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Circulating immune markers in advanced renal cell carcinoma during immunotherapy with interferon gamma

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Abstract Circulating immune markers sICAM-1, sELAM-1, sMHC-I, β_2-MG, sCD4 and sCD8 were evaluated prior to and during immunotherapy with biologically active doses of interferon gamma (IFN-γ) in 16 patients with advanced renal cell carcinoma (RCC) over a period of 12 months. Compared to 20 healthy controls, significantly ($P < 0.01$) elevated baseline levels of circulating adhesion molecules sICAM-1 (mean 1166 vs 230 ng/ml) and sELAM-1 (70 vs 17 ng/ml) were found in all patients. Compared to responders ($n = 2$) or patients with stable disease ($n = 2$), progressive disease during therapy ($n = 12$) was associated with significantly ($P < 0.05$) higher mean concentrations of sICAM-1 (1574 vs 962 ng/ml) and sELAM-1 (86 vs 46 ng/ml). Pretherapeutic and intratherapeutic levels of sMHC-I among the RCC patients were significantly ($P < 0.05$) lower than among the controls (0.41 vs 0.8 ng/ml). sCD4 levels clearly showed the same tendency (24 vs 33 U/l). sCD8 baseline levels, by contrast, were significantly ($P < 0.05$) elevated (564 vs 336 U/l), reflecting either activation of the NK-cell subset or increased synthesis of CD8+ T-suppressor cells. Again, significantly ($P < 0.05$) higher intratherapeutic sCD8 concentrations were observable with progressive disease than with response to therapy or stable disease (721 vs 355 U/l). Interestingly, although the biologically active dose of IFN-γ was defined by an increase in β_2-MG release of at least 30% within 48 h after injection, none of the other markers showed any significant alteration following IFN-γ administration, suggesting that IFN-γ in vivo does not produce changes in circulating markers of activation that might be expected on the basis of its effects in vitro.The finding of significantly elevated concentrations of sICAM-1, sELAM-1 and sCD8 in the presence of low sCD4 and sMHC-I levels might be of clinical significance for indicating ongoing tumor progression.

Key words Renal cell carcinoma · Circulating immune markers · Immunotherapy · Interferon gamma

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Immunotherapeutic approaches in the treatment of advanced renal cell carcinoma (RCC) are currently used, with response rates varying between 15 and 20% [12]. The demonstration of circulating and cellular immune responses in patients with RCC justifies the assumption that systemic immunological factors of the host might be operative that can differentiate responders from nonresponders [35].

Interaction of intercellular adhesion molecule-1 (ICAM-1) with its ligands CD11a/CD18 and CD11b/CD18 is critical for contact mechanisms of antigen-presenting cells with lymphocytes [5]. ICAM-1 expression has also been described to correlate with the risk of metastatic disease [15, 23], and increased levels of circulating ICAM-1 (sICAM-1) have been measured in patients with malignant or inflammatory conditions [11, 27]. Since IFN-γ represents the most potent upregulator of ICAM-1 expression, monitoring of its release would seem likely to yield information on IFN-γ-induced activity in vivo [5, 32].

Endothelial leukocyte adhesion molecule-1 (ELAM-1) mediates adhesion of resting lymphocytes and is, therefore, the most likely inducer of initial lymphocyte binding to endothelial cells (EC) [26, 13]. Binding of polymorphonuclear cells (PMN) to activated EC results in activation of CD11b/CD18-dependent functions, such as interaction with ICAM-1. In this way, ELAM-1 might be crucially involved in the migration of tumor cells [17].

CD4, phenotypically expressed by matured inducer/helper T-cell subsets, is involved in the recognition by T cells of antigens within the antigenic pocket of the MHC-II complex and plays a major role in immunity. CD8 is expressed by cytotoxic or suppressor T-cell subsets and by the majority of CD56+ NK cells [30, 18]. Advanced cancers show an increased activity of CD8+ NK cells and, to some extent, T cells [31, 20]. Moreover, increased serum concentrations of sCD8, a 52-kDa homodimer secreted by activated CD8+ cells, have been described in various types of cancer, and its release has been linked to suppressor and cytotoxic activity [28, 14, 37]. Similarly, sCD4 presumably reflects T-helper cell activity.

