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Lisa Sengeløv · Claus Kamby · Poul Geertsen
Lisbeth Juhler Andersen · Hans von der Maase

Predictive factors of response to cisplatin-based chemotherapy and the relation of response to survival in patients with metastatic urothelial cancer

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Abstract *Purpose*: To identify pretreatment variables predicting overall and complete response to cisplatin-based chemotherapy for metastatic urothelial cancer, and to study the relation between response and the duration of survival. *Patients and methods*: A total of 119 evaluable patients with recurrent locally advanced or metastatic urothelial cancer received cisplatin-based combination chemotherapy in four consecutive phase II studies from 1987 to 1997. The relationship of pretreatment variables and response was evaluated with logistic regression, and prognostic factors for survival were analyzed with Cox's multivariate model. *Results*: Response was achieved in 49% of the patients with a complete response rate of 15%. Good performance status and absence of bone metastases were independently predictive of overall response. Good performance status and normal hemoglobin were independently predictive of complete response. Median survival was 8.9 months. Performance status, alkaline phosphatase, s-creatinine, liver and bone metastases were independent prognostic factors for survival. Median survival was 12.4 months in responding patients and 6.3 in non-responding patients. Response to chemotherapy was included in the multivariate model and was the strongest prognostic factor for survival. *Conclusion*: The presence of bone metastases, low hemoglobin or poor performance status predicts decreased chance of response to chemotherapy. Response to chemotherapy is an independent prognostic factor for prolonged survival in patients with metastatic urothelial cancer.

Key words Bladder cancer · Chemotherapy · Predictive factors · Response

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L. Sengeløv (✉)
Oncology Clinic, The Finsen Center, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark
e-mail: lisa.sengelov@dadlnet.dk
Tel.: +45-35453545; Fax: +45-38114268

L. Sengeløv · C. Kamby · P. Geertsen
Department of Oncology, Herlev University Hospital, Copenhagen, Denmark

L. J. Andersen · H. von der Maase
Department of Oncology, Aarhus University Hospital, Aarhus, Denmark

C. Kamby
The Finsen Center, Department of Oncology, Copenhagen University Hospital, Denmark

Introduction

New combinations of chemotherapy with cisplatin have shown encouraging efficacy in metastatic urothelial cancer [1]. The observed increase in response rates may be caused by improved chemotherapy, but changes in patient characteristics (selection bias), and differences in response assessment may also influence the results. The existing knowledge of factors that are likely to independently influence response to anticancer drugs in metastatic urothelial cancer is limited. Some studies with neoadjuvant chemotherapy have found response to be related to tumor stage [2–5]. No relationship has been demonstrated between different biochemical markers and response to chemotherapy [6–8].

Prolongation of survival and palliation are the main endpoints when chemotherapy is used in disseminated urothelial cancer. Response is a prerequisite for palliation because it is believed that the beneficial effect of chemotherapy is obtained when objective response is achieved. Response has been an important prognostic factor for survival in univariate analyses [5, 9, 10]. Achievement of response, however, may have no value of its own, but only select patients with a favorable prognosis. By analyzing a series of patients with disseminated urothelial cancer treated at our institutions according to four regimens of cisplatin-based combination chemotherapy, we were able to investigate the relationship between clinical prognostic factors at presentation and responsiveness to chemotherapy and

survival. Finally, we assessed the prognostic value of response on survival when data were stratified according to the established prognostic factors to disclose whether response to chemotherapy added prognostic information of survival.

Patients and methods

The study included 129 patients receiving chemotherapy in the 10-year period between January 1987 and January 1997. Patients were included in four consecutive phase II trials at the Departments of Oncology, Herlev and Aarhus University Hospitals, and The Finsen Center, Department of Oncology, Copenhagen University Hospital, Denmark (Table 1) [11–14]. The eligibility criteria were: histologically proven transitional cell carcinoma (TCC) of the urothelial tract (bladder, urethra, ureter or renal pelvis) and recurrent locally advanced (non-resectable, radioresistant) and/or metastatic disease. Patients with potentially curable local disease were not included. Recurrent locally advanced disease was defined as a recurrence in the bladder, in the surgical bed after cystectomy or as metastases in pelvic nodes. Distant recurrences were presence of metastases outside the pelvis. Evaluable or measurable lesions had to be present. No prior systemic chemotherapy was allowed, and performance status score (PS) should be 0–2 (WHO-ECOG) [15]. There should be no history of other malignancies, and adequate renal, hepatic and hematological functions were required.

