles of chemotherapy while 2 patients received 2 cycles and 3 patients received 1 cycle. The treatment was generally well tolerated. Grade 3/4 neutropenia developed in 4 patients (29%) and grade 3/4 thrombocytopenia developed in 3 patients (21%). One patient developed febrile neutropenia. After surgery, pCR was achieved in one patient (7% of whole group). The median interval between the last dose of neoadjuvant chemotherapy and the time of surgery was 45 days (range 17-106 days) and this interval was significantly correlated with post-operative pathological T stage of the tumor ($r= 0.844$, $p= 0.017$). Gemcitabine-carboplatin combination represents a feasible alternative to gemcitabine-cisplatin regimen with moderate activity and favorable toxicity profile. Shorter interval between the completion of chemotherapy and the time of surgery was associated with higher rates of response.

Keywords: Cancer of the bladder, Neoadjuvant treatment, Gemcitabine, Carboplatin

ÖZET

Mesane Kanserinin Neoadjuvant tedavisinde Gempitabin Karboplatin Kombinasyonu

Mesane kanserli hastalarda böbrek fonksiyonlarındaki bozukluk ya da performans statusunun kötü olması nedeniyle cisplatin kullanımı güç olabilir. Bu hastalarda alternatif olarak karboplatin kullanılabilir. Bu çalışmada kliniğimizde mesane kanseri nedeniyle neoadjuvant gempitabin-karboplatin (GCb) rejimi ile tedavi edilen hastaları retrospektif olarak inceledik.

Kas tabakasına invaziv mesane kanseri olan hastalara 3 kür neoadjuvant gempitabin (1000 mg/m², 1. ve 8. günler, 21 günde bir) ve karboplatin (AUC= 4 Calvert formülüne göre, 3 haftada bir 1. gün) tedavisi uygulandı ve daha sonra opere edildi. Patolojik tam yanıt oranları ve güvenilirlik parametreleri değerlendirildi.

Öndört hastanın verileri incelendi. Ortanca yaş 62 (55-79 aralığında) idi ve tüm hastalar erkekti. Ortanca kreatinin klerensi 51 ml/dk (29-72 ml/dk. aralığında) idi. Dokuz hasta 3 kür, 2 hasta 2 kür ve 3 hasta 1 kür tedavi aldı. Tedavi genellikle iyi tolere edildi. Dört hastada (%29) grad 3/4 nötropeni, 3 hastada (%21) grad 3/4 trombositopeni saptandı. Bir hastada febril nötropeni gelişti ve antibiyotik tedavisi verildi. Cerrahi sonrası 1 hastada (%7) patolojik tam yanıt elde edildi. Kemoterapinin son dozu ile cerrahi arasında geçen ortalama süre 45 gündü (17-106 gün aralığında) ve bu süre ile patolojik T evresi arasında anlamlı ilişki saptandı ($r= 0.844$, $p= 0.017$). Gemcitabin-karboplatin tedavisi orta düzeyde etkinlik gösteren ve yan etki profili iyi olan bir tedavi rejimidir ve gemcitabin-sisplatin rejimine alternatif olarak kullanılabilir. Kemoterapinin tamamlanmasından cerrahiye kadar geçen sürenin kısa olması daha iyi yanıt oranları ile ilişkili bulunmuştur.

Anahtar Kelimeler: Mesane kanseri, neoadjuvant kemoterapi, gemcitabin, karboplatin

INTRODUCTION

Bladder cancer is the second most common genitourinary cancer.¹ Although cystectomy is the mainstay of treatment, failure rates are between 30-45% after surgery alone, therefore adjunctive therapies are needed.² The benefit of adjuvant chemotherapy after surgery is not currently robust but neoadjuvant chemotherapy has a more established role in the management of bladder cancer. A recent meta-analysis of phase 3 randomized trials has demonstrated a 5% absolute survival benefit with neoadjuvant chemotherapy.³ Methotrexate-vinblastine-doxorubicin-cisplatin (MVAC) regimen has emerged as the standard regimen for neoadjuvant setting in the past but it has been replaced by gemcitabine-cisplatin because of similar efficacy and lower toxicity of this regimen in the advanced setting.⁴