Class-I major histocompatibility antigen (MHC-I), a human leukocyte antigen (HLA), is the receptor for CD8+ cytotoxic T cells, with the amount of MHC products apparently determining the susceptibility of target cells to being lysed [6]. MHC production also influences malignant transformation and the metastatic behavior of tumor cells [10, 33]. HLA-1 expression by various cell types is stimulated by human interferons, IFN-γ having the strongest effect [2, 9]. Serum levels of β_2-microglobulin (β_2-MG), the short extracellular polypeptide chain of the MHC-I molecule, are considered to reflect functional membrane MHC-I expression and are utilized for defining biologically active doses of IFN-γ in oncological immunotherapy [22, 1].

The purpose of the present study was to investigate whether concentrations of immune markers in patients with advanced RCC differ from those in normal individuals and whether these parameters are correlated with the course of disease or with response to immunotherapy.

Material and methods

Subjects

Sixteen patients with advanced disease following nephrectomy because of RCC (11 male, 5 female; mean age 65.3, range 49–78 years) were treated in an open phase II trial with biologically active doses of IFN-γ. Time from nephrectomy to progression ranged from 2 to 101 months (mean 32 months). Staging procedures for tumor size and location included computerized tomography of chest and retroperitoneum, as well as bone scan. All patients presented with single to multiple lung metastases ranging from 0.5 to 4 cm in size; three in addition had bone metastases, a tumor in the contralateral kidney, or local tumor recurrence with retroperitoneal lymph node involvement, respectively. Only one of these patients had received previous 10-month immunomodulatory therapy with coumarin and cimetag, which was stopped 3 months before starting IFN-γ treatment because of progression of multiple lung metastases.

The biologically active dose was defined by an increase in serum β_2-MG of more than 30% at 48 h after injection. A mean dose of 200 (50–500) ng rIFN-γ (Imukin, Boehringer, Germany) was administered subcutaneously once a week, 3 times a month. Five venous blood samples were collected from every patient on 5 consecutive days before initiation of IFN-γ therapy for baseline evaluation as well as immediately before and 48 h after IFN administration, 3 times within the 1 month, and then once monthly over 1 year, representing a total of 33 samples/patient. Additionally a total of 100 serum samples served as controls. Five serum samples each were taken for five consecutive days from 20 sex- and age-matched healthy subjects (blood donors and medical staff, 9 female, 11 male; mean age 62.3, range 43–76 years) without malignant or evident infectious disease, as well as with normal renal function and normal blood count. Serum was removed from the clot immediately after clotting and stored frozen at $-20\,^{\circ}C$ until determination of sICAM-1, sELAM-1, sCD4, sCD8 and sMHC-I. β_2-MG was evaluated routinely immediately after collection of serum samples.

Analysis of serum parameters

Concentrations of sICAM-1, sELAM-1, sCD4, sCD8 and sMHC-I were analyzed in duplicates using sandwich enzyme immunoassays (enzyme-linked immunosorbent assay (ELISA) kits for the determination of released immune markers in human serum according to the manufacturer's recommendations (sICAM-1 and sELAM-1 ELISA: Bender Medical Systems, Austria; CD4 and CD8 test kit: T-Cell Diagnostics, Cambridge, UK; s-HLA-STAT TM Class I: Sang Statistical Medical Corporation, Calif., USA).