Staging assessment before treatment included physical examination, chest X-ray, abdominal CT scan, hematological, renal and hepatic tests. Most of the patients had a bone-scintigraphy and X-rays or CT scans of suspected areas [16]. Patients not evaluated with bone-scintigraphy and without symptoms of bone metastases were categorized in the group without bone metastases. Assessment was repeated two weeks after the third course (11 weeks after start of treatment). Response was evaluated by two independent observers, using the WHO criteria with classification into complete response (CR), partial response (PR), no change (NC) and progressive disease (PD) [15]. For the purpose of this study, the response variables were considered binary either CR versus not CR or overall response (OR = CR + PR) versus no response.

All patients received cisplatin-based chemotherapy from 1987 to 1997, and the regimens are listed in Table 1 [11–14]. Ten patients were non-evaluable, two patients died from toxicity after the first course, five patients went off study after the first course due to toxicity, two patients refused evaluation, and one patient died from other causes, leaving 119 patients for evaluation. Patients with response received up to 8 cycles of chemotherapy. The local Ethic Committees, Copenhagen County and Aarhus County, approved the protocols and written informed consent was obtained from all patients.

Statistical methods

Data were analyzed using BMDP statistical software package 4F, 1L, 2L, LR and New System (BMDP Statistical Software, Cork, Ireland). A P value less than 0.05 was considered significant. Response and survival were related to 19 potential predictive factors including sex, age, histology (pure TCC vs mixture), grading (histological grade 2–3 vs 4) [17], localization of primary tumor (bladder vs other), performance status (0 vs 1 vs 2) [15], extent of disease (locally advanced vs metastatic), number and localization of metastatic sites [16, 18], biochemical and hematological variables, and treatment protocol. The chemotherapeutic regimen was tested in four variables evaluating one regimen against the others. Variables representing blood tests were analyzed both as binary variables (abnormal vs normal) and interval scaled.

All evaluable patients were included in the response analyses. The relationship of each factor on response to chemotherapy was studied using univariate analyses (Fisher's exact test/Pearson's chi-square test) and multivariate logistic regression analysis. Variables with a univariate P value less than 0.1 were included in the multivariate analysis. The regression coefficients were estimated by the maximum likelihood method and model reduction was performed stepwise using the likelihood ratio test calculating the probability of being a responder.

The duration of survival was defined as the time from initiation of chemotherapy until death or censoring. Patients who died from other causes were considered censored events. Patients with early progression who did not survive 11 weeks (time of response assessment) were not included in the analysis of response in relation to survival (Landmark method) [19]. This method eliminates the bias caused by the 'guarantee time survival' effect among the responders. Median survival was estimated using the Kaplan-Meier method [20], and differences between groups were analyzed using the log-rank test. A multiple logistic and Cox's regression model with stepwise variable selection using the maximum partial

Table 1 Outcome according to four different protocols of cisplatin-based chemotherapy

	Period of treatment	No. of eligible patients	No. of evaluable patients	Complete response (%)	Overall response (%)	Median survival months (95% CI)[a]
Cisplatin,100 mg/m^2, q3 weeks, methotrexate, 250 mg/m^2, with leucovorin rescue, q3 weeks [9]	1987–90	34	31	2 (6)	17 (55)	6.8 (5.5–8.8)
Cisplatin, 100 mg/m^2, q3 weeks, methotrexate, 250 mg/m^2, with leucovorin rescue, q3 weeks carboplatin 200 mg/m^2, q3 weeks [10]	1991–94	55	51	8 (16)	21 (41)	9.3 (6.7–13.5)
Cisplatin, 100 mg/m^2, q3 weeks, methotrexate, 30 mg/m^2/day 1 and 8, q3 weeks, mitoxantrone, 10 mg/m^2, q3 weeks [11]	1994–95	15	12	1 (8)	5 (42)	8.5 (5.9–11.7)
Cisplatin, 75 mg/m^2,q3 weeks, docetaxel, 75 mg/m^2, q3 weeks [12]	1996–97	25	25	7 (28)	15 (60)	14.2 (8.9–17.6)

[a] Brookmeyer-Crowley confidence interval

likelihood ratio method (MPLR) were used. Proportional hazard plots were made to assure the assumption of proportional hazards. Relative risks were calculated to estimate the magnitude and the direction of the effect, and confidence intervals for relative risks were calculated. Significant prognostic factors were entered pair-wise to analyze for interaction.

Results

Table 2 shows characteristics of the 119 evaluable patients. Cystectomy had been performed in 52 patients (44%) and radiotherapy was first-line treatment in 29 patients (24%). In the remaining 38 patients, the primary treatment was either a local resection or biopsy if distant metastases were diagnosed concurrently.

Predictive factors for response

The objective OR rate was 49% (95% CI 39%, 58%), and the CR rate was 15% (95% CI 9%, 23%). Table 1 shows the OR and CR rates achieved in the four studies. Patients receiving cisplatin and docetaxel had the highest response rate, but the difference was not statistically significant.

