Are Angiogenic Factors, Cytokines, and Soluble Adhesion Molecules Prognostic Factors in Patients with Renal Cell Carcinoma?1

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ABSTRACT

Angiogenesis has an important role in the progression of solid tumors. Therefore, we measured the blood levels (ELISA) of angiogenic factors [basic fibroblast growth factor (bFGF), hepatocyte growth factor/scatter factor, and vascular endothelial growth factor (VEGF)] and soluble adhesion molecules [E-selectin, intercellular adhesion molecule (ICAM-1), platelet endothelial cell adhesion molecule-1, and vascular cell adhesion molecule-1] in 76 consecutive patients with untreated renal cell carcinoma and 41 healthy controls to evaluate their prognostic value.

The serum levels of bFGF, hepatocyte growth factor, and VEGF were significantly higher in patients with renal cancer than they were in healthy subjects. bFGF and VEGF values were significantly higher in patients with disseminated cancer (N+ or M+) than they were in those with undisseminated (M−N−) cancer: median = 27 pg/ml, range = 5–1118, n = 15 versus median = 8 pg/ml, range = 1–149, n = 61 (P = 10−4) for bFGF; and median = 883 pg/ml, range = 200–2317, n = 15 versus median = 278 pg/ml, range = 0–1704, n = 61 (P = 0.006) for VEGF. The blood levels of ICAM-1 and vascular cell adhesion molecule-1 were significantly higher, and the levels of E-selectin and platelet endothelial cell adhesion molecule-1 were significantly lower in patients with renal cancer than they were in controls. Plasma ICAM-1 was higher in metastatic patients (M+) than they were in nonmetastatic (M−) patients: median = 687 ng/ml, range = 294–1091, n = 12 versus median = 408 ng/ml, range = 217–1375, n = 64 (P = 10−4). ICAM-1 and bFGF blood values were correlated with the size of the primary tumor. The interleukin 6 and tumor necrosis fac-

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INTRODUCTION

Renal cell carcinoma is the most common malignant tumor that arises from the kidney. There is no adequate treatment for patients with renal cell carcinoma that is not cured by surgery: the operation used is generally radical nephrectomy. The prognostic indicators for patients with renal cell carcinoma are mainly local and metastatic extension of the tumor, and the presence or absence of metastasis at the time of diagnosis remains the main factor in determining survival (1). There is a need for prognostic and predictive factors to identify the subsets of renal cell carcinoma patients with low versus high risk at the time of diagnosis.

Many observations show that angiogenesis plays an important role in the growth, progression, and metastasis of solid tumors (2). A number of studies have reported an association between intratumor microvessel density and tumor aggressiveness (3). Renal cell carcinomas are hypervascular tumors (4, 5) for which the microvessel count could have a prognostic significance (4). The switch of a tumor to the angiogenic phenotype is believed to involve a change in the local equilibrium between angiogenic inducers and inhibitors (2, 6). A pattern of expression of bFGF, and VEGF in a wide variety of human and animal cancers has emerged (6). Overexpression of bFGF (7) and VEGF (8, 9) by malignant epithelial cells as compared to their expression in normal kidney has been shown in renal cell carcinoma. Moreover, elevated levels of bFGF and, now, VEGF are being detected in the urine and/or serum of a significant fraction of tumor-bearing patients (6, 10, 11), including, for bFGF, patients with renal cell carcinoma (12–14). HGF/scatter factor is an angiogenic factor (2, 15) that is expressed by the kidney (16) and a mitogen for kidney epithelial cells (17).

Increased circulating levels of TNF-α (18, 19) and IL-6 (20, 21) have been reported by others and by us (22) in renal cell carcinoma patients. Local production of IL-6 by kidney carcinoma has been demonstrated (23). There is evidence of TNF-α

1 The abbreviations used are: bFGF, basic fibroblast growth factor; VEGF, vascular endothelial growth factor; HGF, hepatocyte growth factor/scatter factor; TNF-α, tumor necrosis factor-α; IL, interleukin; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular adhesion molecule-1; PECAM-1, platelet endothelial cell adhesion molecule-1; CRP, C-reactive protein; CI, confidence interval.
and IL-6 production by neoplastic renal epithelial cells (24, 25), but these cytokines could also be produced by the mononuclear cells infiltrating the tumor (26).

