Pergamon

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Prognostic Factors and Survival in Patients With Metastatic Renal Cell Carcinoma Treated With Chemotherapy or Interferon-α

S.D. Fosså, A. Kramar and J.-P. Droz

Prognostic factors and survival were analysed in 295 patients with metastatic renal cell carcinoma (MRCC), treated with either chemotherapy (1975–1990) or interferon (IFN) (1983–1990). The 3-year survival was 8 and 24% in the chemotherapy and IFN groups, respectively ($P < 0.001$). In the univariate analysis, age ≤ 60 years, prior nephrectomy, more than 1 year since initial diagnosis and treatment for metastatic disease, ECOG performance status 0 or 1, absence of liver metastases, lower erythrocyte sedimentation rate (first hour), and ≤ 10% weight loss, within the past 6 months, were correlated with improved survival. Sedimentation rate, performance status and weight loss remained independent prognostic factors from the results of a Cox regression analysis. Three prognostic groups were identified from a combination of these factors. In the poor and intermediate risk groups, no significant survival difference was observed between patients treated with chemotherapy and those treated with IFN. The 3-year survival estimates for good risk patients were 15 and 48% in the chemotherapy and IFN groups, respectively. Therefore, in MRCC, sedimentation rate, performance status and weight loss are easily assessable and reproducible prognostic variables for the identification of risk groups. We hypothesise that IFN may increase survival in good risk patients, but is as ineffective as chemotherapy in poor risk patients with MRCC.

Key words: metastatic renal cell carcinoma, chemotherapy, interferon-α, prognostic factors, survival
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INTRODUCTION

METASTATIC RENAL cell carcinoma (MRCC) represents one of the most chemo-resistant malignancies in medical oncology. However, immunomodulatory treatment with interferon-α (IFN) and/or interleukin-2 (IL-2) has shown response rates of about 10–30% [1–3]. The considerable inter- and intra-patient variability of the disease makes the comparison of survival rates obtained from the different phase II studies problematic. In spite of irrefutable objective responses, even complete responses, the question still remains of whether immunomodulatory treatment has any beneficial impact on survival in all treated patients, or only in certain subgroups. In an attempt to study this, the present retrospective investigation analysed survival rates and prognostic factors in two groups of patients with MRCC, receiving either chemotherapy or IFN.

PATIENTS AND METHODS

Patient population

Between 1975 and 1990, a total of 159 non-randomised patients, referred to the Institute Gustave Roussy, were included in several phase II trials evaluating different cytotoxic agents or drug combinations (CHEMO group: CCNU 61 patients, weekly epi-rubicin 40 patients, ellipticine 16 patients, dacarbazine/cyclophosphamide/cisplatin/doxorubicin/vindesine 14 patients, ifosfamide 19 patients, methyl-GAG/alkeran 9 patients [4]. During approximately the same period (1983–1990), 136 patients were treated at the Norwegian Radium Hospital with IFN-α (IFN group) administered intramuscularly, three times a week, at doses ranging from 18 to 36 × 10^6 U, with or without vinblastine [2]. As the combined IFN-vinblastine therapy did not have any significant influence on survival [5], it was felt justified to pool patients into one group (IFN group). 49 patients also received 20 mg of low-dose prednisone daily which was reduced to 10 mg per day after 4 weeks in order to decrease treatment-related morbidity.

Statistical methods

All patients' pretreatment and outcome characteristics were entered into a combined database, enabling the investigation of prognostic factors for MRCC. In the univariate and multivariate analyses, the following variables were evaluated: age, sex, ECOG performance status (PS), weight loss within the previous 6 months (WL), erythrocyte sedimentation rate (ESR), time since initial diagnosis and treatment for metastatic disease (DTI), presence of specific metastatic sites and prior nephrectomy. Combinations of important variables were then used to form groups of similar prognosis in order to compare the treatment groups adjusted for these prognostic indicators.