The distribution of patient characteristics according to OR and CR is presented in Table 2. Good performance status score and absence of bone metastases were associated with an increased OR in univariate analyses. Good performance status, normal hemoglobin, absence of bone metastases and few metastatic sites were associated with an increased CR. High OR and CR rates were also seen in patients with normal LDH, normal s-creatinine, and in patients without liver metastases, but only a small number of cases had abnormal values of these variables. Data did not indicate that patients with location of the primary tumor outside the bladder or tumor of mixed histology had less probability of obtaining CR or OR.

Eighteen patients (15%) had local recurrence only (without distant metastases). Of these patients, recurrence after cystectomy was recorded in 7 patients, locally advanced tumors with enlarged pelvic lymph nodes in 8, and 3 patients had recurrence after radiotherapy. The rate of response was 29% in patients with local recurrence after cystectomy and 88% in the group of patients with locally advanced tumors and enlarged lymph nodes. One patient in the group with local recurrence after radiotherapy responded.

On a complete data set from 114 patients, a multivariate logistic regression model disclosed performance status and bone metastases independently related to OR (Table 3). The presence of bone metastases almost halved the response rate. In the group with the most favorable combination (PS = 0, no bone metastases), the predicted probability of response was 78% and the observed response rate 80%. In the 'poorest group' (PS = 2, bone metastases), the predicted probability of response was 12% and the observed rate 13%.

Performance status and hemoglobin level were independently related to CR in a multivariate logistic regression model (Table 3). The predicted probability of CR in the 'best' patient group (PS 0 and normal hemoglobin) was 39% and the observed CR rate 38%. The predicted probability in the 'poorest' group was 1% and none of these patients had CR. The type of combination chemotherapy had no significant impact on CR or OR in multivariate analysis.

Prognostic factors for survival

The median observation time was 40 months (range 26–92 months) at the date of analysis (April 1999), and 109 patients had died (92%). Ten patients were still alive, eight without evidence of disease. None were lost to follow-up. Bladder cancer was the cause of death in 107 patients; two patients died of treatment-related toxicity. The overall median survival was 8.9 months (95% CI 8.1, 10.9, range 0.02–92+). Survival was examined in relation to all pre-treatment variables. Performance status, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, s-creatinine, and presence of liver and bone metastases were all significantly related to survival. Multivariate analysis showed that performance status, bone metastases, alkaline phosphatase, liver metastases and s-creatinine were independent determinants of survival. We found a significant interaction between liver metastases and alkaline phosphatase and made a new variable joining these two determinants. The relative hazards and the corresponding *P* values are shown in Table 4. Patients with none, one or two poor prognostic factors shown in Table 4 had an estimated 1-year survival of 50%, and 12% were alive after 4 years. Patients with poor values of three or all four prognostic factors had an estimated 1-year survival of 7%, and less than 1% were alive after 2 years.

Impact of response on survival

Median survival of patients with CR was 20.2 months, in all responding patients (CR + PR) 12.4 months, and in non-responding patients (NC + PD) 6.3 months. The 5-year survival rate of patients with CR was 44%. None of the patients with PR survived 5 years, the 2-year survival rate being 8%. Survival beyond 2 years was only observed in one patient with NC, and none of the patients with PD survived more than 9 months. Figure 1 shows the estimated survival curves according to response.

Survival was less than 11 weeks in 8 patients (7%) with early progressive disease. These patients were excluded from the following survival analysis, to eliminate bias from 'guarantee time' survival of responders, leaving 111 patients for analysis. Response to chemotherapy was included in a multivariate analysis together with the

Table 2 Overall and complete response to chemotherapy according to patient characteristics. *TCC* transitional cell carcinoma, *ASAT* aspartate aminotransferase, *LDH* lactate dehydrogenase, *AP* alkaline phosphatase