Cell adhesion molecules mediating homotypic and heterotypic cellular interactions are implicated in tumor progression (27). Cell adhesion to the vascular wall is regulated by the expression on endothelial cells of adhesion molecules, such as E-selectin, VCAM-1, ICAM-1, and PECAM-1 (28). In renal cell carcinoma, these adhesion molecules are expressed by endothelial cells at the site of the tumor (29, 30), and VCAM-1 and ICAM-1 are expressed by neoplastic epithelial cells (30). The endothelial expression of E-selectin, VCAM-1, and ICAM-1 is stimulated by cytokines, such as TNF-α and IL-1 (28). This expression could be down-regulated by bFGF on tumor-infiltrating endothelial cells in renal cell carcinoma (31). An increase in E-selectin- and VCAM-1-mediated adhesion of renal cancer tumor cells to IL-1β- or TNF-α-treated endothelial cells has been reported, suggesting that this cytokine modulation of adhesion molecule expression plays a role in the metastatic process (32).

Soluble forms of these adhesion molecules are present in the supernatant of cytokine-activated endothelial cells (33, 34) and in the circulation of normal subjects, with abnormal levels being reported in human malignancies (34, 35).

To evaluate markers of angiogenesis in renal cancer patients, we measured bFGF, HGF, VEGF, E-selectin, ICAM-1, PECAM-1, and ICAM-1 blood concentrations in a group of 76 consecutive patients with untreated renal cell carcinoma. The IL-6 and TNF-α blood levels of these patients have been previously published (22). The relationships between angiogenic factors, soluble adhesion molecules, and cytokine blood values before treatment and the survival of these patients with renal cell carcinoma have been analyzed.

PATIENTS AND METHODS

Patients

This study was conducted between January 1990 and September 1992, according to the principles of the Declaration of Helsinki and the regulations of our institution. It is part of an Institutional Review Board protocol for which patients gave oral informed consent. Seventy-six consecutive patients with untreated clear-cell-type renal cell carcinoma, admitted to the Department of Urology of La Pitié Salpêtrière Hospital or Saint-Antoine Hospital (both in Paris, France), and 41 healthy subjects were studied. Patients with a renal tumor that was associated disease were excluded.

Sixty-one patients with renal cell carcinoma were men, and 15 were women. Their ages ranged from 29 to 87 years (mean ± SD, 61.4 ± 12.1 years). Before surgery, all patients underwent clinical and chest X-ray examinations, bone scan, abdominal ultrasonography, and abdominal computerized tomography. In nine patients, distant metastases were diagnosed before surgery. For three other patients, the distant metastases were discovered during the month following nephrectomy. Staging was done according to the tumor-node-metastasis classification, modified for T3, as described previously (22). Clinical preoperative and histopathological findings were collected for staging at the time of operation. T and N were always defined as pT and pN. The 69 patients who underwent surgery (T1, n = 5; T2, n = 47; T3, n = 12; T4, n = 5) had nephrectomies (radical, n = 65; partial, n = 2; enucleation, n = 2) and dissection of the lymph nodes of the latero-aortocaval area. The patients with lymph node invasion were staged as N+. Metastasis was defined according to the clinical findings, if no histopathological data on distant metastasis were available. The three patients who were diagnosed as metastatic during the first month following surgery were staged as M+ for the purpose of this analysis. We have previously published the TNF-α, IL-1β, IL-6, and CRP blood values of a series of 78 patients with untreated renal cell carcinoma. including these 76 patients (22). Two patients in this group (men of 43 and 62 years, T1, N−M−) were excluded from the present study because plasma and serum aliquots were no longer available. TNF-α, IL-6, and CRP data of the other 76 patients were included in this study for survival analysis.

Controls

Normal healthy subjects were recruited from among blood donors (n = 41, 32 men and 9 women; age, mean ± SD, 38.8 ± 7.1 years; range, 27–57 years) and formed a control group to establish the normal blood levels of angiogenic factors (bFGF, HGF, and VEGF) and soluble adhesion molecules (E-selectin, ICAM-1, PECAM-1, and VCAM-1). The absence of disease was assessed by clinical examination and routine laboratory tests, including screening for anti-HIV, anti-hepatitis B core antigen, anti-hepatitis C virus, and anti-human T leukemia virus antibodies, hepatitis B surface antigen, serum aminotransferase, and serological tests for syphilis.

Blood Collection

Venous blood was collected into dry or EDTA-coated sterile tubes from controls at routine blood donor session and from patients the day before treatment. Serum and plasma were separated and immediately frozen (-80°C) in aliquots of 0.5 ml until assay.

