Review

Immunotherapeutic Approaches for Renal Cancer

(cancer / immunotherapy / interferon / interleukin / intra-lymphatic / kidney / LAK / renal carcinoma / transfer factor)

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Renal carcinoma is no doubt one of the strangest urologic tumours. Its multifaceted symptoms can defy the most perceptive physician, for more often than not the symptoms do not suggest a renal pathology.

Its frequency and mortality are not negligible. In the United States, there are 27 600 new cases of renal cell carcinoma each year, and 11 300 die from this cancer. Indeed, 30% of the patients have already developed metastases at the time of the initial diagnosis or at the time of the first relapse. Considering the resistance to chemotherapy and/or radiotherapy of this tumour, the prognosis remains bleak.

The peak age of incidence is sixty years, and affected men outnumber affected women two to one. Among the risk factors, cigarette smoking and exposure to cadmium are the most frequently cited, whereas familial forms have been associated with genetic translocations between chromosomes 3 and 8 or chromosomes 3 and 11. Furthermore, phakomatoses, e.g. von Hippel-Lindau disease, whose gene has been linked to the *raf-1* oncogene on chromosome 3, are associated with this cancer.

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Abbreviations: BCG – bacillus Calmette-Guerin, BRM – biological response modifiers, CCNU – chloroethyl-cyclohexy-nitrosourea, CR – complete response, CTL – cytotoxic T lymphocytes, DTH – delayed type hypersensitivity, 5-FU – 5-fluoro-uracil, IFN – interferon, IL-2 – interleukin 2, LAK – lymphokine activated killer cells, LN – lymph node, MHC – major histocompatibility complex, MLTC – mixed lymphocyte tumour cell cultures, MRCC – metastatic renal cell carcinoma, NDV – Newcastle disease virus-modified, PBMC – peripheral blood mononuclear cells, PR – partial response; RCC – renal cell carcinoma, Renca – murine renal cell carcinoma line, SD – stable disease, TF – transfer factor.

Conventionally, renal carcinomas are classified following the cell type and growth pattern. Cell types comprise clear, spindle, and oncocytic cells, whereas growth patterns include acinar, papillary, and sarcomatoid varieties. However, this classification has been modified in order to reflect the different types of adenocarcinomas more precisely by including morphological, histochemical, and molecular criteria. Thus, five carcinoma types have been identified. They comprise clear cell, chromophobic, chromophilic, oncocytic, and collecting duct types. Each of these types has a unique pattern of growth, cell of origin, and cytogenetic characteristics.

Despite many efforts, treatment of metastatic renal cell carcinoma (MRCC) has been proved disappointing over the years. No single treatment protocol or programme for MRCC has been uniformly effective. Thus, most physicians usually rely on novel therapies, including biologic response modifiers, investigational anticancer agents, differentiation agents such as retinoic acid, vaccines, or gene therapy.

Conventional treatment

Surgery

Standard therapy for localized renal cell carcinoma (RCC) is radical nephrectomy that includes removal of the kidney together with Gerota's fascia, the ipsilateral adrenal gland, and the regional hilar lymph nodes. Partial nephrectomy has become more popular, especially for patients with small tumours, those at risk for bilateral tumours, and those in whom the contralateral kidney is at risk because of the presence of other systemic diseases, such as diabetes and hypertension.

However, one of the main problems associated with partial nephrectomy is the possibility of tumour relapse, many renal tumours being multicentric. Local recurrence rates are 4 to 10%, but lower rates have been reported when partial nephrectomy was carried out for small (< 3 cm) lesions and the contralateral kidney was normal.

Neverthess, the role of surgery in the management of metastatic disease, either at initial presentation or later in a patient's course, remains controversial. Indeed, even when extensive surgery is carried out, the prognosis of most patients remains poor. Nephrectomy in patients with widespread metastatic disease, as a way of potentially improving their response to systemic therapy, has also been controversial. Although many research protocols require such resection, the practice should be viewed as uncertain. Nonetheless, a patient who does respond to systemic therapy should be considered for nephrectomy.

Chemotherapy

Several drugs have been used with variable, but unimpressive results (Table 1). For instance, a regimen combining oxaliplatin, 5-fluorouracil (5-FU), and folinic acid in fourteen MRCC patients previously treated with immunotherapy didn't produce any objective response (Chaouche et al., 2000). Using a combination of weekly intravenous gemcitabine with continuous infusion of 5-FU, Rini and co-workers observed only seven partial and five minor responses in 39 patients. The duration of response for the partial responders was 2–14 months.