Variable	No. of patients	Overall response (% PR + CR)	Univariate analyses (*P*)[a]	Complete response (% CR)	Univariate analyses (*P*)[a]
All patients	119	49		15	
Sex					
Male	97	51		14	
Female	22	41	0.483	18	0.742
Age					
≤64	64	44		14	
>64	55	55	0.273	16	0.800
Prior radiotherapy					
No	91	46		17	
Yes	28	57	0.388	11	0.559
Grade of primary tumor (3)					
1–3	90	50		17	
4	26	42	0.513	8	0.353
Histology of primary tumor					
TCC	99	48		15	
Mixture	20	55	0.627	15	1.000
Localization of primary tumor					
Bladder	94	49		16	
Other	25	48	1.000	12	0.761
Performance status score					
0	26	77		31	
1	64	48		14	
2	29	24	<0.001	3	0.018
Hemoglobin (5)					
Normal	56	45		21	
Low	58	42	0.461	7	0.032
Creatinine (1)					
Normal	104	51		16	
Elevated	14	36	0.395	7	0.692
ASAT (5)					
Normal	97	50		16	
Elevated	17	35	0.297	6	0.459
LDH (4)					
Normal	78	54		15	
Elevated	37	35	0.074	11	0.578
AP (3)					
Normal	70	53		17	
Elevated	46	41	0.257	11	0.428
Lung metastases					
Present	87	46		16	
Absent	32	56	0.409	13	0.778
Liver metastases					
Absent	90	52		18	0.234
Present	29	38	0.205	9	
Bone metastases					
Absent	97	55		19	
Present	22	23	0.009	0	0.023
Localized vs disseminated					
Recurrence in pelvis only	18	56		28	
Disseminated disease	101	48	0.613	13	0.146
Number of metastatic sites					
1	45	60		27	
2	38	42		16	
3	28	39		0	
4	8	50	0.26	0	0.011

[a] Fisher's exact test/Pearson's chi-square test. Numbers in parentheses represents patients with missing values

Table 3 Logistic regression analysis of predictive factors for response to chemotherapy in 114 patients with a complete set of values. The odds ratio represents the relation between odds for success for two persons when the value of the variable is changed one increment. (odds for success (x)/odds for success (x + 1))

	Category	Odds ratio	95% confidence interval	*P* value
Overall response				
Performance status	0 vs 1 vs 2	2.94	1.55–5.57	< 0.001
Bone metastases	Absent vs present	3.12	1.01–9.64	0.035
Complete response				
Performance status	0 vs 1 vs 2	2.96	1.19–7.34	0.009
Hemoglobin	Normal vs abnormal	3.55	1.02–12.3	0.032

Table 4 Cox multivariate regression analysis of survival in 116 patients with complete data set. *CI* confidence interval

Variable	Category	β-coefficient	Relative hazard	95% CI	*P* value
Performance status	0 vs 1 vs 2	0.62	1.87	1.35–2.59	0.0002
Bone metastases	Absent vs present	0.76	2.14	1.27–3.60	0.0041
Alkaline phosphatase + liver metastases	Normal and no liver metastases vs abnormal or liver metastases	0.59	1.80	1.17–2.76	0.0075
Serum creatinine	Normal vs abnormal	0.68	1.97	1.10–3.54	0.0224

established prognostic factors and was the first explanatory variable selected in the model. Estimated coefficients of the model with estimated relative risks of death with confidence intervals (CI) are presented in Table 5. The model shows that the risk of death is reduced by 50% in the case of response. This is also illustrated in Fig. 2, in which survival according to OR adjusted for the effect of the important variables is shown. Complete response was included in the model instead of OR and was also a highly significant prognostic factor (data not shown). Finally, we evaluated the importance of each chemotherapeutic regimen in the prognostic model. None of the combinations seemed to influence outcome significantly although the combination of cisplatin and docetaxel reached a *P* value of 0.08.

Discussion

Systemic chemotherapy has been increasingly used in disseminated urothelial cancer, and several drug combinations have shown promising activity. The overall