Patients' characteristics were compared using χ^2 tests for

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discrete variables and Student's t-test for continuous variables. Survival time was calculated from treatment start to death or last news, whichever came first. All patients were followed until death or to October 1991 in the CHEMO group, and until 31 December 1992 in the IFN group. Survival was estimated according to the Kaplan–Meier method, and differences between survival curves were assessed by the log rank test. Independent prognostic variables were identified by a Cox regression analysis, using a backward procedure to eliminate non-influential variables. A P value < 0.05 was used to select significant variables. Once a model was obtained, a forward procedure was used to make sure that any variable omitted during the first stage did not significantly modify prognosis.

RESULTS

Patient population

Patients' pretreatment characteristics in the two treatment groups are shown in Table 1.

Significant pretreatment differences were observed between the two groups. Patients in the CHEMO group were more frequently male patients, had a poorer PS and more WL than patients in the IFN group. More patients in the IFN group had previous nephrectomy, and a longer DTI.

The response rates of the different treatment schedules in the CHEMO group have been reported previously, summating to a total response rate of 2% for all patients [4]. The overall response rate in the IFN group was 20%.

There was no difference in survival for patients from the CHEMO group treated before 1983 as compared with those treated thereafter. Survival curves from the total CHEMO group and the IFN group are presented in Figure 1. The 3-year survival estimates are 8 and 24% in the chemotherapy and IFN groups, respectively. The difference is statistically significant (log rank, $P < 0.001$).

Table 1. Patients' details

	CHEMO group	IFN group	P
No. of patients	159	136	
Males	119 (75%)	81 (60%)	0.005
Females	40 (25%)	55 (40%)	
Median age (years)	56	60	0.075
Range	(20–75)	(35–75)	
Nephrectomy	199 (75%)	127 (93%)	0.001
DTI*			
≤ 12 months	117 (74%)	76 (56%)	0.001
> 12 months	42 (26%)	60 (44%)	
Performance status			
0/1	96 (60%)	120 (88%)	0.001
≥ 2	63 (40%)	16 (12%)	
Lung metastases	103 (65%)	84 (62%)	0.59
Liver metastases	34 (21%)	23 (17%)	0.33
Sedimentation rate† (mm)			
< 50	75 (51%)	78 (57%)	
50–99	45 (30%)	36 (26%)	0.33
≥ 100	28 (19%)	22 (16%)	
Mean (range)	55 (1–146)	50 (2–150)	
Weight loss‡			
≤ 10%	86 (54%)	123 (90%)	0.001
> 10%	73 (46%)	13 (10%)	
ESR/WL§			
No	76 (48%)	105 (77%)	0.001
Yes	83 (52%)	31 (23%)	

* Interval from diagnosis to start of systemic treatment. † Missing values for 11 patients in the CHEMO group. ‡ During the last 6 months. § Yes: erythrocyte sedimentation rate ≥ 100 mm and/or weight loss > 10%.

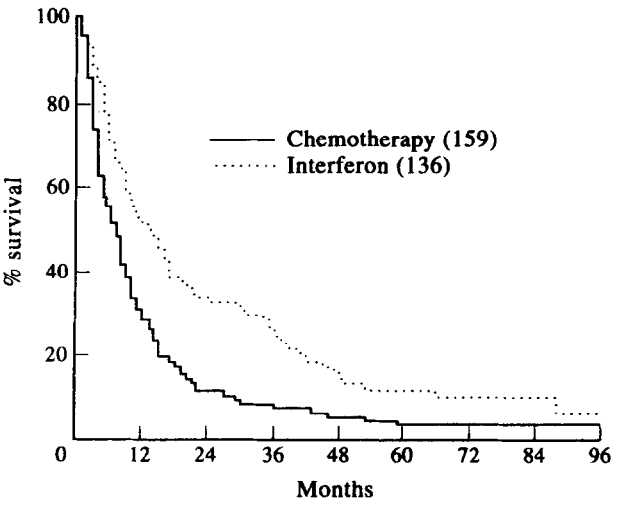

Figure 1. Survival for patients with MRCC treated either with IFN (... IFN group, 136 patients) or without IFN but with different types of chemotherapy (—— CHEMO group, 159 patients).