The antitumour activity of zeniplatin, a third-generation, water-soluble platinum compound, has been assessed by Aamdal and co-workers. Only four MRCC patients were treated, and none responded. The main toxic effects were leucopoenia, nausea, and vomiting. Unexpected and serious nephrotoxicity was also observed, and for this reason, the studies were terminated before the planned number of patients had been included. A possible explanation for the nephrotoxicity may be drug interactions, but no definite conclusions were drawn.

Docetaxel (Taxotere, RP56976), a semi-synthetic analogue of paclitaxel, with a broad range of *in vitro* antitumour activity, was also evaluated in a phase II study. Twenty patients entered into the study, but no objective response was seen, except for one patient who showed a mixed response (Mertens et al., 1994). Similarly, no results were observed in 16 patients treated with fotemustine (Lasset et al., 1993).

Obviously, chemotherapy alone produces rather poor clinical results, but numerous adverse side effects that severely impair the quality of life. The data obtained in the last ten years on 451 patients (Table 1) show that in 4.6% of the cases, only a clinical response is obtained, with a median survival ranging from 2.5 to 12 months. These numbers agree with those of Yagoda et al. (1995), who carried out an evaluation of the various chemotherapy regimens used in 4542 patients during 82 phase II trials in previous years.

Immunotherapeutic attempts

Cytokine therapy is based on observations suggesting that this cancer may be responsive to immunotherapy. Indeed, it is well known that renal cancer can elicit an immune response in the host leading to spontaneous remissions. Although rare, this phenomenon has led many investigators to study agents that can stimulate the body's immune system. The agents that have been studied most extensively are interferon (IFN), interleukins (ILs), cytokines, and cellular-based therapies, in various combinations.

Table 1. MRCC treated with chemotherapy only

Authors	No. of patients	CR (%)	PR (%)	MR (%)	SD (%)	Median survival months	Range	Drugs
Liu et al., 2001	17	1 (6)	3 (17)	0	0	10	3-16	tamoxifen, vinblastine, 5-FU
Chaouche et al., 2000	14	0	0	0	2	nd	nd	oxaliplatin, 5-FU, folinic acid
Rini et al., 2000	39	0	7 (17.9)	5	nd	nd	nd	gemcitabine, 5-FU
Hao et al., 2000	17	0	3 (17.6)	0	nd	8	3-11	hydroxyurea, vinblastine
Pyrhonen et al., 1999	81	0	2 (2.4)	nd	nd	9	nd	vinblastine
Ritchie et al., 1999	168	0	4 (7)	0	15 (27)	2.5	0.5-5	MAP
Lummen et al., 1998	14	0	0	0	nd	nd	-	titanocene
Henriksson et al., 1998	63	2 (3.1)	0	0	0	12	nd	tamoxifen
Aamdal et al., 1997	4	0	0	0	0	nd	nd	zeniplatin
Mertens et al.,1994	20	0	0	1	0	nd	nd	docetaxel
Lasset et al., 1993	14	0	0	0	4	nd	nd	fotemustine
Totals	**451**	**3 (0.6)**	**19 (4)**	**6 (1.3)**	**21 (4.6)**	**2.5-12**	**0.5-11**	
Yagoda et al. 1995*	4542	59 (1.3)	213 (4.7)	-	-	-	-	83 phase II trials

* patients treated with chemotherapy from 1985 to 1995
() – % of response; MR – minor response; MAP – medroxyprogesterone acetate

Recombinant IFN

Utilization of IFN α, β, or γ alone has produced responses in approximately 12 to 20 percent of the treated patients. IFNs display multiple activities, inter alia an important anti-proliferative activity against renal cell carcinomas *in vitro*, are stimulatory to cell-mediated immunity, and can modulate the expression of major histocompatibility complex (MHC) molecules. The patients' response has been seen in many anatomic areas. However, patients who had had prior nephrectomy, but with only one pulmonary metastasis, and otherwise in good health, display a higher response rate. Duration of the response is usually less than two years, but longer-lasting remissions have been noted in a few patients.

IFNs have been combined with other immune modifiers and/or chemotherapeutic agents, but these combinations produced no real improvement in larger-scale trials. Several trials have combined IFN with IL-2 and chemotherapy (e.g., fluorouracil), and have shown some encouraging preliminary results (Gebrosky et al., 1997).

