Neoadjuvant M-VEC (Methotrexate, Vinblastine, Epirubicin, Cisplatin) Chemotherapy in Locally Invasive Transitional Cell Carcinoma of the Bladder

LOKAL İNVAZİF MESANE DEĞİŞİCİ EPİTEL KANSERİNDE NEOADJUVAN M-VEC (METOTREKSAT, VİNBLASTİN, EPİRUBİSİN, SİSPLATİN) KEMOTERAPİSİ

Sümer BALTACI*, Yaşar BEDÜK*, Önder YAMAN*, Erdal YILMAZ*, Orhan GÖĞÜS*

*Dept of Urology, Medical School of Ankara University, Ankara, TURKEY

Summary

The aim of the study was to assess the antitumor activity of neoadjuvant M-VEC (Methotrexate, Vinblastine, Epirubicin, Cisplatin) for T3a-T4, N0/N+, MO bladder tumors and to compare the clinical and pathologic response after chemotherapy and surgery.

A series of 62 patients with infiltrating, locally advanced bladder cancer (stage T3a-T4, N0/N+, MO) were treated with neoadjuvant systemic chemotherapy regimen of M-VEC. After patients underwent chemotherapy, clinical restaging and pathologic restaging (partial or radical cystectomy) was planned.

Fifty-four patients were évaluable for response. A clinical response was attained in 40.7%. Twenty-six patients (48.1%) had stable disease, and six (11.1%) had progression. After chemotherapy, 13 patients underwent radical cystectomy and 2 patients underwent partial cystectomy Five of them were pTO (33.3%). In 6 of the 15 patients (40%), the clinical stage understaged the pathologic stage. In only 6 patients (40%) clinical restaging was accurate. Of 4 patients who were TO prior to surgery, I had residual invasive tumor in the pathologic specimen.

The large restaging error raise questions concerning bladder préservation protocols following neoadjuvant chemotherapy. Limitations of M-VAC or M-VEC in the treatment of invasive bladder cancer must be realized and new chemotherapeutic agents or combination regimens must be identified.

Key Words: Bladder cancer, Chemotherapy, Neoadjuvant, M-VEC

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Özet

Çalışmanın amacı; T3a-T4, N0/N+, MO mesane tümörlerinde neoadjuvan M-VEC (Metotreksal, Vinblaslin, Epirubisin, Sisplatin) kemoterapisinin antitümör aktivitesini değerlendirmek ve kemoterapi ve cerrahi sonrası klinik ve patolojik sonuçları karşılaştırmak idi.

İnfiltre ve lokal yerleşimli mesane tümörü (klinik evre; T3a-T4, N0/N+, MO) olan 62 hastaya, neoadjuvan sistemi/c M-VEC kemoterapisi uygulandı. Kemoterapi sonrası hastalar klinik ve patolojik (parsiyel veya radikal sistektonıi) olarak tekrar değerlendirildi.

54 hasta cevap için değerlendirmeye alındı. Klinik cevap %40.7 olarak bulundu. 26 hastada (%48.1) stabil hastalık ve 6 hastada (%11.1) progresyon saptandı. Kemoterapi sonrası 13 hastaya radikal sistektonıi, 2 hastaya da parsiyel sistektonıi yapıldı. Bu hastalardan 5 'inde patolojik evre pTO (%33) idi. 15 hastanın 6'sında (%40) klinik evre patolojik evrenin altında idi. Sadece 6 hastada (%40) k/inik yeniden evrelendirme doğru yapılmıştı. Cerrahi öncesi T0 evreli 4 hastanın birinde patolojik numunede invazif tümör saptandı.

Neoadjuvan kemoterapiyi takiben mesane koruma protokolleri, geniş yeniden evrelendirme hataları yüzünden endişe yaratmaktadır, invazif mesane tümörleri tedavisinde kullanılan M-VAC veya M-VEC'in yararları tartışmalı olduğundan yeni kemoterapi ajanları veya kombinasyon rejimleri belirlenmelidir.