Methods

Assay of Angiogenic Factors. The serum levels of bFGF, HGF, and VEGF were assayed with sandwich enzyme immunoassay methods (Quantikine; R&D Systems, Minneapolis, MN) using capture monoclonal and horseradish peroxidase-conjugated polyclonal antibodies that were specific for each factor. Standard curves were constructed using serial dilutions of recombinant human bFGF, HGF, or VEGF (165 amino acid form). The minimum detectable concentrations were estimated to be 1 pg/ml for bFGF, 40 pg/ml for HGF, and 9 pg/ml for VEGF. The intra- and interassay variations of these techniques were all <10%. Each sample was tested in duplicate. Median control values were: for bFGF, 2 pg/ml (range, 1–7 pg/ml; n = 36); for HGF, 755 pg/ml (447–1287 pg/ml; n = 36); and for VEGF, 236.5 pg/ml (45–733 pg/ml; n = 36).

Soluble Adhesion Molecule Assay. The serum (E-selectin) and plasma (ICAM-1, PECAM-1, and VCAM-1) levels of soluble adhesion molecules were determined with sandwich enzyme immunoassay techniques using capture and horseradish peroxidase-conjugated monoclonal antibodies that were specific...
for each molecule. In each assay, standard curves were constructed using serial dilutions of purified preparations of the corresponding adhesion molecule. The minimum detectable blood levels of E-selectin and VCAM-1 (Parameter: R&D Systems, Minneapolis, MN) are estimated by the manufacturer to be <2 and 100 ng/ml, respectively. The minimum detectable blood level of ICAM-1 (T Cell Diagnostics, Cambridge, MA) is 30 ng/ml, and that of PECAM-1 (Bender, Vienna, Austria) is 1 ng/ml. The intra- and interassay variations of these techniques were all <10%. Each sample was assayed in duplicate. Median control plasma values were: for E-selectin, 47 ng/ml (range, 14–85 ng/ml; n = 29); for VCAM-1, 568 ng/ml (395–945 ng/ml; n = 29); for ICAM-1, 344 ng/ml (208–614 ng/ml; n = 29); and for PECAM-1, 67 ng/ml (28–135 ng/ml, n = 29).

### Statistical Analysis

Values for angiogenic factors and soluble adhesion molecule blood levels in the different groups are given as median and range. The figures show the individual values (mean of two measurements) of each parameter. The differences in angiogenic factors and soluble adhesion molecule blood values between the different groups of subjects were analyzed using the nonparametric Mann-Whitney rank-sum test. The Kruskal-Wallis test was used to evaluate the relationship between blood levels of the different parameters and the clinical staging characteristics of the renal cancer patients. Correlation coefficients between the different parameters were calculated using the nonparametric Spearman rank test. Some patients with renal cell carcinoma were older than their corresponding normal controls; for this reason, the Spearman correlation coefficients between the age of the cancer patients and the different blood parameters were calculated.

For survival analysis, the stopping date was March 1, 1996. The overall survival rates were measured from the date of treatment (i.e., the date of surgery for 69 patients) to the study end points, which were the stopping date, the date of death from any cause, or the time of the last visit before the patient was lost to follow-up. Survival curves were estimated by the method of Kaplan and Meier. Univariate analysis was performed using logarithmic rank tests. Results for comparison of major end points were regarded as significant if the two-sided *P* was <0.05. Features that were independently associated with overall survival were identified in multivariate analysis for proportional hazard regression.

Statistical analysis was performed using the BMDP statistical software package (BMDP Statistical Software, Los Angeles, CA).

### RESULTS

**Serum Angiogenic Factors in Patients with Renal Cell Carcinoma.** bFGF, HGF, and VEGF blood levels were significantly higher in the 76 patients with renal cell carcinoma than they were in the 36 controls: bFGF, median = 10.5 pg/ml, range = 1–149 pg/ml versus median = 2 pg/ml, range = 1–7 pg/ml (*P* < 10^−4; Fig. 1A); HGF, median = 1.234 pg/ml, range = 496–14,765 pg/ml versus median = 755 pg/ml, range = 447–1,287 pg/ml (*P* < 10^−4); and VEGF, median = 354.5 pg/ml, range = 0–2,317 pg/ml versus median = 236.5 pg/ml; range = 45–733 pg/ml (*P* = 0.004). In patients with distant metastases (*n* = 12), bFGF serum levels were significantly higher than they were in patients with nonmetastatic renal cancer (*n* = 64; *P* = 0.0016; Fig. 1B and Table I). HGF and VEGF blood values were not statistically different in patients with or without metastases, but VEGF plasma levels were significantly higher in patients with lymph node invasion and/or distant metastases (*n* = 15) than they were in patients with undisseminated renal cancer (*n* = 61; Table I).

