Original Study

Postchemotherapy Lymphadenectomy in Patients With Metastatic Urothelial Carcinoma: Long-Term Efficacy and Implications for Trial Design

Andrea Necchi,[1] Patrizia Giannatempo,[1] Salvatore Lo Vullo,[2] Elena Farè,[1] Daniele Raggi,[1] Nicola Nicolai,[3] Luigi Piva,[3] Davide Biasoni,[3] Tullio Torelli,[3] Mario Catanzaro,[3] Silvia Stagni,[3] Massimo Maffezzini,[3] Luigi Mariani,[2] Roberto Salvioni[3]

Abstract

There is no clear indication for postchemotherapy surgery in patients with metastatic urothelial cancer (UC). We analyzed the contribution of postchemotherapy lymphadenectomy on survival in patients treated at our center. Twenty-eight patients were identified and results compared with those of a nonsurgically treated cohort. Surgery and response to chemotherapy were prognostic for progression-free (PFS) and overall survival (OS). If confirmed, results might have implications in daily practice and clinical trials.

Background: The contribution of postchemotherapy pelvic (PLND) or retroperitoneal lymphadenectomy (RPLND) on survival in patients with advanced and metastatic UC is still unclear. **Patients and Methods:** Between September 1986 and May 2012, 157 patients with locally advanced or metastatic UC received first-line chemotherapy consisting of mMVAC (modified methotrexate, vinblastine, doxorubicin, and cisplatin), according to our policy. Patients with subdiaphragmatic nodal disease and/or local recurrence only and who experienced at least stable disease (SD) were selected. Fifty-nine patients were identified, 28 of whom underwent surgery, 31 started consolidation chemotherapy with or without radiotherapy or observation. The prognostic effect of candidate factors on survival was evaluated using Cox proportional hazard regression models. **Results:** A total of 14 PLND and 14 RPLND patients were identified after they had achieved a complete response (CR; n = 7) or a partial response (PR) and SD (n = 21). Median follow-up was 88 months (interquartile range, 24-211 months). Median PFS was 18 (95% confidence interval [CI], 11-not estimated) and 11 (95% CI, 5-19) months, respectively, in favor of the surgical cohort and curves were statistically different (log-rank test, $P = .009$). In multivariate analysis, postchemotherapy surgery was significantly prognostic for PFS and OS and response to chemotherapy (PR and SD vs. CR) was prognostic for PFS and trended to significance for OS. A model including these 2 factors showed bootstrap-corrected Harrel C statistics for PFS and OS of 0.65 and 0.68, respectively. **Conclusion:** In well selected patients with UC like those who achieved a clinical benefit with chemotherapy and had nodal metastatic disease, there was a survival advantage in removal of disease residuals.

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[1]Department of Medical Oncology
[2]Clinical Epidemiology and Trials Organization Unit
[3]Department of Surgery, Urology Unit
Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

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Address for correspondence: Andrea Necchi, MD, Department of Medical Oncology, Medical Oncology 2 Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Via G. Venezian 1, 20133 Milano, Italy
Fax: +39 02 2390 3150; e-mail contact: andrea.necchi@istitutotumori.mi.it

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Introduction

The landscape of therapeutic options for metastatic urothelial cancer (UC) is unchanged since a few decades ago, since the introduction of MVAC (the combination of methotrexate, vinblastine, doxorubicin, and cisplatin) with a reported 65% to 70% complete (CR) or partial response (PR) and a median survival approximating 14 months.[1,2] Comparable survival estimates were further achieved with cisplatin and gemcitabine (CG), which became a standard of care based on the results of a single phase III trial reporting a better tolerability, and, because of its easier administration in an outpatient setting.[3,4] The picture, however, is that of a relapse or disease progression after response, occurring in most patients except for those (5%-10% at best) who benefit from a durable survival (eg, cure). Attempts to improve the results by modifying the original MVAC schedule or adding taxanes to CG resulted in equal efficacy, indicating the need for a paradigm shift in this disease.[5-7] At our institute, patients with unresectable locally advanced disease, metastatic disease, or recurrence after surgery were sequentially administered modified schedules of MVAC (mMVAC), either in or outside clinical trials, and global results suggested an overlapping efficacy with a slightly better tolerability over the original regimen.[7] Defining the optimal postchemotherapeutic indication of patients still having disease residuals is still an unmet need that suffers substantial heterogeneity because of a number of factors including the entity of tumor shrinkage, sites of residual disease needing a demanding technical quality, and performance status. As a result of the absence of clinical recommendations on this issue, some patients are indifferently offered either surgery, or observation only, or additional treatment with non-cross–resistant agents, or radiotherapy.