Anahtar Kelimeler: Mesane tümörü, Kemoterapi, Neoadjuvan, M-VEC

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Correspondence: Önder YAMAN
Şehit Ersan Caddesi
Pembe Köşk Sitesi
B-1 Blok No: 15
06580, Çankaya, Ankara. TURKEY

In patients with nonmetastatic locally invasive bladder carcinoma, either radical cystectomy or radiation therapy or both provides an expected overall survival rate of 20-50% (1-4). Most patients who succumb to bladder cancer following such local treatment modalities do so from metastatic dis-

ease and this led to the integration of chemotherapy in the treatment of locally invasive nonmetastatic tumors (5-7). There is no doubt that transitional cell carcinoma (TCC) of the bladder is responsive to chemotherapy and in some cases it also permits bladder preservation (5,6). Neoadjuvant systemic M-VAC (Methotrexate, Vinblastine, Doxorubicin and Cisplatin) chemotherapy achieves a 50-70% response rate with 25-40 complete response (8). In our series we replaced doxorubicin by the less toxic epirubicin and used neoadjuvant M-VEC regimen. The objectives of this study were to assess the antitumor activity of neoadjuvant M-VEC for T3a-T4, N0/N+, MO bladder tumors and to compare the clinical and pathologic response after chemotherapy and surgery.

Materials and Methods

Between July 1992, and June 1997, 62 patients (age range 37-75, mean 59.6 years) with biopsy proved, locally advanced TCC of the bladder were entered prospectively in a protocol combining a transurethral resection and neoadjuvant M-VEC systemic chemotherapy: There were 56 men and 6 women. Entry to the study required T3a-T4, N0/N+, MO TCC of the bladder, a Karnofsky performance status of at least 60%, no previous systemic chemotherapy, a creatinine clearance of> 60ml/min. and a serum creatinine not exceeding 1.8mg/dl and no major respiratory, cardiac, metabolic central nervous system disease. Oral informed consent was obtained from all patients. Pretreatment evaluation included history, physical examination, chest roentgenogram, echocardiography, excretory urography, complete blood count, liver function tests, blood urea nitrogen, serum creatinine, creatinine clearance, abdominopelvic and transrectal ultrasonography, abdominal and pelvic computerized tomography, urine cytology and transurethral resection of the bladder (TURB). The TURB was done to assess the degree of muscle infiltration and not with the intention of removing all existing infiltrating tumor. Random prostatic urethra biopsies were also taken before chemotherapy to assess the urethral involvement. The chemotherapy was administered in 21-day cycles as follows: methotrexate 30mg/m^2 and vinblastin 3mg/m^2 were both given on days 1 and 8 and epirubicin 30mg/m^2 and cisplatin 60mg/m^2 were both given on day 1. Methotrexate and Vinblastine dose modifications for hematologic toxicity were made as described by Harker et al (9). In addition, methotrexate was not given when the creatinine clearence decreased below 50ml/min. Cisplatin was administered at full dose when the creatinin clearance was >60ml/min. A 50% reduction in cisplatin dosage was made for a creatinine clearance between 50-60 ml/min and no cisplatin was administered when the creatinine clearance decreased to <50 ml/min.

Three cycles of M-VEC administration were planned. Thereafter, the disease was restaged by cytology, cystoscopy and biopsy, chest radiography, ultrasonography and CT scan, TURB and bone scan when indicated.

A clinical complete remission (cCR) was defined as complete disappearance of all disease including negative urinary cytology. A clinical partial remission (cPR) was defined as >50% decrease in size of-measurable lessions by cystoscopy and/or noninvasive staging with downstaging by 2 or more T categories or if a patient attained TO status at TURB but had either thickening of the bladder wall or positive cytology. A stable disease (cSD) was defined as <50% decrease in size of measurable lesions and progressive disease was defined as >25% increase in size of measurable disease (10,11).

After postchemotherapeutic clinical restaging in patients with complete or partial response, either a partial or radical cystectomy were offered within 1 month of completion of M-VEC. In case of stable disease the patients were either operated or given radiotherapy or additional chemotherapy according to the clinical stage of the disease and the performance status of the patients.