Combined therapies

Because of the poor results of chemotherapy or immunotherapy when used alone, protocols combining the use of cytotoxic drugs and cytokines were devised.

Schmidinger and co-workers (2000a) treated thirty-seven patients with progressing MRCC, who had already received treatment with IFN or IL-2, vinorelbine (30 mg/m^2, i.v.) for 22 days, and IFN-α-2c (4 800 000 U, s.c.) three times a week. Partial response (PR) occurred in 8% of the patients, whereas stable disease, with a median duration 8 and a range 3 to 35+ months, was observed in 46%. Median overall survival was 15 (range 1–49) months. No major toxicity was observed. Furthermore, patients who failed first-line treatment with biological response modifiers (BRM) had a greater chance to enter PR or stable disease (SD) under combined, low-toxicity therapy using vinorelbine and IFN-α-2c.

Naglieri et al. (1998) studied the impact of the association doxorubicin and epirubicin with IL-2 and IFN, and they observed a better survival. Patients were randomized to receive either IL-2 and IFN-α or IL-2 and 4-epirubicin. In 38 patients, two complete and two partial responses were observed, whereas 21 patients had stable disease. The authors considered these results as *"encouraging"*.

In 1999, a randomized study using IFN and medroxyprogesterone acetate showed poor activity of the latter: only 12% of partial responses in 168 patients treated were noticed, with a median survival of 2.5 months (Ritchie et al., 1999).

13-cis retinoic acid has also been used in MRCC, often in association with IFN and IL-2. The recent observations of Casali et al. (1998) appear promising despite the limited number of patients. 13-cis-retinoic acid was administered at 1 mg/Kg/day, and IFN-α-2a s.c. at 3 x 10^6 U/day. All patients had been previously treated with chemotherapy in association with immunotherapy. The treatment was not discontinued until neoplastic progression occurred. Two partial responses and five stabilizations were noticed with mild side effects.

Treatment with 5-FU and IFN-α was also used (Gebrosky et al., 1997). Twenty-one patients with advanced RCC underwent treatment with continuous intravenous infusion of 5-FU, 200 mg/m^2/day, and subcutaneous injections of recombinant IFN-α-2b, 1 x 10^6 U/day. An objective response was observed in nine patients (43%): a complete response (CR) in four patients (19%) (two with lung, one with bone, and one with liver metastasis), and a partial response in five (24%). The mean survival rate was 44 months for the complete responders, 42 for the partial responders, and 20 for the non-responders. The overall mean duration of response was 23 months. Responders entered progression to disease at a mean of 14 months after the initial response to therapy. Mild, dose-dependent toxicity was related to 5-FU infusion. Nearly all toxicities subsided with the temporary cessation and/or dose decreasing of the 5-FU infusion. Results were considered promising, but additional investigations are warranted.

It is mention worth that using vinblastine and IFN, Paolorossi et al. (1995) obtained two PRs in 13 treated patients, whereas Lopez-Hanninen and co-workers (1995) concluded that the second-line outpatient chemo/immunotherapy regimen of s.c. r-IFN-α and i.v. 5-FU showed a limited, albeit significant efficacy in pre-treated patients with progressive MRCC.

It seems that if chemotherapy alone produces disappointing clinical results, those are improved when IFN is added. The data obtained in 487 patients, and reported in 12 studies in the last 10 years (Table 2), show 15.5 % of CR+PR, and a median survival ranging from 9 to 23 months when IFN is added to chemotherapy. These observations are in agreement with those of Bukowski (2000, 2001).

IL-2

Table 3 shows results observed in the last ten years in MRCC patients, based on the utilization of IL-2 administered using various techniques: i.v. (continuous or bolus), s.c., by inhalation and intralymphatically. In many studies, to IL-2 administration were added other immunomodulators such as IFN, LAK cells, and transfer factor (TF).

In the past ten years, forty-four studies have been published. The median survival of the 3823 treated patients ranged from a minimum of 8.6 to a maximum of 39.5 months; 2–12 months being the median survival in 785 MRCC patients who did not undergo immunotherapy, reported in three different studies (Table 3).

In 12 studies (1473 patients), the overall response rate was 14.2% (range 5.3–58%), with 2–9.1% of CR and 5–58% of PR. The median survival in 926 patients,