However, a comparison of pretreatment patient characteristics indicated that the patient population treated by chemotherapy was different from that treated by IFN. It was, therefore, felt necessary to compare subgroups of patients who were better balanced with regard to pretreatment prognostic parameters.

Table 2 presents the results of the univariate analysis with respect to the different pretreatment variables. They include age, nephrectomy, DTI, PS, presence of liver metastases, ESR, WL and treatment.

Differences in survival according to gender and the presence of lung metastases were non-significant.

In the multivariate analysis, three variables had an independent prognostic influence on survival: ESR (mm in the first hour) ($P < 0.001$), WL (> 10% weight loss within the previous 6 months is coded 1, otherwise 0) ($P = 0.012$) and PS (2 or 3 is coded 1, otherwise 0) ($P = 0.021$). DTI was at the limit of significance at $P = 0.041$. Treatment group adjusted for either the first three variables or all four variables was statistically significant ($P = 0.04$). The model retained for establishing a prognostic index included only the first three variables. The reasons for not including DTI are discussed further. The prognostic index was constructed according to the following scoring system:

$$\text{Index} = 0.01^* \text{ESR} + 0.40^* \text{WL} + 0.40^* \text{PS}$$

(* regression coefficients of the final Cox model) using the coding mentioned earlier. The sedimentation rate was used in a continuous measurement since it was log-linearly related to the hazard rate. When this variable was coded as a three-level indicator variable, the regression coefficients were, respectively: 0.58 (50 < ESR < 100) and 1.35 (ESR > 100), with ESR < 50 used as the baseline reference hazard. The higher the ESR, the lower the chances of survival. Patients with a score < 0.5 were classified as good risk and patients with a score ≥ 1 were

Table 2. Univariate analysis (all patients)

	3-year survival rate (16%)	RR	Log rank P value
Males (n = 200)	18%		
Females (n = 95)	10%	0.99	0.69
Age			
≤ 60 years (n = 182)	18%		
> 60 years (n = 113)	12%	1.33	0.015
Nephrectomy			
Yes (n = 246)	18%		
No (n = 47)	9%	1.96	0.0001
DTI			
≤ 12 months (n = 193)	13%		
> 12 months (n = 102)	21%	0.64	0.0004
Performance status			
0/1 (n = 216)	20%		
≥ 2 (n = 79)	4%	2.24	0.0001
Lung metastases			
No (n = 108)	16%		
Yes (n = 187)	16%	0.94	0.67
Liver metastases			
No (n = 238)	18%		
Yes (n = 57)	8%	1.64	0.0011
Sedimentation rate (mm)			
< 50 (n = 153)	26%		
50–99 (n = 81)	7%	1.80	
≥ 100 (n = 50)	3%	3.87	0.0001
Weight loss			
< 10% (n = 209)	21%		
≥ 10% (n = 86)	2%	0.58	0.0002
SR WL			
No (n = 181)	24%		
Yes (n = 114)	2%	3.19	0.0002
Prognostic index			
Good < 0.5 (n = 121)	31%		
Intermediate 0.5–1 (n = 70)	11%	2.0	
Poor > 1 (n = 93)	2%	4.0	0.0001
Treatment			
Chemotherapy (n = 159)	8%		
IFN (n = 136)	24%	0.58	0.0001

RR, relative risk; SR WL, sedimentation rate and/or weight loss > 10%.

classified as poor risk. All other patients were classified as intermediate risk.

For example, good risk patients (n = 121) included those with no or less than 10% WL (WL = 0), a PS of 0 or 1 (PS = 0) and an ESR of less than 50 (ESR < 50). This group also included those patients with either more than 10% WL (WL = 1) or a PS ≥ 2 (PS = 1), but not both, and an ESR less than 10 (ESR < 10).

Intermediate risk patients (n = 70) included patients with either WL = 0 and PS = 0 with ESR < 100, or patients with either WL or PS = 1, but not both, and ESR between 10 and 59, or patients with both WL = 1 and PS = 1 and ESR < 20.