Principle of the method

An anti-sICAM-1, sELAM-1, sCD4, sCD8 or sHLA-I monoclonal coating antibody (mAb) was first adsorbed onto polystyrene microtiter wells. Immune marker present in the sample or standard binded to mAb adsorbed to the microwells; unreacted sample components were removed by washing. A horseradish peroxidase (HRP)-conjugated anti-sICAM-1, -sELAM-1, -sCD4, -sCD8 mAb or anti-β_2 microglobulin polyclonal antibody (used in the sHLA-I ELISA) directed against a second epitope on the molecule of the individual marker was then added and binded to the marker captured by the first mAb, completing the sandwich. Unbound HRP-conjugated anti-immune marker was removed during a washing stage and *O*-phenylenediamine (OPD) substrate solution reactive to HRP was added to the wells. A colored product was formed in direct proportion to the amount of marker present in the sample. The reaction was terminated by addition of a stop solution, and absorbance at 450 nm for sICAM-1 and sELAM-1 and 490 nm for sCD4, sCD8 and sHLA-I was measured. For each group of microwell strips assayed a separate standard curve was prepared from five to six standard dilutions of the individual marker in duplicate. Unknown values were determined from this standard curve by using the average absorbance value of specimen duplicates. Results for duplicates of samples which were not within 20% of the mean were not used and repeated in another assay. Moreover, control samples of known low and high concentrations of the individual markers were established as external standards and run as an additional control with each assay.

Serum β_2-MG was analyzed routinely by using a microparticle enzyme immunoassay (MEIA) for quantitative analysis (IMx β_2-Microglobulin, Abbot, Germany).

For intra- and interassay precision the intra- and interassay coefficients of variation (CV, %) were calculated and found to be within reasonable ranges for reproducibility of results (Table 1).

Statistics

Differences between patients and controls, patient subgroups and serum concentrations before and 48 h after IFN-γ administration were analyzed using the Mann-Whitney U test for unpaired observations and Wilcoxon's matched-pairs signed rank test for paired observations. The level of significance was $P < 0.05$.

Results

Out of 16 patients with advanced RCC, an objective response to IFN-γ therapy was demonstrable in two cases. One patient with a solitary lung metastasis of 0.5 cm showed a complete response. One patient presented with a partial response of multiple lung metastases up to 4 cm. Two patients showed stable disease, one of them presenting with two lung metastases up to 3 cm in size and one with three lung metastases ranging from 5 to 7 mm in size. Twelve patients suffered tumor progression during therapy, all of them presenting with multiple lung metastases ranging from 1 to 5 cm in size; three of them in addition had bone metastases, a tumor in the contralateral kidney, or local tumor recurrence with retroperitoneal lymph node involvement, respectively, when starting IFN-γ therapy.

sICAM-1

The normal individuals showed a mean ICAM-1 concentration of 230 ± 65 (118–312) ng/ml. At 1166 ± 594 (410–2900) ng/ml, pretherapeutic levels among the RCC patients were significantly elevated ($P < 0.01$, Table 2). When baseline levels were subdivided according to the outcome of therapy, the highest concentrations were found in nonresponders to immunotherapy. On the other hand, a direct correlation with the extent of metastatic disease and sICAM-1 concentrations could not be established. sICAM-1 levels remained consistently elevated in all patients during treatment but, interestingly, patients with progressive disease exhibited significantly ($P < 0.05$) higher concentrations (mean 1547 ± 562, range 920–4000 ng/ml) than responders or patients with stable disease (mean 962 ± 466, range 280–2100 ng/ml; Fig. 1). There was no significant difference between mean sICAM-1 levels immediately before and 48 h after IFN-γ injection, indicating that IFN-γ has no regulatory effect on sICAM-1.

sELAM-1

The controls showed a mean sELAM-1 level of 17 ± 2.6 (0–20) ng/ml. At 70 ± 29 (43–150) ng/ml, all RCC patients exhibited significantly elevated pretherapeutic levels ($P < 0.01$; Table 2), nonresponders to immunotherapy again presenting with higher concentrations. A correlation of sELAM-1 concentration with tumor mass was not apparent. During

Table 1 Overall intra- and interassay coefficients of variation (CV, %) for sICAM-1, sELAM-1, sCD4, sCD8, sHLA-I ELISA and β_2-MG MEIA

	Intra-assay CV (%)	Interassay CV (%)
sICAM-1	5.5	7.8
sELAM-1	3.7	4.1
sCD4	4.0	4.6
sCD8	6.1	8.4
sHLA-I	3.2	6.6
β_2-MG	5.1	7.6

