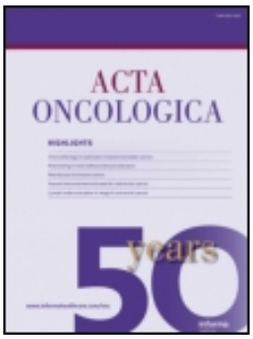

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ORIGINAL ARTICLE

Predictive factors for response and prognostic factors for long-term survival in consecutive, single institution patients with locally advanced and/or metastatic transitional cell carcinoma following cisplatin-based chemotherapy

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Abstract

Purpose. The study was undertaken to identify pre-treatment clinical and histopathological factors of importance for response and survival after cisplatin-based combination chemotherapy, in patients with locally advanced or metastatic transitional cell carcinoma of the urothelium. *Patients and methods.* Clinical, laboratory and histopathological data from 178 consecutive patients, representing all patients treated between 1991 and 2001 in a single institution, were collected. Correlations between these data and response and survival after chemotherapy were analysed using univariate and multivariate analyses. *Results.* Absence of visceral metastasis was the only parameter with independent correlation to the response to chemotherapy. Two of the analysed parameters were independently associated with increased survival: good performance status (PS $\leq$1) and absence of visceral metastases. Stratification of the patient material according to number of these risk-factors present showed strong association with survival. *Conclusion.* It was possible to predict survival from pre-treatment clinical parameters and consequently it is possible to select groups with a high and low probability of obtaining long term survival following cisplatin-containing chemotherapy.

Despite radical surgical and radiotherapeutic treatments offering excellent results in terms of local control, 20–40% of patients diagnosed with invasive bladder cancer will eventually develop metastasis and succumb to the disease. These patients have a median life expectancy between three and six months if left untreated. There is little doubt that the advancement of chemotherapy has improved the life expectancy of these patients over the past decades. A range of chemotherapeutic drugs have been tested against transitional cell carcinoma, however cisplatin is still considered the single most efficient drug in treatment of these tumours used alone [1] or in combination [2]. Although direct evidence or quantification of the survival benefit from chemotherapy vs. best supportive care has never been investigated in prospective studies, indirect evidence can be inferred from the survival benefit demonstrated by multidrug chemotherapy over single drug treatment [3]. Various combination regimens with cisplatin have prolonged the survival of patients with advanced bladder cancer to between 13 and 24 months [4,5], and response rates above 75% [4] have emphasized that bladder cancer must be considered a chemotherapy sensitive disease. Although chemotherapy trials have demonstrated long-term survival in a small proportion (up to 5–6%) of patients, this treatment modality is still considered palliative.

Cisplatin containing combination chemotherapy in bladder cancer is toxic treatment with significant side effects. Its use should preferably be warranted by a high probability of a survival benefit in the individual patient. Demonstration of significant predictive factors for response and survival will facilitate and optimise selection of patients in this respect.

In order to investigate the predictive power of commonly available clinical and histopathological parameters for the outcome of chemotherapy and survival, we have collected and analysed data from all patients receiving platinum based chemotherapy for transitional cell carcinoma at our institution over

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a 10-year period from 1991 to 2001. Previous studies have indicated that pre-treatment prognostic information on survival can be gained from performance status score, presence of visceral metastases and elevated serum levels of alkaline phosphatase [5–10]. Similarly response to chemotherapy is associated with the presence of visceral metastases, level of haemoglobin and performance status [8,9].

Material and methods

Patients

The study included a total of 178 consecutive patients receiving first line platinum containing combination chemotherapy for locally advanced (T4B, N2-3) and/or metastatic (M1) transitional cell carcinoma (TCC) at the Department of Oncology, Aarhus University Hospital, Denmark, in the 10-year period between 1991 and 2001. All patients had transitional cell carcinoma of the urothelial tract (urethra, bladder, ureters or renal pelvis) histologically diagnosed or confirmed at our institution. All patients received one of seven cisplatin-based combination chemotherapy schedules as shown in Table I and were included in either one of four phase II protocols, one phase III protocol or were treated with the standard regimen at the relevant time (MVAC or GC). Patients were treated to a maximum of 6 cycles unless progression or unacceptable toxicity appeared. Patients receiving standard treatment were prospectively followed under the same conditions as in the protocols.

Table I. Chemotherapy regimes 1991–2001.