Poor risk patients (n = 93) included patients with either WL = 1 or PS = 1 and ESR ≥ 60 and patients with both WL = 1 and PS = 1 and ESR ≥ 70 and all patients with ESR ≥ 100. The classification system used is presented in Table 3.

Table 3. Classification system of the prognostic index

WL	PS	ESR < 10	< 20	< 50	< 60	< 100	≥ 100
0	0	G	G	G	I	I	P
0	1	G	I	I	I	P	P
1	0	G	I	I	I	P	P
1	1	I	I	P	P	P	P

G, good risk; I, intermediate risk; P, poor risk; WL, weight loss > 10% within the previous 6 months = 1, otherwise = 0; PS, ECOG performance status < 2, 0; performance status ≥ 2, 1; ESR, erythrocyte sedimentation rate (mm first hour). Index = 0.01 ESR + 0.4 (WL + PS).

Survival curves according to these defined prognostic groups are presented in Figure 2 showing statistically significant differences (P = 0.04).

Figures 3a–c present treatment comparisons in each of the three prognostic groups, respectively. The role of IFN treatment is more pronounced in the good risk group.

DISCUSSION

There are several limitations connected with any study which attempts to evaluate the role of a particular treatment from retrospective or historical data. Firstly, the experimental conditions are different, and patients are selected according to different protocols and inclusion criteria. In some cases, it may be possible to compare a group of treated patients with a group of untreated patients in order to evaluate the impact of a specific treatment, but it is next to impossible to identify a completely untreated group of patients in whom the pretreatment characteristics are similar between the two groups. The present investigation and its results cannot replace the validity of a prospective, randomised, phase III study. However, the performance of such a study, though scientifically desirable, appears extremely difficult in the context of clinical oncology today.

The present investigation is retrospective in nature and, although the time frame was similar between the two groups, the patients treated with IFN had different pretreatment characteristics than those treated in another institution with chemotherapy. Thus, any comparison between the two groups had to take into account this variability.

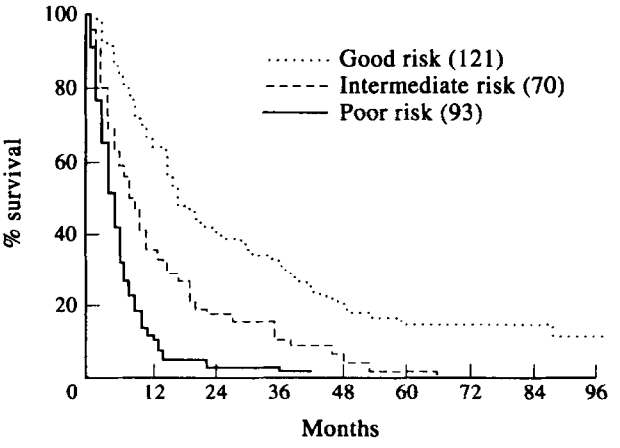

Figure 2. Survival in 284 patients with MRCC according to risk groups: (...) good risk group (121 patients), (---) intermediate group (70 patients), (——) poor risk group (93 patients).