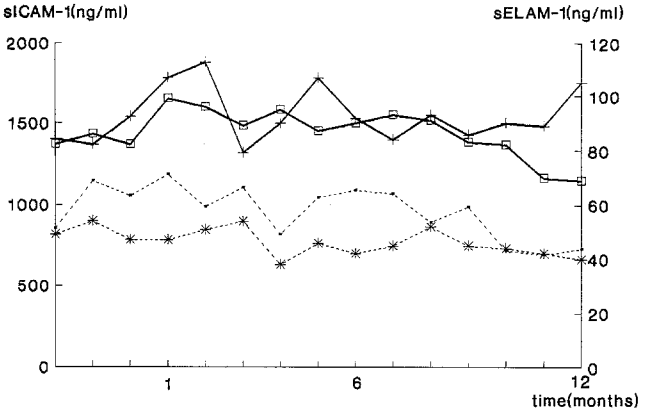

Fig. 1 Kinetics of mean sICAM-1 and sELAM-1 concentrations in RCC patients related to response to therapy. *CR* complete response, $n = 1$; *PR* partial response, $n = 1$; *SD* stable disease, $n = 2$; *PD* progressive disease, $n = 12$. Significantly higher concentrations of both adhesion molecules in PD. ---■--- CR, PR, SD; —|— PD(sICAM-1); ---*--- CR, PR, SD; –□– PD(sELAM-1)

Table 2 Baseline levels of circulating immune markers (mean ± SD) in controls and RCC patients subdivided according to response to IFN-γ therapy

	Controls ($n = 20$)	RCC patients ($n = 16$)			
		Complete response ($n = 1$)	Partial response ($n = 1$)	Stable disease ($n = 2$)	Progressive disease ($n = 12$)
ICAM-1 (ng/ml)	230 ± 65	462 ± 83*	801 ± 102*	917 ± 256*	1296 ± 623*
ELAM-1 (ng/ml)	17 ± 2.6	50 ± 5*	48 ± 3*	51 ± 3*	77 ± 33*
CD4 (U/l)	33 ± 16	25 ± 7	26 ± 6	18 ± 4	25 ± 11
CD8 (U/l)	336 ± 162	337 ± 84	369 ± 6	392 ± 114	628 ± 219*
MHC-I (ng/ml)	0.8 ± 0.92	0.29 ± 0.12*	0.34 ± 0.03*	0.28 ± 0.11*	0.45 ± 0.46*
β_2-MG (mg/l)	1.2–2.4[a]	1.98 ± 0.94	1.87 ± 0.04	1.72 ± 0.2	3.92 ± 1.6

[a] Established normal range
* Statistically significant difference ($P < 0.05$) compared to controls

therapy, significantly ($P < 0.05$) higher concentrations were observed in nonresponders (mean 86.2 ± 39, range 46–155 ng/ml) than in responders and patients with stable disease (mean 46.4 ± 10.4, range 34–75 ng/ml; Fig. 1). No significant difference emerged between sELAM-1 levels immediately before and 48 h after injection of IFN-γ, indicating that sELAM-1 expression is not influenced by IFN-γ.

sCD4 antigen

Mean sCD4 concentraton in the control group was 33 ± 16 (5–65) U/l. With a mean of 24 ± 10 (10–55) U/l, pretherapeutic levels were low among the RCC patients, in no case exceeding the normal range and not significantly different from those in the control group (Table 2). Concentrations of sCD4 remained low during therapy, and no rise was detected following IFN-γ injection. A correlation of serum sCD4 levels with course of disease was not apparent, nor was there a difference when comparing responders (mean 26.5 ± 10.6, range 14–69 U/l) to nonresponders (mean 27.3 ± 9.2, range 18–78 U/l; Fig. 2).

sCD8 antigen

Mean sCD8 concentration in the control group was 336 ± 162 (140–523) U/l. At 564 ± 205 (200–900) U/l, the RCC patients showed significantly ($P < 0.05$) elevated pretherapeutic levels (Table 2). When the results were subdivided according to outcome of immunotherapy, only progressive disease was preceded by significantly elevated CD8 concentrations (mean 628 + 219 U/l). A direct correlation of sCD8 levels with tumor mass was not observable. A statistically significant increase in sCD8 levels 48 h after as compared to immediately before IFN-γ injection was demonstrable in only two patients with partial response or stable disease (mean 769 ± 167, range 500–999 U/l vs 534 ± 121, 250–660 U/l; $P < 0.05$), arguably indicating to an IFN-γ-induced stimulation of cytotoxic T-cell activity. Progressive disease during therapy was associated with significantly ($P < 0.05$) higher sCD8 levels than response to therapy or stable disease (mean 721 ± 162, range 300–999 U/l vs 355 ± 118, 210–660 U/l; Fig. 2).