Trial	No. of patients
Cisplatin 100 mg/m^2, carboplatin 200 mg/m^2, methotrexate 250 mg/m^2 (phase II) [15]	24
Cisplatin 100 mg/m^2, methotrexate 30 mg/m^2, mitoxantrone 10 mg/m^2 (phase II) [16]	14
Gemcitabine 1000 mg/m^2, cisplatin 35 mg/m^2 (phase II) [17]	18
Gemcitabine 1000 mg/m^2, cisplatin 70 mg/m^2 vs. Methotrexate 30 mg/m^2, vinblastine 3 mg/m^2, doxorubicin 30 mg/m^2, cisplatin 70 mg/m^2 (phase III) [18]	43
Gemcitabine 1000 mg/m^2, cisplatin 70 mg/m^2, paclitaxel 175 mg/m^2 (phase II) [19]	12
Methotrexate 30 mg/m^2, vinblastine 3 mg/m^2, doxorubicin 30 mg/m^2, cisplatin 70 mg/m^2 (standard)	44
Gemcitabine 1000 mg/m^2, cisplatin 70 mg/m^2 (standard)	23
Total	178

Seven chemotherapy regimes used to treat a total of 178 patients with transitional cell carcinoma at our institution between 1991–2001.

Patients presenting with locally advanced disease, obtaining a significant partial or complete response to chemotherapy, were offered consolidating surgery or, more often, radiotherapy when applicable.

Methods

Diagnostic work-up and staging of patients prior to treatment included CT scans of thorax, abdomen and pelvis, bone scintigraphy in case of bone pain or other skeletal symptoms and ultrasound with fine needle aspiration of lesions unresolved by CT scan. All patients were followed with CT scans every 3rd month until progression.

Patient files, laboratory and radiographic data were retrieved from archives. Patient characteristics, laboratory test results, staging procedures and the histopathology of the tumour prior to chemotherapy were recorded. Continuous numerical data were dichotomised, using either median values (age) or local laboratory normal limits (Table II, first column) as cut-off points. Visceral metastases were defined as metastases outside the urothelial tract, the bladder bed and the lymphatic system. Histopathology data included tumour grade ($\leq$ 3 vs. 4) [11] and tumour type (pure TCC vs. TCC with squamous or adenomatous differentiation). Pre-treatment TNM [12] status for each patient was re-evaluated using reports from the urologic surgeons, pathology reports and reports from diagnostic imaging (x-ray, CT scans, ultrasonography and bone scintigraphy).

Response to chemotherapy was graded using the WHO-criteria [13] into complete response (CR), partial response (PR), no change (NC) and progressive disease (PD). This was done after every two or three cycles of chemotherapy according to the trial protocols and finally four weeks after the last cycle. Most data were collected prospectively as patients were treated in research protocols (Table I).

Statistics

Fifteen clinical, histopathological and laboratory parameters were tested for their association with response and survival after chemotherapy. Survival time was calculated from the start of chemotherapy until death or censoring (September 2006) giving a follow up period between 5 and 15 years. All 178 patients were included in the survival analysis. Parameters were compared in univariate analyses using log rank test. Survival distributions were estimated using the Kaplan-Meier method [14]. Variables with p-values equal to or below 0.1 in univariate analyses were included in multivariate

Table II. Prognostic factors for survival (univariate analyses).

	N	Median survival (months)	P	CR+PR (%)	NC+PD (%)	P
All patients	178	12.10		57 (46%)	68 (54%)	
Performance status						
≤ 1	140	14.80		50 (53%)	45 (47%)	
≥ 2	38	5.23	0.000	7 (23%)	23 (77%)	0.005
B-haemoglobin						
♂≥8,4; ♀≥7,4 mmol/l	82	15.43		31 (53%)	27 (47%)	
♂<8,4; ♀<7,4 mmol/l	96	10.30	0.001	26 (39%)	41 (61%)	0.101
S-creatinine						
≤ 120 μmol/l	155	12.43		52 (46%)	60 (54%)	
> 120 μmol/l	23	11.73	0.336	5 (38%)	8 (62%)	0.585
GFR (1)						
≥ 60 ml/min	161	13.07		53 (47%)	60 (53%)	
< 60 ml/min	16	9.57	0.027	4 (33%)	8 (66%)	0.370
S-ALAT (1)						
≤ 40 U/l	161	12.70		54 (47%)	60 (53%)	
> 40 U/l	16	8.60	0.318	3 (30%)	7 (70%)	0.291
S-LDH (1)						
≤ 500 U/l	152	13.13		51 (50%)	50 (50%)	
> 500 U/l	25	7.63	0.000	6 (26%)	17 (74%)	0.034
S-alkaline phosphatase (1)						
≤ 270 U/l	119	13.53		40 (52%)	37 (48%)	
> 270 U/l	58	8.57	0.001	17 (36%)	30 (64%)	0.087
Lung metastasis (1)						
No	143	13.13		47 (50%)	48 (50%)	
Yes	34	7.90	0.037	10 (34%)	19 (66%)	0.156
Liver metastasis (9)						
No	135	14.93		46 (51%)	44 (49%)	
Yes	34	7.80	0.000	9 (32%)	19 (68%)	0.079
Bone metastasis						
No	145	13.23		49 (50%)	49 (50%)	
Yes	33	7.63	0.001	8 (30%)	19 (70%)	0.060
Visceral metastasis (2)						
No	89	18.03		33 (65%)	18 (35%)	
Yes	87	8.47	0.000	24 (33%)	48 (67%)	0.001
Histology (1)						
Pure TTC	149	12.70		46 (44%)	59 (56%)	
TTC with squamous or adenomatous differentiation	28	11.27	0.517	11 (58%)	8 (42%)	0.257
Grade of primary tumour (2)						
≤ 3	129	12.07		44 (47%)	50 (53%)	
4	47	12.70	0.689	13 (42%)	18 (58%)	0.637