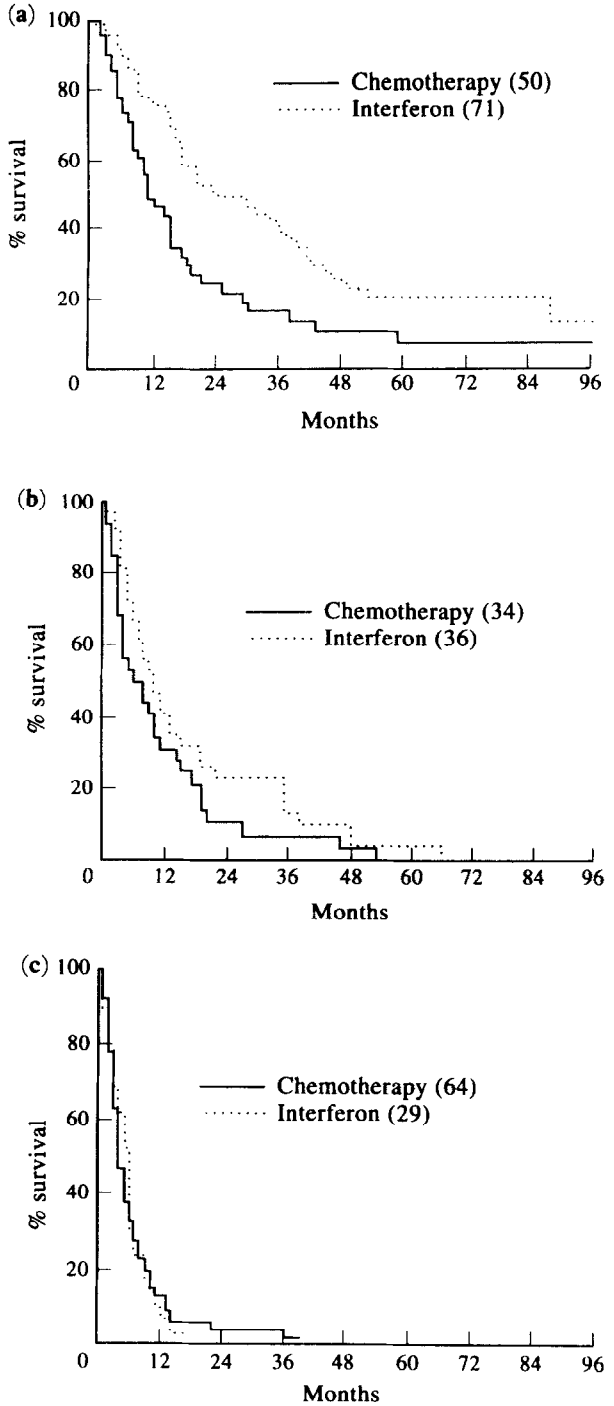

Figure 3. Survival in patients with MRCC according to risk group and treatment. (a) Good risk group, (——) chemotherapy (50), (....) IFN (71). (b) Intermediate risk group, (——) chemotherapy (34), (....) IFN (36). (c) Poor risk group, (——) chemotherapy (64), (....) IFN (29).

The present study identified three prognostic variables in MRCC which would assist the clinician in discriminating between those patients who might benefit from IFN treatment from those who would not. In our investigation, a combination of PS, WL and ESR were prognostic for survival. The importance of these variables has been reported previously [6]. Other authors have also shown the importance of a good PS [7–9]. Palmer and colleagues [7] made the distinction between PS 0 and 1. However, in the clinical situation, it is often difficult, or even impossible, to distinguish between these two categories for a population of middle-aged and elderly patients.

The number of metastatic sites is another prognostic variable often used [7–9]. In particular, the presence of lung metastases as the only metastatic site has been claimed to be a particularly important indicator of favourable outcome [9]. However, this variable largely depends on the intensity of the pretreatment workup. If, for example, computer tomography of the brain is performed routinely, even in asymptomatic patients, more brain metastases will be found than in patients in whom this investigation is not routinely performed. In order to avoid the diagnostic bias connected with the number of pretreatment tests performed, we restricted the study of prognostic variables to clinical and biological variables which are routinely available, such as PS, ESR and the presence of lung or liver metastases, the latter two factors assessed by chest X-ray and liver ultrasonography, respectively. These variables are also generally reproducible from one institution to another.

The good risk group, as defined in this study, contained 20 patients with liver or brain metastases, although it may seem preferable to allocate such patients to the intermediate or poor risk group. The presence of brain metastases has an unfavourable outcome, but was only present in 4% of patients. The overall results were not modified when the analysis was limited to patients without brain metastases. Other studies found liver metastases to be an important prognostic indicator [6], and its contribution to prognosis in this study was at the limit of statistical significance ($P = 0.06$), when adjusted for ESR, PS and WL. The classification system could easily be modified accordingly (Table 3). When good risk patients with liver or brain metastases were considered in the intermediate risk group there was no modification of the conclusions. However, when the 20 patients were considered poor risk, a significant survival advantage became apparent for patients treated with IFN in the intermediate risk group.