Results

Of the 62 patients 4 were lost to follow-up after 1 or 2 cycles of chemotherapy. Two patients refused further therapy after 1 cycle of chemotherapy due to severe gastrointestinal symptoms (nausea and vomiting of grade 3-4). In another 2 patients we stopped therapy after the first cycle due to granulocytopenic sepsis and pneumonia in one and acute renal failure in the other. These two patients were died due to these complications. The remaining fifty-four of the patients were therefore considered évaluable for response. Although at least 3 cy-

Table 1. Clinical staging before neoadjuvant M-VEC chemotherpy

Clinical Stage	No. Of Patients
T3a,N0,M0	8
T3a,N+,M0	2
T3b,N0,M0	18
T3b,N+,M0	2
T4,N0,M0	23
T4.N+.M0	1
Total	54

cles of M-VEC chemotherapy were planned, some patients received M-VEC therapy ranging from 2 upto 6 cycles depending on their response status. The clinical stages of these patients before chemotherapy are shown on Table 1.

Clinical Response

The overall clinical response rate (cCR + cPR) was 40.7%. Of the 54 patients 8 (14.8%) achieved a cCR and 14 (25.9%) achived a cPR. Twenty-six (48.1%) patients had stable disease and 6 (11.1%) had progression.

Patients who attained a cCR or downstaging were encouraged to undergo pathologic staging by a radical or partial cystectomy, but only 15 patients accepted the surgery. The remaining 39 patients had clinical restaging only. Of these 39 patients 6 had progression as mentioned before and they died of the disease after a median follow-up of 6 months (range 5-8). Twenty-six patients had stable disease and only two of them accepted partial cystectomy and the remaining 24 either refused surgery or were not found to be suitable for pathologic staging due to poor health condition or the extent of the disease. Of these 24 patients, 11 progressed in lungs, kidney and bone and died in 8 to 16 months.

The remaining 13 patients are still alive with disease after a median follow-up of 19 months (range 6-49 months)

Of 8 patients achieving a cCR after M-VEC therapy, 4 refused surgery and received a median of 5 cycles of chemotherapy (range, 4 to 6). These 4 patients are free of disease after a median follow-up of 18.4 months (range 12-51 months).

Of 14 patients achieving a cPR after chemotherapy, 5 refused surgery and received a median of 5 cycles of chemotherapy (range 4 to 6). One of these 5 patients died of renal failure 6 months later and the other 4 are still alive with disease after a median follow-up of 19.2 months (range 15-25 months).

Pathologic Response

Pathologic staging and a comparison of clinical and pathologic staging can be made in 15 patients. The clinical stage after chemotherapy and the pathologic stage as a result of surgery, are compared on Table 2.

In 6 of the 15 patients (40%), the clinical stage understaged the pathologic stage. Correlation of the clinical and pathologic responses for 15 patients revealed that in only 6 patients (40%) was clinical restaging accurate.

Table 2. Pathologic staging compared with clinical staging after neoadjuvant M-VEC chemotherapy

Clinical Stage After M-VEC	Pathologic Stage After M-VEC					
	No	pTO	pT1	pT2	pT3a	pT3b
TO	4	3		1*		
T1	7	2	1		1	
T2	2			1		1
T3a	" I" '					
T3b	2			1		1
Total	15	5	1	6	1	2

**This patient had pT2 disease in the bladder, but had two positive lymph nodes*

Table 3. Incidence of overall toxicity

Toxicity	No
Renal toxicity	13
Oral mucositis	12
Severe Gaslrointsetinal symptoms	6
Pneumonia	5
Leukopenia (Grade 3-4)	14
Trombocytopenia (Grade 3-4)	10
Anemia	13
Sensorial neurotoxicity	1

Toxicity

Toxicity was evaluated in all 62 patients. Nausea, vomiting and alopecia were encountered almost in all patients. The overall toxic effects resulting from chemotherapy are shown on Table 3.