Patient characteristics and the results of the univariate analyses concerning the pre-treatment prognostic factors for survival and predictive factors for response. The numbers in brackets (..) in the first column represent number of missing values. Abbreviations: CR, complete response, PR, partial response, NC, no change, PD, progressive disease, TCC, transitional cell carcinoma.

analyses using Cox regression model. P-values less than 0.05 (two-sided test) were considered significant.

The relationship between clinical parameters and the response to chemotherapy was examined in univariate analyses using χ^2-test. Variables with

p-values equal to or below 0.1 in univariate analyses were included in multivariate analyses using a binary logistic regression model. P-values less than 0.05 (two-sided test) were considered significant.

All statistical analyses were performed using the SPSS 13.0 statistical package (SPSS Inc., IL, USA)

Results

The investigated clinical, histopathological and laboratory data of potential prognostic importance are listed in Table II along with results of the univariate analyses of their association with response to and survival after chemotherapy.

Male/female ratio was 4:1 (141 males of 178, 79%), and the median age for the cohort of patients was 59 years (range 36 to 75 years) at the initiation of chemotherapy. Median performance status score was 1, and 140 patients (79%) had a score of 0 or 1.

A large group of patients had subnormal haemoglobin at presentation (96 of 178, 54%), whereas only a minority showed reduced renal function. Thus 13% (23 of 178) had elevated S-creatinine level and 9% (16 of 177) a GFR below 60 ml/min. Nine percent of the patients had elevated ALAT (16 of 177), 14% (25 of 177) had elevated LDH while one third of the patients showed increased S-alkaline phosphatase level (58 of 177, 33%).

Approximately half of the patients (89 of 176, 51%) were treated on the basis of locally advanced primary disease stage (T4B and/or N >1) whereas the other half (87 of 176, 49%) had remote metastatic (M1) disease at the start of therapy. The number of patients with metastatic spread to the lungs, liver, or bone was similar. Nineteen percent (34 of 177) had lung metastasis, 20% (34 of 169) had liver metastasis and 19% (33 of 178) had bone metastases.

Number of missing laboratory data and staging procedures are shown in the brackets in Table II.

Predictive factors for response

One hundred and twenty-five patients were evaluable for response to chemotherapy. Of these, 22 patients (18%) had a CR and 35 patients (28%) a PR for an overall response rate of 46%. Fifty patients (40%) had no change and 18 patients (14%) showed progressive disease as best response (Table II). Univariate analyses demonstrated performance status, S-LDH and visceral metastases to be statistically significantly related to response (Table II). Of patients in good performance status (PS $\leq$ 1) 53% responded to the treatment while only 23% of the patients with a low performance score (PS > 1) achieved a response. The majority of patients had normal levels of S-LDH and 50% of these patients responded to the treatment, whereas only 26% of the patients with elevated S-LDH obtained response. Patients with visceral metastasis demonstrated a response rate of 33% compared to 65% in patients without such organ involvement. In univariate analyses elevated S-alkaline phosphatase, presence of liver metastases and bone metastases all showed p-values below 0.1 and these parameters were included in the multivariate regression analysis. This analysis established that presence or absence of visceral metastasis was the only independent predictive factor for response in the present material (p = 0.04) (Table III).