Neither prior nephrectomy nor the interval between diagnosis and treatment was introduced in the model, since they are not exclusively related to the natural history of the disease, but are largely dependent on therapeutic decision.

The 2-year survival rate of patients from the IFN group was similar to that published by Palmer and colleagues [7] for IL-2-treated patients. However, our series appears more extensive as two-thirds of Palmer's patients had < 2 years follow-up. The 5-year survival rate in the good prognosis group was very close to that published by Rosenberg [3] for patients treated with IL-2 lymphokine-activated killer cells.

Our investigation was retrospective and the evolving conclusions must, therefore, be viewed with some reservations. However, the study revealed that the population of patients with MRCC contained two major subgroups. The poor prognosis group (intermediate and high risk) was characterised by WL and/or poor PS and/or high first hour ESR. Treatment with IFN did not seem to have any effect on survival. In the good prognosis group, which contained approximately 40% of the patients, IFN treatment seemed to prolong survival. Thus, only patients with good risk characteristics may benefit from IFN treatment.

The limitations of our study, which used historical controls, strongly advocate the use of randomised trials in proving any hypothetical survival advantage of biological response modifier treatment in metastatic renal cell carcinoma.

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O^6-Alkylguanine-DNA Alkyltransferase Activity in Schistosomiasis-associated Human Bladder Cancer

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O^6-Alkylguanine-DNA-alkyltransferase (ATase) activity was measured in extracts of 55 bladder tissue samples (46 tumour and nine uninvolved mucosal tissue) from Egyptian patients with schistosome-associated bladder carcinoma. Activity varied from 2.0 to 16.2 fmole ATase/μg DNA (mean ± S.D.; 5.6 ± 4.0) or from 28 to 351 fmole ATase/mg protein (117 ± 71). ATase levels in schistosome-associated bladder cancer tissues (5.6 ± 4.0 fmole ATase/μg DNA) tended to be lower than those observed in normal human bladder mucosal tissue (8.5 ± 4.4 fmole ATase/μg DNA). In a previous study (Badawi *et al.*, *Carcinogenesis*, 1992, 13, 877–881) DNA-alkylation damage (O^6-methyldeoxyguanosine) was found in 44/46 of these schistomosome-associated bladder cancer samples at levels ranging from 0.012 to 0.485 μmole O^6-MedG/mole deoxyguanosine. We now report an inverse correlation between the levels of methylation damage and ATase activity ($r = -0.67$; $P < 0.001$). These observations encourage further investigations of the possible role of environmental alkylating agents in the aetiology of early bladder cancer associated with schistosomiasis.
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INTRODUCTION

CARCINOMA OF the urinary bladder is the most abundant neoplasm in Egypt [1]. It also occurs with high frequency in different parts of Africa and in the Middle East [2]. The induction of bladder cancer has long been speculated to be in a causal association with urinary schistosomiasis caused by *Schistosoma haematobium*, which is endemic in these regions. The relationship between the two conditions has been extensively investigated, and the weight of evidence associating *S. haematobium* infection with bladder cancer is now more than sufficient to assume its validity. [1–3].

Various hypotheses have been proposed to explain the carcinogenic process induced by schistosomiasis in the bladder [1]. However, most concern has been directed towards the possible role of the *N*-nitroso compounds [1, 4], an important class of environmental carcinogens, in this process. Their presence has been demonstrated in the urine of schistosomal-infected subjects, including those with bladder cancer, at levels significantly higher than in normal individuals [4–6], and their putative roles as causative agents in the pathogenesis of some human cancer has been reviewed [7].

N-Nitroso compounds or their breakdown products can react with cellular DNA to form a complex spectrum of adducts, of which O^6-alkylguanine (O^6-RG) is thought to be the most significant as this is formed in larger amounts than the other promutagenic base O^4-alkylthymine, particularly in the case of methylating agents [8]. The persistence of O^6-RG in different tissues and cells depends strongly on the capacity of the cellular DNA repair system, and has been correlated with the cytotoxic, mutagenic, carcinogenic and other biological effects of this