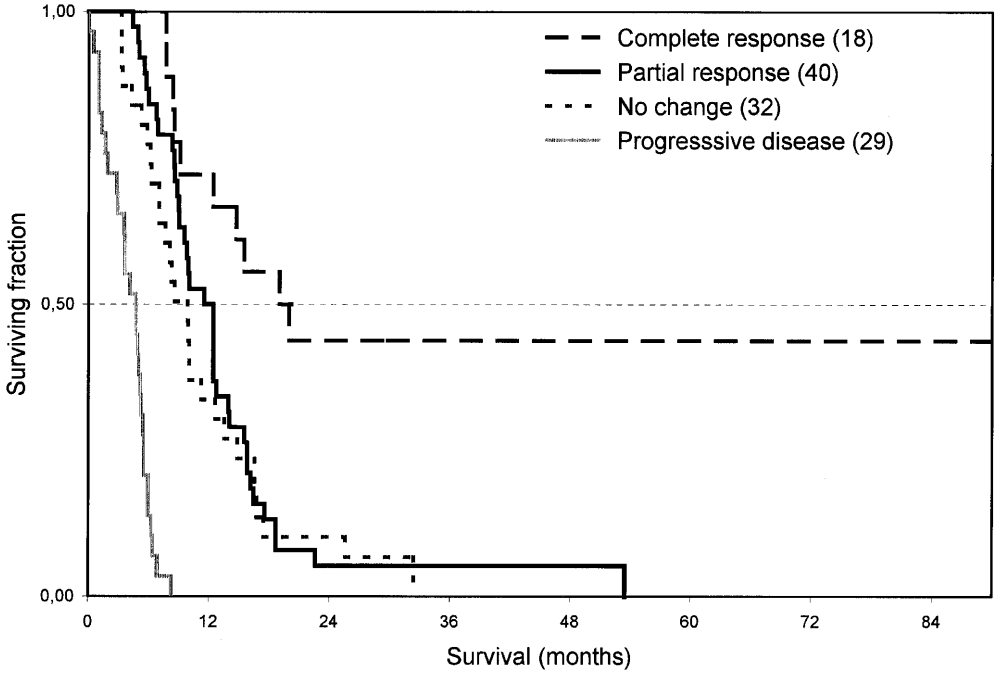

Fig. 1 Survival according to response category in 119 patients

Table 5 Cox multivariate regression analysis of survival in 107 patients with complete set of variables surviving more than 11 weeks and including response as an variable. *CI* confidence interval; *CR* complete response; *PR* partial response; *NC* no change; *PD* progressive disease

Variable	Category	β-coefficient	Relative hazard	95% CI	*P* value
Response (overall)	Yes vs no (CR + PR vs NC + PD)	0.74	2.09	1.33–2.28	0.0012
Performance status	0 vs 1 vs 2	0.44	1.55	1.09–2.21	0.0147
Bone metastases	Present vs absent	0.77	2.16	1.22–3.82	0.0080
Alkaline phosphatase + liver metastases	Normal and no liver metastases vs abnormal or liver metastases	0.59	1.81	1.15–2.84	0.0101
Serum creatinine	Normal vs abnormal	0.72	2.06	1.13–3.76	0.0180

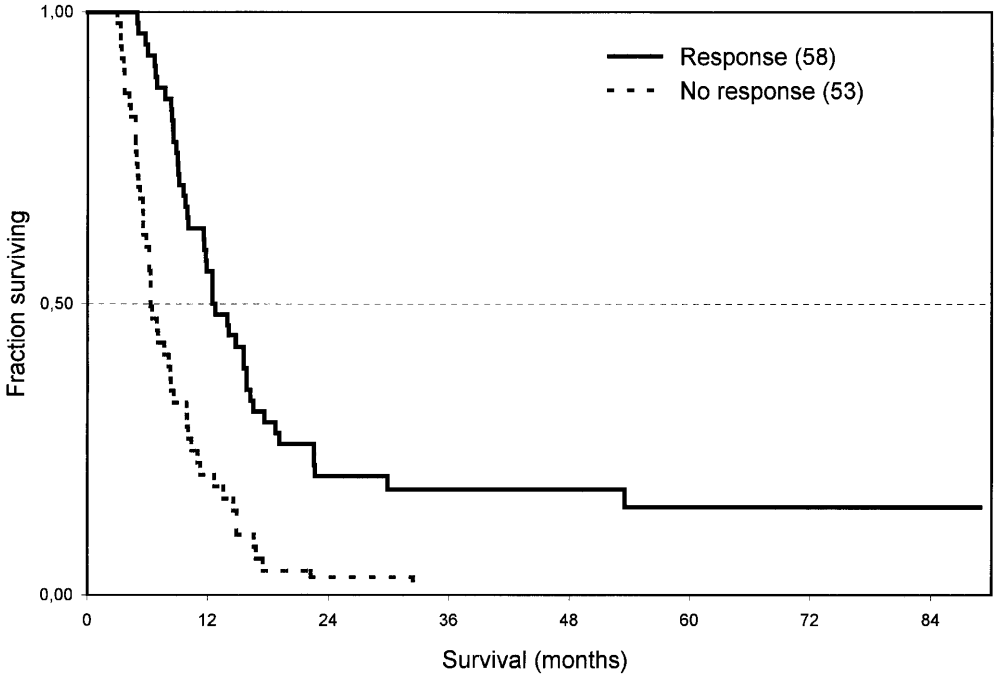

Fig. 2 Estimated survival categorized according to response. The estimated survival curves were adjusted for the effect of the independent prognostic factors; performance status, abnormal alkaline phosphatase and liver metastases, bone metastases and the level of serum creatinine ($n = 111$). The difference between the two survival curves suggests an independent effect of being a responder on survival and not a selection of patients with good prognostic features in the group of responders because the survival estimates are adjusted for this imbalance

outcome is, however, still poor and the toxicity of these regimens is serious. Patients with reduced probability of response will not benefit from the chemotherapy and, thus, only suffer from the side effects.