Prognostic factors for survival

The overall median survival was 12.1 months (95% CI: 10.52–13.67) with a 9.6% censoring rate at a follow-up time of minimum 61 months. The five-year survival rate was 11.2%. Univariate analyses demonstrated performance status, B-haemoglobin, GFR, S-LDH, S-alkaline phosphatase, visceral metastases and presence vs. absence of lung metastases, liver metastases and bone metastases (Table II) to be significantly related to survival. Cox' multivariate regression analysis showed that performance status (PS $\leq$1 vs. PS $\geq$2) and visceral metastasis (absent vs. present) were independent prognostic factors for survival (Table IV).

For patients with PS $\leq$1, the median survival was 14.8 months (95% CI: 12.98–16.62) vs. 5.2 months (95% CI: 3.37–7.10 months) in patients with PS $\geq$ 2. Patients with visceral metastases shoved a median survival of 8.5 months (95% CI: 6.97–9.96) vs. 18.0 months (95% CI 15.19–20.88) in patients with only bladder involvement or nodal spread.

Risk groups

Based on the result of the Cox regression model patients were retrospectively divided into three groups, according to the number of independent prognostic factors they presented with prior to chemotherapy (Table V). The group of patients

Table III. Predictive factors for response (multivariate analysis).

Variables	P	Odds ratio	95% CI
Performance status	0.084	2.567	0.882–7.471
LDH	0.187	2.185	0.685–6.975
AP	0.582	1.303	0.508–3.343
Visceral metastasis	0.039	2.835	1.054–7.625

Results of binary logistic regression analysis including 117 patients evaluable for response. Eight patients were excluded because of missing values. Abbreviations: CI, confidence interval.

Table IV. Prognostic factors for survival (multivariate analysis).

Variables	P	Odds ratio	95% CI
Performance status	0.001	2.194	1.408–3.420
B-haemoglobin	0.110	1.352	0.934–1.956
GFR	0.281	1.375	0.771–2.454
S-LDH	0.226	1.386	0.817–2.352
S-alkaline phosphatase	0.691	1.088	0.718–1.647
Visceral metastasis	0.001	2.779	1.526–5.060

Results of Cox multivariate regression analysis including 167 patients. Eleven patients were excluded because of missing values. Abbreviations: CI, confidence interval.

with no risk factors contained 48 patients (27%). The median survival in this group was 18 months (95% CI: 15.58–20.49) and the five-year survival was 21% (Figure 1). The groups of patients having one or two risk factors encompassed 95 (54%) and 33 (19%) patients respectively. Patients with one risk factor had a median survival time of 13.2 months (95% CI: 10.13–16.33) and patients with two risk factors had a median survival time of 5.2 months (95% CI: 3.28–7.18). As seen in Table V this difference was highly significant ($p < 0.0001$). All long term survivors (> 60 months) were found among patients with 0 or 1 risk factors (Figure 1).

Separating the patients according to the number of adverse prognostic factors was also found to predict response to chemotherapy. Amongst patients with no adverse prognostic factors a response rate of 63% (12 of 19) was seen, whereas patients with one or two adverse prognostic factors responded in 53 and 18% of cases respectively (Table VI). This association was highly significant in univariate analysis ($p = 0.002$).

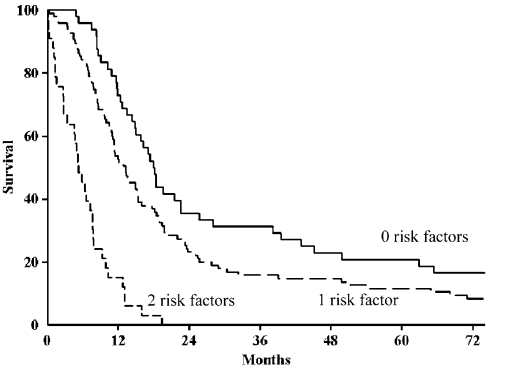
Discussion

Locally advanced or metastatic transitional cell carcinoma is, based on the relative high response rates (39–78%) [4,8] obtained with systemic combination chemotherapy, a chemotherapy sensitive disease. The long-term survival is, however, still poor and chemotherapy is curative in only a very limited number of patients.

Table V. Risk factors influence on survival.

No. of prognostic factors	N(%)	Median survival	P
0	48(27%)	18.03	
1	95(54%)	13.23	< 0.0001
2	33(19%)	5.23	

The influence of numbers of adverse prognostic factors (risk factors) on survival.



Time (months)		0	12	24	36	48	≥60
Patients at risk	0 risk factors	48	35	17	15	11	10
	1 risk factors	95	51	22	9	15	14
	2 risk factors	33	5	0	0	0	0

Kaplan-Meier plot stratified by number of prognostic factors prior to chemotherapy.