Six patients were hospitalized for fever in association with granulocytopenia (WBC<10007ml). Renal toxicity defined as a greater than 0.4 mg/lOOml increase in the baseline serum creatinine level occured in 13 patients. No patient had cardiac toxicity. Due to these toxic effects some delay was mandatory (7-16 days) on the scheduled M-VEC cycles in 24 patients. As mentioned before, one patient died of granulocytopenic sepsis and the other of acute renal failure during chemotherapy cycles [Mortality rate: 2/62 (3.23%)].

Discussion

Although combination chemotherapy is an effective regimen for advanced TCC of the bladder, with an apparent superiority of regimens using cisplatin and methotrexate, there is still insufficient information to obtain a definitive answer to the question of whether neoadjuvant cisplatin-based chemotherapy improves the survival of patients with locally advanced bladder cancer (12-15). M-VAC, CMV and M-VEC neoadjuvant chemotherapy regimens have become the most popular and attractive therapeutic options in these patients. The highest number of major responses have been reported by M-VAC regimen and it is considered as reference treatment (12,16). However, different results have been obtained due to various patient entry criteria, stage assessment, the chemotherapeutic regimen administered and choice of subsequent treatment. Neoadjuvant M-VAC trials demonstrated overall clinical response rates of 40 to 78%, with complete response rates of 13 to 41% (5,14). In our study group, M-VEC produced an overall clinical response rate of 40.7% and a cCR rate of 14.8%. Initially, we thought that our low clinical response rates might be due to the high number of patients with T3b and T4 disease. However, Scattoni et al. in their neoadjuvant CMV trial, reported that they obtained a higher percentage of pCRs and pPRs in the group of patients with T3b and T4 tumor in contrast to the patients with T2a-T3a disease (17). However, Hatcher et al. reported that response was not related to initial clinical stage or the chemotherapeutic combination selected (6). On the other hand, Splinter et al. analyzed the effect of pretreatment chemotherapy in 123 patients from 8 centers and reported that 50% of the patients with T2 tumor achieved significant downstaging compared with only 25% of patients with a clinical T4 tumor (18).

In the current study, 15 patients underwent pathologic evaluation by radical (13 patients) or partial cystectomy (2 patients). Four patients who had no clinical evidence of disease (TO) after TURB and chemotherapy underwent radical cystectomy and 3 had no pathologic disease (pTO) and 1 [25%] had a pT2 disease.

Other investigators reported that 40-52% of the patients who were TO had residual tumor in the surgical specimen (17,19). Only Hatcher et al reported tb'-t 100%) of their patients who were TO had residual tumor in the surgical specimen (6). The difference between these reports may possibly be a consequence of a less or more aggresive transurethral resection. In this very small series clinical stage understaged the pathologic stage in 40% of the patients. As mentioned before, 30-40% understaging had been reported in the literature, so our results are in correlation with these reports. This inaccuracy in clinical staging precludes safe bladder preservation in patients with cCR.

Toxicity was similar to other studies [13,17]. The most common side effects observed were renal insufficiency, mucositis and myelosupression. In the current series, 3.2% of the patients died of drug-related causes. No cardiac toxicity was encountered. Therefore as Witjes et al, reported recently that even in experienced hands, M-VAC chemotherapy remains a toxic and potentially lethal therapy.

Most other side effects are acceptable or can be treated (20). A dose delay was necessary in 38.7% of our patients which is somewhat higher than that of the literature (17,21). This delay might also be a reason for our low complete and overall response rates. The most important effect of toxicity in our patients was that they often were unwilling to undergo further surgical staging. In our study group chemotherapy was found to be stressfull and patients who attained total or important relief of their symptoms were often unwilling to undergo further surgical staging. For this reason only 27.8% of our patients were pathologically staged.

In conclusion, we confirmed the inaccuracy in clinical restaging with 60% clinical over or understaging. Although 5 of 15 pathologically staged patients can achieve a pathologic complete response, we cannot completely eradicate pathological residual tumor in patient in whom we obtained cCR (25% PT2 disease). These findings are of serious concern relative to staging accuracy in bladder preservation protocols following neoadjuvant chemotherapy. Also, although M-VAC is considered a standard treatment option, its limitations in the treatment of invasive bladder cancer must be realized and new chemotherapatic agents or combination regimens must be identified.

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