We evaluated 119 patients who had received different combinations of cisplatin-based chemotherapy in order to identify factors related to response. The OR and the CR rates in this study are comparable to those accomplished in other phase II and phase III studies of combination chemotherapy, including cisplatin with response rates ranging from 39–68% and CR rates in the range of 6–37% [21–26]. In the present study, the analysis of predictive factors for CR is hampered by the fact that only 18 patients (15%) achieved a CR. Such few events will make the confidence intervals wide, and the results may be less certain due to the risk of over-fitting [27]. The analyses are also weakened by the fact that five patients had to be omitted due to missing values.

We found that performance status score, level of hemoglobin and bone metastases were significantly related to response to chemotherapy. The optimal candidates for chemotherapy are patients in PS 0, or patients in PS 1 with normal hemoglobin and without bone metastases. This group constituted 51 (43%) of the total number of treated patients. The impact of PS on treatment efficacy has been reported previously [22, 25, 28]. Igawa et al. [29] found that PS was predictive of response in univariate analysis, but the effect was not significant in multivariate analysis. This may have been due to the categorization of PS (0–2 vs 3–4), together with the large number of variables tested in 54 patients. The negative impact of bone metastases on response rate is well known [30], partly because slow or missing healing of the bone makes obtainment of complete remission difficult. Most of the patients with bone metastases had distant metastases in other localizations, and bone metastases may be a marker of widely disseminated disease rather than a specific localization of poor response. The presence of bone metastases, however, had a stronger predictive value than number of metastatic sites in univariate analysis. The presence of bone and liver metastases has been reported to be

associated with a decreased chance of achieving a response [22] and, even if response occurs, long-time survivors are uncommon [31]. In one study, an independent effect on response has been shown for lung, liver and bone metastases grouped as one variable [22].

We found a normal level of hemoglobin to independently predict CR. This may be due to the correlation of complete response and tumor burden, as CR in the univariate analysis was related to the number of metastatic sites. Thus, hemoglobin may be a more accurate measurement of tumor burden. In addition, the level of hemoglobin may also relate to the oxygenation status of the tumor, which may influence tumor cell responsiveness [32]. The impact of base-line blood test levels in relation to response has not previously been reported in metastatic bladder cancer, and our findings call for confirmation. We could not demonstrate that prior treatment influenced the likelihood of response in general, but the chance of response was reduced in patients with local recurrence only after cystectomy.

Achievement of response did not relate to localization or to histology of the primary tumor in this study, in contrast to what has been suggested earlier [24, 33]. However, multivariate analysis was not performed in these studies [33] and the primary tumor may not have an independent effect. A recent study in 203 patients receiving M-VAC also showed that the site of the primary tumor (bladder vs other sites) did not affect the probability of response [34].

Renal and liver function tests were related to CR in univariate analysis, but not in the multivariate analyses. The impact of these tests may be explained by the other independent factors or the result may be due to underfitting because of a small number with abnormal tests.

The rate of CR was increased in the protocol with cisplatin and docetaxel but, overall, the treatment regimen was not an independent predictive factor. Patient selection and stage migration may account for some of the increase in CR and OR.

The impact on survival of PS, bone metastases, alkaline phosphatase, liver metastases and s-creatinine for patients that are eligible to chemotherapy are in accordance with several phase II and phase III studies [21, 22, 31, 35–37]. Most studies have proposed that PS and extent or localization of metastatic disease are the most important prognostic factors for survival [21, 22, 31]. Blood tests and renal function are often not included in the analyses, and these variables may add valuable information.

Response to chemotherapy had an independent effect on survival. Although these finding do not allow any conclusion about a causal relationship between the effect of chemotherapy and survival, they add to the suggestion that chemotherapy has a beneficial effect on outcome in metastatic urothelial cancer. It was estimated that the median survival doubled in responding patients, and response distinguished survival better than any of the pretreatment variables included in the analysis. The prognostic importance of achieving response has not previously been investigated in metastatic urothelial cell cancer in a multivariate analysis, and some reservations have to be made regarding the results: The weakness of the analysis is that the response is stratified according to pretreatment variables at baseline and not of these variables measured at the time of response evaluation. The value of the pretreatment factors could have changed during the treatment period, thus changing the prognostic importance of response. Furthermore, the results may have been influenced by the heterogeneity of treatments, since we included patients from four different trials with changing chemotherapy regimens, even though regimen was not an independent prognostic factor. Finally, response may only be a marker of some unknown factor not included in the analysis, thus representing a selection bias. The patients were all eligible for phase II studies and represent a selected population. The results may not be transferred to consecutive patients. We were able to demonstrate a good agreement between the observed and the predicted responses in different categories of patients, but the models need verification in an independent group of patients.