The results of this study confirm previous studies. In 1992 Loehrer et al. [8] found that performance status, absence of visceral metastasis and no weight loss was associated with improved survival and response to chemotherapy. Bajorin [6] and colleagues from the Memorial Sloan-Kettering Cancer Centre and later Bellmunt [7] and the Spanish Oncology Genitourinary Group found that visceral metastasis and performance status had profound impact on survival. A phase II study by Stadler et al. [5] showed that visceral metastasis was the only prognostic parameter for survival, whereas Sengelov et al. [9] found that survival was influenced by performance status, bone and liver metastasis, alkaline phosphatase and s-creatinine. Thus, presence of visceral metastasis and low performance status have, both in this study and in earlier clinical trials, been shown to be adverse prognostic factors for survival in patients with advanced or metastatic transitional cell carcinoma. The most likely explanation is that these parameters reflect an increased tumour burden and advanced cancer disease state. Presence of only locally advanced disease status or unresectable local relapse without recognizable systemic spread indicates relative lack of tumour aggressiveness and metastatic potential. The observed prolonged survival in these patients might well, at least in part, be a consequence of a more indolent nature of these tumours per se along with a product of a beneficial effect of chemotherapy.

Sengelov [9] found that response to chemotherapy was influenced by performance status, visceral metastasis and low haemoglobin, whereas Loehrer et al. [8] found that response was influenced by performance status, weight loss and visceral metastases. The present study found presence of visceral metastases to be the only independent predictive

Table VI. Risk factors influence on response.

No. of prognostic factors	N	CR+PR (%)	NC+PD (%)	P
0	19	12 (63%)	7 (37%)	
1	76	40 (53%)	36 (47%)	0.002
2	28	5 (18%)	23 (82%)	

The influence of numbers of adverse prognostic factors (risk factors) on response.Abbreviations: CR, complete response, PR, partial response.

factor for response to chemotherapy. The reason why TCC seems to responds better to chemotherapy in T and N sites than in visceral metastatic sites is not clear, but could well be a consequence of inherent biologic differences between tumours with and without metastatic propensity as mentioned above.

Since only a minority of the chemotherapy administered to patients with metastatic bladder cancer results in long term survival – in the present study just above 10%-prolongation of survival and palliation of symptoms remain the major goals for the vast majority of patients treated. Selection of patients for chemotherapy, and omitting toxic and potentially harmful treatment to patients unlikely to benefit is thus a key challenge. Thorough review of the available literature and prospective analyses of the actual chemotherapy administered has been the aim of a large coherent series of publications from Sweden [20,21]. They concluded that although with cisplatin based multidrug chemotherapy response rates were high, the lack of randomised comparisons with best supportive care precludes definite conclusions regarding survival benefit gained. The differences observed in median survival between less intensive regimes (4.5 months with metotrexate/vinblastine [22]) and recent, more intensive chemotherapy (up to 13–15 months with cisplatin based regimes [2]) however strongly suggests a survival benefit in selected patient groups. The basis on which to select patients for chemotherapy is however undocumented. Phase II protocols are often restricted to patients in relative good general condition without significant comorbidity. Data derived from such studies are consequently biased compared to the patient populations of everyday practise. The present study comprises data from consecutive patients – thus a patient population representative of the full clinical spectrum of patients requiring treatment.

The paucity of sufficiently large, prospective trials to provide a secure evidence base for these routine decisions stresses the need for initiation and design of protocols to answer these questions and constitute the justification for retrospective analyses like the present.

In our study stratification according to risk factors defines a group of patients with relatively good prognosis (nodal and local disease only) and a group with a very short expected survival (visceral metastatic disease and/or low performance status). Although it can not be concluded from these data that patients in the latter group, "bad prognosis patients", do not obtain a survival benefit from chemotherapy, less than 40% of the patients in our study survive to the end of planned chemotherapy (6 months). The toxicity of relevant chemotherapy regimes is significant; its influences on immediate quality of life are, as mentioned above, not well documented. This, along with the fact that response rates are found to be significantly lower (only 18 vs. 63% and 53% with zero and one risk factor) warrants cautious consideration and discussion with patients in this group regarding other, more immediate means of symptom palliation.

Finally, stratification according to known prognostic factors is important in future randomised clinical trials. Selecting patients with high probability of responding and minimising the differences in patient populations reduces the risk of selection bias making differences attributable to differences in efficacy of the examined therapeutic combinations more evident.

Declaration of interest: The authors report no conflict of interest. The authors are responsible for the content and writing of the paper.

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