When the 64 patients without metastases were considered, their bFGF serum levels were significantly higher than the bFGF serum levels of controls (*P* < 10^−4), and they correlated positively with the size of the primary tumor (*P* = 0.04 for three groups: T1+T2, T3a+T3b, and T4). HGF and VEGF blood values of the 64 nonmetastatic patients were significantly higher than the values of the controls (*P* < 10^−4 and *P* = 0.03, respectively), but they did not correlate with the size of the primary tumor (*P* = 0.91 and 0.35, respectively).

![Graph](https://example.com/graph.png) **Fig. 1** Individual serum values of bFGF in healthy subjects and patients with renal cell carcinoma (A) and in patients with nonmetastatic or metastatic renal cell carcinoma (B). Data points, means of two determinations; bars, median values.
Table 1  bFGF, HGF, and VEGF blood values (in pg/ml) in patients with undisseminated or disseminated renal cell carcinoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>bFGF</th>
<th>HGF</th>
<th>VEGF</th>
</tr>
</thead>
<tbody>
<tr>
<td>M- (n = 64)</td>
<td>9.5 (1-149)</td>
<td>1158 (496-5,590)</td>
<td>267.5 (0-1704)</td>
</tr>
<tr>
<td>M+ (n = 12)</td>
<td>25.5 (5-118)</td>
<td>2,527 (956-14,765)</td>
<td>920.5 (209-2317)</td>
</tr>
<tr>
<td>P</td>
<td>0.0016</td>
<td>0.89</td>
<td>0.080</td>
</tr>
<tr>
<td>M- N- (n = 61)</td>
<td>8 (1-149)</td>
<td>1133 (496-5,590)</td>
<td>278 (0-1704)</td>
</tr>
<tr>
<td>N+ and/or M+ (n = 15)</td>
<td>27 (5-118)</td>
<td>2350 (956-14,765)</td>
<td>883 (209-2317)</td>
</tr>
<tr>
<td>p</td>
<td>10^-4</td>
<td>0.30</td>
<td>0.0058</td>
</tr>
</tbody>
</table>

a M-, without metastases; M+, with metastases; N-, without lymph node invasion; N+, with lymph node invasion.

b Values represent median; numbers in parentheses represent range.

c P for M- versus M+.

d P for M-N- versus N+ and/or M+.

Fig. 2  Individual plasma values of ICAM-1 in healthy subjects and patients with renal cell carcinoma (A) and in patients with nonmetastatic or metastatic renal cell carcinoma (B). Data points, means of two determinations; bars, median values.

Soluble Adhesion Molecules in Patients with Renal Cell Carcinoma. E-selectin, ICAM-1 (Fig. 2A), PECAM-1 and VCAM-1 blood values were all significantly different in 76 patients with renal cell carcinoma, as compared to 29 controls. ICAM-1 and VCAM-1 plasma levels were significantly higher in patients with renal cancer: ICAM-1, median = 433 ng/ml; range = 217-1375 ng/ml versus median = 344 ng/ml, range = 208-614 ng/ml (P = 0.0002); and VCAM-1, median, 677 ng/ml, range = 386-2713 ng/ml versus median = 568 ng/ml, range = 395-945 ng/ml (P < 10^-4). In patients with renal cancer, VCAM-1 blood values were correlated with age (r^2 = 0.43, n = 76, P = 10^-4), as reported previously in normal subjects (36). Age did not account for the higher VCAM-1 values because differences were still significant when VCAM-1 blood concentrations of patients younger than 57 years old (n = 45) were compared with those in age-matched controls (n = 29, P < 10^-4). E-selectin and PECAM-1 blood values were significantly lower in patients with renal cell carcinoma than they were in controls: E-selectin, median = 38 ng/ml, range = 2-122 ng/ml versus median = 47 ng/ml, range = 14-85 ng/ml (P < 10^-4); and PECAM-1, median = 41 ng/ml, range = 22-156 ng/ml versus median = 67 ng/ml, range = 28-135 ng/ml (P < 10^-4).