In conclusion, our results show that PS is the most important predictor of response to chemotherapy in metastatic urothelial cancer. In addition, normal hemoglobin predicted CR and absence of bone metastases predicted OR. The distribution of these factors is important when CR and OR are compared among different phase II studies and may increase the possibilities of selecting patients with increased chances to benefit from the treatment. Future studies should include new biomolecular markers, and continue to include the clinical predictors suggested. Objective response was a strong prognostic factor for survival, even though it does not allow any conclusion about causal association.

References

1. Roth BJ, Bajorin DF (1995) Advanced bladder cancer: the need to identify new agents in the post M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) world. J Urol 133: 894
2. Prout GRJ, Shipley WU, Kaufman DS, Heney NM, Griffin PP, Althausen AF, et al (1990) Preliminary results in invasive bladder cancer with transurethral resection, neoadjuvant chemotherapy and combined pelvic irradiation plus cisplatin chemotherapy. J Urol 144: 1128
3. Sagaster P, Flamm J, Flamm M, Mayer A, Donner G, Oberleiter S, et al (1996) Neoadjuvant chemotherapy (MVAC) in locally invasive bladder cancer. Eur J Cancer 32A: 1320
4. Angulo JC, Sanchez-Chapado M, Lopez JI, Flores N (1996) Primary cisplatin, methotrexate and vinblastine aiming at bladder preservation in invasive bladder cancer. J Urol 155: 1897
5. Sternberg CN, Arena MG, Calabresi F, De Carli P, Platania A, Zeuli M, et al (1993) Neoadjuvant M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin) for infiltrating transitional cell carcinoma of the bladder. Cancer 72: 1975
6. Sandlow J, Cohen MB, Robinson RA, Dreicher R, Williams RD (1994) DNA ploidy and P-glycoprotein expression as predictive factors of response to neoadjuvant chemotherapy for invasive bladder cancer. Urology 43: 787
7. Cook AM, Huddart RA, Norman A, Dearnaley DP, Horwich A (1998) The utility of tumor markers in assessing the response