The toxicity of cisplatin based combinations precludes their use in a portion of patients with bladder cancer as these patients often have abnormal renal function tests or poor performance status. Carboplatin is not nephrotoxic and generally better tolerated and represents a feasible option for these patients. To our knowledge, the efficacy of gemcitabine carboplatin (GCb) combination was previously reported in the advanced setting but only one study was reported in the neoadjuvant setting.⁵ We evaluated retrospectively the patients treated with neoadjuvant GCb in our clinic to assess the efficacy and toxicity of this regimen as neoadjuvant chemotherapy.

PATIENTS AND METHODS

This retrospective study was performed in Atatürk Education and Research Hospital, Ankara. Patients with muscle invasive bladder cancer who did not

have distant metastases were treated with 3 cycles of gemcitabine (1000 mg/m² days 1, 8 q3w) and carboplatin (AUC= 4 according to the Calvert formula, day 1, q3w) combination. Patients were subsequently operated and radical cystoprostatectomy was performed. Radiotherapy was administered for those who refused surgery or deemed unfit for surgery after the completion of chemotherapy. Demographic and clinical features of the patients were recorded along with laboratory data and pathology results. Creatinine clearance was calculated with Cockcroft-Gault formula. The primary end point of this study was to determine the response rate of the regimen. Secondary end point was safety. Treatment response was expressed in terms of pathological complete response (pCR) rates. Statistical analysis was performed with SPSS software version 13.0. Descriptive analysis was performed for demographic and clinical characteristics of the patients. Spearman test was used for correlation analysis. Statistical significance was set at a p value of less than 0.05.

RESULTS

Fourteen patients with bladder cancer who underwent neoadjuvant GCb were assessed. Median age of the patients was 62 (range 55-79) and all were males. Median hemoglobin level was 11.5 g/dl (range 9.1-15.1 g/dl) and median creatinine clearance was 51 ml/min (range 29-72 ml/min). Nine patients completed 3 cycles of chemotherapy while 2 patients received 2 cycles and 3 patients received 1 cycle. The treatment was generally well tolerated. Chemotherapy dose reductions were made in 3 patients (21%). Gemcitabine dose was reduced in 2 patients and carboplatin in 1 patient. Treatment delays occurred in 6 patients (43%) mainly because of

hematologic toxicity. Grade 3/4 neutropenia developed in 4 patients (neutrophil nadir 400 /mm³) and grade 3/4 thrombocytopenia developed in 3 patients (thrombocyte nadir 8000 /mm³). One patient developed febrile neutropenia and subsequently recovered with antibiotic therapy. Granulocyte-colony stimulating factor was given to 5 patients (36%) as primary or secondary prophylaxis.

After completion of neoadjuvant chemotherapy, radical cystoprostatectomy was performed in 7 patients. Four patients received radiotherapy mainly because they refused surgery or were considered unfit for surgery by their primary doctor. Three patients were lost to follow up after chemotherapy. Pathological complete response was achieved in one patient (7% of whole group). Among the remaining 6 patients who were operated, 2 patients had pT3N1 disease, 2 patients had pT3N0 disease and 2 patients had pT2N0 disease. The median interval between the last dose of neoadjuvant chemotherapy and the time of surgery was 45 days (range 17-106 days) and this interval was significantly correlated with post-operative pathological T stage of the tumor ($r=0.844$, $p=0.017$). Median interval between the initial diagnosis and cystectomy was 135 days (range 45-261 days).

Median follow up was 9 months (range 4-50 months). One patient died on follow up because of a disease-unrelated cause.