Plasma ICAM-1 values in patients with metastatic renal cancer were significantly higher than they were in patients with localized disease (Fig. 2B and Table 2), but the E-selectin, VCAM-1, and PECAM-1 blood levels did not differ significantly between these two groups (Table 2). VCAM-1 plasma levels were significantly higher in patients with lymph node invasion and/or distant metastases (median = 816 ng/ml, range = 525-1551 ng/ml, n = 15) than they were in patients with undisseminated cancer (median = 647 ng/ml, range = 386-2713 ng/ml, n = 61; P = 0.04).

The ICAM-1 plasma levels of the 64 nonmetastatic patients were significantly higher than the levels in controls (P = 0.0003) and correlated with the size of the tumor (P = 0.001). Blood concentrations of PECAM-1 and VCAM-1 were also significantly different in the 64 patients without metastases, as compared to controls (P < 10^-4 and P = 0.006, respectively), but E-selectin concentrations did not differ significantly between these two groups (P = 0.2). None of these three soluble adhesion molecule levels correlated with the size of the tumor (P = 0.8, 0.3, and 0.2, respectively).

Correlations between the Different Blood Parameters. Blood concentrations of bFGF in patients with renal cell carcinoma were correlated with those of IL-6 (r^2 = 0.45, n = 76, P < 10^-4), ICAM-1 (r^2 = 0.41, n = 76, P = 0.0002), and VEGF (r^2 = 0.25, n = 76, P = 0.033). Blood concentrations of ICAM-1 in patients were correlated with those of IL-6 (r^2 = 0.42, n = 76, P = 10^-4), VCAM-1 (r^2 = 0.38, n = 76, P = 0.0007), and TNF-α (r^2 = 0.28, n = 76, P = 0.014).
Survival Analysis. The median follow-up was 56.3 months (range = 37.5–74.8 months). For survival analysis, the choice of cutoff was guided by the higher (HGF, ICAM-1, IL-6, TNF-α, VEGF, and bFGF) or lower (E-selectin and PECAM-1) value of the 95% CI or by the mean + 2 SD (bFGF and CRP) of the blood levels in controls. Univariate analysis of the survival curves demonstrated the benefit of the absence of metastasis and of low CRP, bFGF, ICAM-1, IL-6, or TNF-α before treatment (Table 3 and Fig. 3). Multivariate analysis showed that only pretreatment plasma TNF-α was an independent prognostic factor (P < 0.001).

Predictive Value of These Parameters in Patients with Renal Cell Carcinoma. Blood concentrations of CRP, angiogenic factors, cytokines, and soluble adhesion molecules at the time of diagnosis were analyzed for their predictive value (37) for metastasis and/or death. A normal pretreatment TNF-α blood level (i.e., <5 pg/ml) had a high positive predictive value for a good prognosis, with good specificity and low sensitivity, but a low negative predictive value (Table 4). Interestingly, a total of fewer than three abnormal blood parameters among CRP, IL-6, TNF-α, bFGF, and ICAM-1 before treatment had the same positive predictive value for a good prognosis and the same specificity but higher negative predictive value and sensitivity than did a normal TNF-α value alone (Table 4).

DISCUSSION

We found elevated blood values of bFGF, HGF, and VEGF in a group of untreated renal cell carcinoma patients. These angiogenic factors were also elevated in nonmetastatic subjects. Here, HGF serum levels were not significantly different in patients with or without metastases, and this parameter did not appear to be a prognostic factor.

Patients with disseminated cancer had significantly higher bFGF and VEGF blood values than did patients with an undissemi nated tumor. Detectable VEGF blood levels have been recently reported in healthy subjects and were increased in a series of patients with malignancies other than renal cell carci noma (11). VEGF and VEGF receptors are strongly expressed in renal cell carcinoma, suggesting that this angiogenic pathway has a role in this tumor (8). Here, VEGF did not appear to be a prognostic factor, but the elevated VEGF blood levels in patients with disseminated renal cell carcinoma suggest that this factor may be useful for follow-up of renal cancer patients.