to chemotherapy in advanced bladder cancer. Proc Am Soc Clin Oncol 17: 311a
8. Scher H, Norton L (1992) Chemotherapy for urothelial tract malignancies: breaking the deadlock. Semin Surg Oncol 8: 316
9. Herr HW, Bajorin DF, Scher HI (1998) Neoadjuvant chemotherapy and bladder-sparing surgery for invasive bladder cancer: ten-year outcome. J Clin Oncol 16: 1298
10. Splinter TAW, Pavone-Macaluso M, Jacqmin D, Roberts JT, Carpentier P, de Pauw M, Sahmoud T (1996) Genitourinary group phase II study of chemotherapy in stage T3–4 N0-X M0 transitional cell cancer of the bladder: prognostic factor analysis. Eur J Cancer 32A: 1129
11. Geertsen PF, Sengeløv L, Larsen SK, von der Maase H (1993) A phase II study of cisplatin plus methotrexate with folinic acid rescue in metastatic or locally recurrent transitional cell carcinoma of the urothelium. Eur J Cancer 29A: 347
12. Sengeløv L, Nielsen OS, Kamby C, von der Maase H (1995) Platinum analogue combination chemotherapy: cisplatin, carboplatin, and methotrexate in patients with metastatic urothelial tract tumors. A phase II trial with evaluation of prognostic factors. Cancer 76: 1797
13. Andersen LJ, Sengeløv L, Kamby C, von der Maase (1998) Cisplatin, methotrexate and mitoxantrone in patients with metastatic or advanced urothelial cancer. Acta Oncol 37: 110
14. Sengeløv L, Kamby C, Lund B, Engelholm SA (1998) Docetaxel (taxotere) and cisplatin in metastatic urothelial cancer: a phase II study. J Clin Oncol 16: 3392
15. World Health Organization (1979) WHO handbook for reporting results of cancer treatment, 48 edn. WHO, Geneva, WHO offset publication
16. Sengeløv L, von der Maase H, Kamby C, Jensen LI, Rasmussen F, Horn T, Nielsen SL, Steven K (1999) Assessment of patients with metastatic transitional cell carcinoma of the urinary tract. J Urol 162: 343
17. Bergkvist A (1965) Classification of bladder tumours based on the cellular pattern. Preliminary report of a clinical-pathological study of 300 cases with a minimum follow-up of eight years. Acta Chir Scand 130: 371
18. Sengeløv L, Kamby C, von der Maase H (1996) Pattern of metastases in relation to characteristics of primary tumor and treatment in patients with disseminated urothelial carcinoma. J Urol 155: 111
19. Anderson J, Cain K, Gelber R (1983) Analysis of survival by tumor response. J Clin Oncol 1: 710
20. Kaplan E, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Stat Assoc 53: 457
21. Mead GM, Russell M, Clark P, Harland SJ, Harper PG, Cowan R, Roberts JT, Uscinska BM, Griffiths GO, Parmar MK (1998) A randomized trial comparing methotrexate and vinblastine (MV) with cisplatin, methotrexate and vinblastine (CMV) in advanced transitional cell carcinoma: results and a report on prognostic factors in a medical research council study. MRC Advanced Bladder Cancer Working Party. Br J Cancer 78: 1067
22. Loehrer PJ Sr, Einhorn LH, Elson PJ, Crawford ED, Kuebler P, Tannock I, Raghavan D, Stuart-Harris R, Sarosdy MF, Lowe BA, et al (1992) A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma. J Clin Oncol 10: 1066
23. Hillcoat BL, Raghavan D, Matthews J, Kefford R, Yuen K, Woods R, Olver I, Bishop J, Pearson B, Coorey G, et al (1989) A randomized trial of cisplatin versus cisplatin plus methotrexate in advanced cancer of the urothelial tract. J Clin Oncol 7: 706
24. Sternberg CN, Yagoda A, Scher HI, Watson RC, Geller N, Herr HW, Morse MJ, Sogani PC, Vaughan ED, Bander N, et al (1989) Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium. Efficacy and patterns of response and relapse. Cancer 64: 2448
25. Logothetis CJ, Dexeus FH, Finn L, Sella A, Amato RJ, Ayala AG, et al (1990) A prospective randomized trial comparing MVAC and CISCA chemotherapy for patients with metastatic urothelial tumors. J Clin Oncol 8: 1050
26. Harker WG, Meyers FJ, Freiha FS, Palmer JM, Shortliffe LD, Hannigan JF, McWhirter KM, Torti FM (1985) Cisplatin, methotrexate, and vinblastine (CMV): An effective chemotherapy regimen for metastatic transitional cell carcinoma of the urinary tract. A Northern California oncology group study. J Clin Oncol 3: 1463
27. Concato J, Feinstein AR, Holford TR (1993) The risk of determining risk with multivariate models. Ann Intern Med 118: 201
28. Trump DL, Elson P, Madajewicz S, Dickman SH, Hahn RG, Harris JE, Vogl SE (1990) Randomized phase II evaluation of carboplatin and CHIP in advanced transitional cell carcinoma of the urothelium. The Eastern Cooperative Oncology Group. J Urol 144: 1119
29. Igawa M, Ohkuchi T, Ueda M, Usui T (1992) Factors affecting the outcome of patients with advanced urothelial cancer following chemotherapy with methotrexate, vinblastine, adriamycin, and cisplatin. Cancer Chemother Pharmacol 30: 77
30. Soloway MS, Ishikawa S, Taylor T, Ezell G (1989) M-VAC or MVC for the treatment of advanced transitional cell carcinoma: metastatic, induction, and adjuvant. J Surg Oncol Suppl 1: 40
31. Saxman SB, Propert KJ, Einhorn LH, Crawford ED, Tannock I, Raghavan D, Loehrer PJ Sr, Trump D (1997) Long-term follow-up of a phase III intergroup study of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J Clin Oncol 15: 2564
32. Feldmann HJ, Molls M, Vaupel P (1999) Blood flow and oxygenation status of human tumors. Clinical investigations. Strahlenther Onkol 175: 1
33. Scher HI, Yagoda A, Herr HW, Sternberg CN, Bosl G, Morse MJ, Sogani PC, Watson RC, Dershaw DD, Reuter V, et al (1988) Neoadjuvant M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) effect on the primary bladder lesion. J Urol 139: 470
34. McCaffrey JA, Dodd PM, Herr H, Vlamis V, Mazumdar M, Higgins G, et al (1998) Nonbladder primary site of transitional cell carcinoma (TCC) does not affect probability of response to MVAC or survival. Proc Am Soc Clin Oncol 17: 337a
35. Geller NL, Sternberg CN, Penenberg D, Scher HI, Yagoda A (1991) Prognostic factors for survival of patients with advanced urothelial tumors treated with methotrexate, vinblastine, doxorubicin and cisplatin chemotherapy. Cancer 67: 1525
36. Fosså SD, Sternberg C, Scher HI, Theodore CH, Mead B, Dearnaley D, Roberts JT, Skovlund E (1996) Survival of patients with advanced urothelial cancer treated with cisplatin-based chemotherapy. Br J Cancer 74: 1655
37. Bajorin DF, Dodd PM, McCaffrey JA, Mazumdar M, Vlamis V, Herr H, et al (1998) M-VAC in transitional cell carcinoma (TCC): prognostic factors and long time survival in 203 patients. Proc Am Soc Clin Oncol 17: 311a