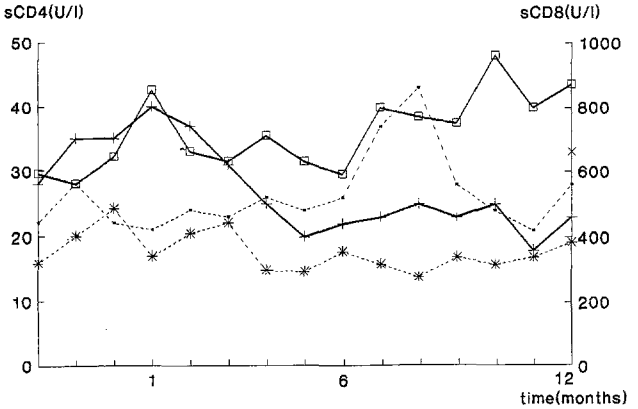

Fig. 2 Serum levels of sCD4 and sCD8 related to response to therapy. Concentrations of sCD4 in RCC patients are markedly lower than the mean sCD4 concentration (33 U/l) in controls. Significantly higher concentrations of sCD8 in progressive disease. ---■--- CR, PR, SD; —|— PD(sCD4); ---*--- CR, PR, SD; –□– PD(sCD8)

β_2-MG

The established normal reference range for β_2-MG concentration was 1.2–2.4 mg/ml. The mean pretherapeutic concentration in RCC patients was 3.4 (1.66–6.11) mg/ml (Table 2). Elevated pretherapeutic levels ranging from 2.6 to 6.11 mg/l were obtained for ten patients, all of whom showed progressive disease during therapy. Interestingly, with a mean of 1.82 (1.29–2.21) mg/l, all patients responding to therapy or presenting with stable disease were within the normal range. A direct correlation with the extent of metastatic disease was not observable. During follow-up β_2-MG concentration was found to be significantly elevated in all patients 48 h after compared to immediately before IFN-γ injection ($P < 0.05$), with a mean rise to 4.58 (1.61–9.13) mg/l, indicating an IFN-γ-induced temporary activation of MHC-I antigen. Thereafter, β_2-MG levels dropped back to 3.41 (1.14–9.17) mg/l at 7 days after IFN-γ administration. A direct correlation of β_2-MG during therapy with course of disease was not apparent. A massive increase in serum β_2-MG concentration was observed in only one patient with tumor progression, which was readily explainable by the presence of a recurrent tumor in the contralateral kidney and decreased renal function.

sMHC-I antigen

The mean sMHC-I level obtained from control sera was 0.8 ± 0.52 (0.16–3.13) ng/l. With a mean of 0.41 ± 0.48 (0.18–2.74) ng/ml, pretherapeutic levels in RCC patients were found to be significantly lower ($P < 0.05$, Table 2). During therapy, concentrations remained low without an apparent correlation with response to therapy or course of disease. An IFN-γ-induced increased release, as observed for β_2-MG, was not detectable.

Discussion

In vitro, IFN-γ has been shown to induce both NK cell activity and cytokine production by monocytes/macrophages and to upregulate expression of MHC antigens

as well as of cell adhesion molecules [24, 25]. Low-dose administration of IFN-γ has been demonstrated to be at least equivalent to high doses in enhancing antibody-dependent cellular and nonspecific cytotoxicity [38].

Interestingly, all patients investigated exhibited higher pretherapeutic levels of sICAM-1, sELAM-1 and sCD8, but lower concentrations of sCD4 and sMHC-I, than normal individuals, whereas β_2-MG concentrations were only elevated in patients with progression during therapy. An IFN-γ-induced increase in circulating immune markers was demonstrated only for β_2-MG. This expression pattern might point to individual subsets whose capacities are decreased, or even downregulated, in a defective process.