An increase in bFGF blood levels in patients with renal cell carcinoma has been reported previously in smaller series (12–14). It has been suggested that the higher bFGF blood levels in metastatic renal cancer patients are associated with lung metastasis (14). Fidler and colleagues (38), in a nude mice model, demonstrated an influence of the organ microenvironment on the angiogenic phenotype of human renal cell carcinoma. In this model, mice with highly vascularized tumors had the highest bFGF tumoral expression and the highest bFGF serum levels (38). Another group has reported that the introduction of the bFGF gene into a mouse renal carcinoma cell line enhances its metastatic potential (39). In humans, Nanus et al. (40) reported that cytoplasmic expression of bFGF in renal cell carcinoma correlates with shorter survival. These studies suggest a role of bFGF expression in growth and metastasis of renal cell carcinoma and the potential interest of determining serum bFGF in this cancer. Here, we found a correlation between bFGF serum levels and the size of the primary tumor in nonmetastatic patients. The renal cell carcinoma patients with increased bFGF serum levels at diagnosis had a shorter survival than did patients

### Table 2

<table>
<thead>
<tr>
<th>Stage</th>
<th>E-selectin</th>
<th>ICAM-1</th>
<th>PECAM-1</th>
<th>VCAM-1</th>
</tr>
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<tbody>
<tr>
<td>M– (n = 64)</td>
<td>39 (10–122)</td>
<td>408 (217–1375)</td>
<td>41 (22–156)</td>
<td>662 (386–2713)</td>
</tr>
<tr>
<td>M+ (n = 12)</td>
<td>33 (2–101)</td>
<td>687 (294–1091)</td>
<td>40 (22–112)</td>
<td>823 (525–1551)</td>
</tr>
<tr>
<td>P</td>
<td>0.22</td>
<td>10^{-4}</td>
<td>0.92</td>
<td>0.08</td>
</tr>
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</table>

* Values represent median: numbers in parentheses represent range.

### Table 3

<table>
<thead>
<tr>
<th>Characteristic (no. of patients)</th>
<th>% survival (95% CI)</th>
<th>P</th>
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<tbody>
<tr>
<td>Metastasis</td>
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<td></td>
</tr>
<tr>
<td>M– (64)</td>
<td>84.9 (75.6–94.2)</td>
<td>&lt;10^{-4}</td>
</tr>
<tr>
<td>M+ (12)</td>
<td>0</td>
<td></td>
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<tr>
<td>CRP</td>
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<tr>
<td>≤9 mg/liter (46)</td>
<td>83.8 (72.6–95)</td>
<td>0.0007</td>
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<tr>
<td>&gt;9 mg/liter (30)</td>
<td>51.3 (32.6–70)</td>
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<tr>
<td>IL-6</td>
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<tr>
<td>≤15 pg/ml (58)</td>
<td>83.6 (73.6–93.6)</td>
<td>10^{-4}</td>
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<tr>
<td>&gt;15 pg/ml (18)</td>
<td>29.4 (7.3–51.5)</td>
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<td>TNF-α</td>
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<td>≤4 pg/ml (19)</td>
<td>100</td>
<td>0.002</td>
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<td>&gt;4 pg/ml (57)</td>
<td>60.9 (47.6–74.2)</td>
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<td>bFGF</td>
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<td>≤6 pg/ml (26)</td>
<td>83.5 (68.4–98.6)</td>
<td>0.04</td>
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<tr>
<td>&gt;6 pg/ml (50)</td>
<td>64 (50–78)</td>
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<tr>
<td>HGF</td>
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<td>≤858 pg/ml (10)</td>
<td>70 (41–99)</td>
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<tr>
<td>&gt;858 pg/ml (66)</td>
<td>70.8 (59.2–82.4)</td>
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<tr>
<td>VEGF</td>
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<td>≤280 pg/ml (35)</td>
<td>76.5 (62–91)</td>
<td>0.58</td>
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<td>&gt;280 pg/ml (41)</td>
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<td>E-selectin</td>
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<td>≤40 ng/ml (43)</td>
<td>67.4 (52.5–82.3)</td>
<td>0.37</td>
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<td>&gt;40 ng/ml (33)</td>
<td>75.1 (59.9–90.3)</td>
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<td>ICAM-1</td>
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<td>≤377 ng/ml (23)</td>
<td>90.9 (82–99.8)</td>
<td>0.009</td>
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<tr>
<td>&gt;377 ng/ml (53)</td>
<td>61.8 (48–75.6)</td>
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<tr>
<td>PECAM-1</td>
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<tr>
<td>≤60 ng/ml (65)</td>
<td>72.9 (61.7–84.1)</td>
<td>0.35</td>
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<td>&gt;60 ng/ml (11)</td>
<td>55.6 (22.5–88.7)</td>
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<td>VCAM-1</td>
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<tr>
<td>≤638 ng/ml (32)</td>
<td>77.5 (62.5–92.5)</td>
<td>0.38</td>
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<tr>
<td>&gt;638 ng/ml (44)</td>
<td>65.6 (50.7–80.5)</td>
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</table>