Data from surgical series in the postchemotherapy setting are scarce in this disease, but as a matter of fact at least a proportion of patients like those who present with locoregional metastases are at greater risk of relapsing at the sites of response than that of developing distant metastases.[8,9] A better understanding of the characteristics of patients who could benefit from an aggressive surgical approach could be useful to improve global outcomes and to better select those who are otherwise best candidates for additional systemic therapy as consolidation or maintenance, in the frame of modern clinical trials. The objective of this study was to assess the contribution of lymphadenectomy after chemotherapy in responding patients with nodal disease or soft tissue recurrence only.

Patients and Methods

Patient Population

We reassessed clinical data of the 157 patients with locally advanced or metastatic urothelial carcinoma who received mMVAC as first-line therapy at Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy.[7] Of those, we selected patients yielding exclusive subdiaphragmatic, abdominal, or pelvic nodal disease and who achieved at least a stable disease (SD) after 4 to 6 cycles of mMVAC in the period September 1986 to May 2012. Eligibility included patients who presented with either nodal metastases at diagnosis or with a nodal or soft tissue relapse after surgery (radical cystectomy or nephroureterectomy).

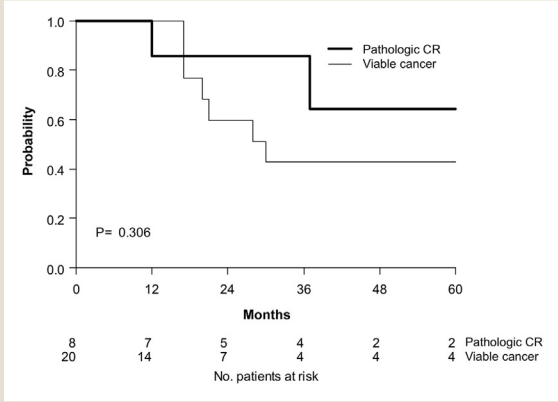
Table 1 Distribution of Clinical Characteristics by Treatment Group

Characteristic	Patients, n (%)	
	Study Group (n = 28)	Control Group (n = 31)
Median Age, Years (IQR)	59 (50-66)	
ECOG PS		
0	25 (89.3)	25 (80.7)
1	3 (10.7)	6 (19.3)
Tumor Primary		
Bladder	17 (60.7)	27 (87.1)
Upper tract	11 (39.3)	4 (12.9)
Disease Extent Before mMVAC		
Regional nodal disease	16 (57.2)	12 (38.7)
Metastatic nodal disease	3 (10.7)	4 (12.9)
Lymph node or soft tissue relapse after surgery[a]	9 (32.1)	15 (48.4)
Tumor Burden		
Single nodal site	9 (32.1)	8 (25.8)
Multiple nodal sites	19 (67.9)	23 (74.2)
Response to First-Line mMVAC		
CR	7 (25.0)	9 (29.0)
PR	17 (60.7)	14 (45.2)
SD	4 (14.3)	8 (25.8)

Data are presented as n (%) except where otherwise stated.
Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; IQR = interquartile range; mMVAC = modified methotrexate, vinblastine, doxorubicin, and cisplatin.
[a]Radical cystectomy or nephroureterectomy, including regional lymphadenectomy in all cases.

Metastatic disease was defined as the involvement of lymph nodes outside the true pelvis and above the aortic bifurcation for primary tumors of the bladder, and as disease outside the boundaries of regional nodes for the renal pelvis and ureteral primaries, according

Figure 1 Kaplan Meier Curves of Overall Survival According to Pathologic Response to Methotrexate, Vinblastine, Doxorubicin, and Cisplatin



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