The generally observed elevation in sICAM-1 expression was markedly higher when succeeded by tumor progression during therapy. Because ICAM-1 is usually only weakly expressed in normal renal tissue, elevated levels might reflect increased ICAM-1 release by tubular and vascular epithelia, as immunohistochemically demonstrated in RCC [19]. What was surprising was the finding that none of the patients showed an IFN-γ-induced increase in sICAM-1 release, because IFN-γ was shown in vitro to induce membrane ICAM-1 expression and, consequently, greater adhesion of CD8+ cells in a dose-dependent manner within 4–48 h of administration [5, 32]. It is unknown whether the measured sICAM-1 originates from tumor cells or leukocytes: the marker might reflect the metastatic potential of tumor cells, as adhesion of lymphocyte function-associated antigen-1 (LFA-1)-positive leukocytes to the primary tumor conceivably promotes tumor cell dissemination [19] or, on the other hand, an enhanced immune response since expression of the adhesion molecules on tumor cells might be designed to make them more palatable to cytotoxic lymphocytes [15, 23, 36].

Therefore, the most plausible interpretation of the significantly elevated sELAM-1 levels in the present series is that they reflect an increased, probably sepsis-like, unspecific immune response induced by the tumor. IFN-γ, however, was shown barely to induce increased ELAM-1 expression, which is supported by the present results [21].

The generally observed increased activity of CD8+ suppressor T cells in cancer patients might be related to a reduced lymphoproliferative response actually promoting tumor progression [39, 29]. A drop in the peripheral-blood CD4/CD8 ratio correlating with tumor progression has been reported in advanced RCC [4]. At the same time, increased numbers of CD56+/CD3+ NK cells are observable. An increased frequency of CD8+ tumor-infiltrating lymphocytes in advanced stages of RCC has been demonstrated based on immunohistochemistry [3]. This shift towards the CD8+ T-cell subset might account for the lower sCD4 levels and for the massive release of sCD8 in all patients investigated. However, as peripheral-blood T cells in general are decreased in advanced RCC [4], a more likely explanation would be that sCD8 release is induced by tumor cells in the bloodstream that activate the NK-cell subset. Functionally, sCD8 may bind to MHC-class I molecules either at the cell membrane or in the serum and thereby block specific antigen recognition by CD8+ T cells while NK cell lysis is still operative. In vivo, IFN-γ induces a temporary rise in CD4+ T-helper cells, which results in activation of cell-mediated cytotoxicity [7]. However, an IFN-γ-induced alteration of sCD4 cannot be confirmed based on the present data. Similarly, a significant rise in sCD8 levels following IFN-γ administration could be observed only in two patients and might be due to temporary stimulation of NK cells.

A downregulation of MHC product expression in tumor cells might prevent them from being recognized by T cells [34]. Interferon-induced expression of MHC antigens has been described both in vivo and in vitro [16, 8]. Although in the present series β_2-MG significantly rose within 48 h of IFN-γ administration, an IFN-induced upregulation was not observable based on total serum sMHC-I. The speculation appears justified that binding of sCD8 to MHC-I might block sMHC-I quantitatively by the ELISA. This would also be consistent with the lower sMHC-I levels in all patients than among the controls. However, these observations do not rule out an IFN-γ-induced stimulation of MHC-I production, which would not necessarily imply its release, since the intracellular portion of the MHC-I molecule has a considerably longer polypeptide chain than β_2-MG.

The finding that baseline levels of these markers of activation in patients with advanced RCC are quite different from levels seen in normal individuals might point to an immunomodulatory defect associated with this disease. IFN-γ in vivo was found not to produce changes in markers that might be expected on the basis of its effects in vitro, which underlines the major problem that currently exists in defining in vitro parameters of response to immunotherapy.

Elevated serum concentrations of circulating adhesion molecules sICAM-1 and sELAM-1 and sCD8 antigen might be of clinical significance in indicating ongoing tumor progression. Further studies of immunomonitoring in RCC patients postsurgery could be of interest in indicating advancement of disease.

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