* The estimated percentage survival (95% CI) 3 years after the diagnosis of renal cell carcinoma is given.
with low bFGF serum levels, but this marker was not an independent prognostic indicator. We report a significant increase in plasma ICAM-1 and VCAM-1 levels and a significant decrease in E-selectin and PECAM-1 blood levels in patients with renal cell carcinoma. We did not find any study on PECAM-1 blood levels in normal subjects or patients. One can suppose that the soluble adhesion molecule plays a local regulatory role in tumor development. It has been shown, in a series of patients with renal cell carcinoma, that tumors exhibiting a high density of PECAM-1 molecules on endothelial cells carry a better prognosis than do tumors with a low PECAM-1 expression (41). Here, circulating PECAM-1 did not correlate with the size of the primary tumor, was similar in patients with or without metastases, and was not a prognostic factor.

Banks et al. (35) have studied E-selectin, ICAM-1, and VCAM-1 in the blood of a large series of patients with malignancies, including a group of 12 patients with renal cancer (35). They found a significant increase in blood ICAM-1 and VCAM-1 concentrations in these patients, but E-selectin did not differ significantly between renal cancer patients and controls (35). In contrast, E-selectin was decreased in their patients with myeloma and increased in their patients with breast, ovarian, or gastrointestinal cancer (35). Recently, a Japanese group reported that E-selectin levels are higher in renal cell carcinoma patients with a low incidence of metastases than they are in patients with a high incidence (42). Here, nonmetastatic patients had higher levels of circulating E-selectin than did the metastatic patients, but this difference was not statistically significant (Table 2). E-selectin did not appear to be a prognostic factor, but this soluble adhesion molecule could play a regulatory role in the development of renal cell carcinoma. It is noteworthy that the soluble form of E-selectin and VCAM-1 have been shown to be angiogenic (43).

The increase in ICAM-1 in the blood of cancer patients has been documented, and the ICAM-1 level is related to the tumor burden (34, 35, 44). Plasma ICAM-1 increase in renal cancer patients, with higher levels in metastatic than in nonmetastatic patients, has been reported in several smaller studies (35, 45, 46). The release of ICAM-1 molecules by renal cell carcinoma cells has been shown in vitro (46). In patients, an inverse correlation has been observed between ICAM-1 renal cell carcinoma expression and blood ICAM-1 level (45). Furthermore, a correlation between renal cell carcinoma ICAM-1 expression and the degree of mononuclear cell infiltration of tumors has been reported, suggesting that this molecule plays a role in the immune reaction to the tumor (47). Here, circulating ICAM-1 correlated with the size of the primary tumor and was a non-independent prognostic factor.

We found that a high level of plasma IL-6 before treatment carries a worse prognosis in patients with renal cell carcinoma.
although this parameter is not an independent prognostic indicator. Similar results have been reported in metastatic renal cell carcinoma patients (20). Here, a normal TNF-α level, measured by a sensitive immunoradiometric assay (22), was highly predictive of a good prognosis. Waase et al. (26) suggested that the degree of TNF-α production in renal cell carcinoma depends on tumor spread to the draining lymph nodes. TNF-α plasma level before treatment was the only parameter that we found to be an independent prognostic marker.

In our series of renal cancer patients, the number of patients with metastatic cancer was small, and the study of more patients would be beneficial for comparison of VEGF, E-selectin, and VCAM-1 in patients with localized renal cancer versus those with metastatic disease. IL-6, TNF-α, bFGF, and ICAM-1 appeared to have a prognostic value in patients with renal cell carcinoma. A longitudinal prospective study has been initiated to evaluate the respective interest of these different parameters for the follow-up of patients who are treated for renal cell carcinoma.

REFERENCES

Angiogenic and Adhesive Molecules in Renal Cancer

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Are angiogenic factors, cytokines, and soluble adhesion molecules prognostic factors in patients with renal cell carcinoma?

C Dosquet, M C Coudert, E Lepage, et al.


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