DISCUSSION

Transitional cell cancer of the bladder is a relatively chemosensitive disease as shown by response rates as high as 70-80 % in the advanced disease setting.² MVAC was the standard treatment regimen in advanced bladder cancer but this regimen was associated with substantial toxicity, mostly being neutropenic infections. Gemcitabine-cisplatin combination has emerged as an alternative to MVAC in phase II studies.^{6,7} Subsequently a phase III multicenter study has demonstrated similar efficacy in terms of PFS and OS with much better toxicity.⁴ After this study, gemcitabine-cisplatin regimen became the new standard of care in advanced-metastatic bladder cancer. Given the activity in the metastatic setting, gemcitabine-cisplatin is often substituted for MVAC for patients receiving neoadjuvant chemotherapy. Pathological complete response rates with

neoadjuvant MVAC regimen was reported to be between 33-40%. Similar rates of pCR were obtained with gemcitabine-cisplatin in some retrospective series in the literature⁸ while some studies reported lower rates of response.⁹ Nevertheless, no previous studies have compared MVAC and gemcitabine-cisplatin head to head in a neoadjuvant trial and gemcitabine-cisplatin is currently recommended as one of the preferred neoadjuvant regimens by NCCN guidelines in the treatment of bladder cancer.¹⁰

Given the renal toxicity of cisplatin-based chemotherapy, adequate renal function is a prerequisite. Therefore carboplatin is mainly utilized instead of cisplatin in patients with low creatinine clearance (≤ 60 ml/min), although response rates and disease specific survival are inferior with carboplatin compared to cisplatin.¹¹ Carboplatin has a more favorable toxicity profile. Hematological toxicity is more frequent with carboplatin particularly when combined with gemcitabine, which is also myelotoxic. Hematological toxicity was also frequently observed in our study, resulting in treatment delays in 43% of the patients and G-CSF use in 36%. However, this toxicity was easily managed and no life threatening episodes of infection or hemorrhage were observed.

Pathologic complete response to neoadjuvant chemotherapy is the most important surrogate marker independently predictive of overall survival.¹² Hence the ability to achieve pCR is considered as a reasonable endpoint in neoadjuvant trials. Pathologic complete response was obtained in one patient in our series among 14 patients (7% by intent-to-treat analysis). This rate is lower than that of reported in the literature.² It is not proper to make overstatements with such a low number of patients, however a few comments can be made; First, the interval between the last dose of chemotherapy and surgery was median 45 days in our study. A delay in cystectomy was previously reported to be associated with advanced pathologic stage and reduced survival.^{13,14} Neoadjuvant chemotherapy itself delays surgery however current evidence suggests that any adverse effect secondary to this delay is compensated by the benefit of chemotherapy. Nevertheless, the prolonged interval between the completion of chemotherapy and cystectomy may negate the beneficial effect of neoadjuvant chemotherapy and reduce

pCR rates, which is strongly correlated with survival. Secondly, The efficacy of gemcitabine-cisplatin in the neoadjuvant setting when compared to MVAC is currently unknown but there are studies which revealed inferior pCR rates with gemcitabine-cisplatin compared to previous studies with MVAC. Furthermore, response rates and disease specific survival are inferior with carboplatin compared to cisplatin. In a randomized trial in patients with advanced bladder cancer¹¹, treatment with methotrexate-carboplatin-vinblastine (M-CAVi) resulted in inferior disease specific survival compared with M-VAC. Complete response was achieved in 3 of 24 patients treated with M-VAC while none in those treated with M-CAVi. Therefore low response rate in our study may also be secondary to the use of a suboptimal regimen in the neoadjuvant setting.

The limitations of our study are small patient number, retrospective nature, and short follow up period. Therefore we can not draw reliable conclusions with these data. We propose that in a predominantly elderly patient population with a high prevalence of renal dysfunction and poor performance status frequently precluding cisplatin-based combination chemotherapy, gemcitabine-carboplatin combination may represent a feasible alternative with moderate activity and favorable toxicity profile. Our findings also suggest that a better coordination between the urologist and oncologist to schedule surgery within a short period after the completion of chemotherapy may result in higher rates of response.

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