Immunotherapy for renal carcinoma: theoretical basis and current standard of care

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Introduction

Carcinoma of the kidney (a.k.a. 'hypernephroma' or renal cell cancer) accounts for 2–3% of all adult cancers, and over 4000 new cases are reported in the UK every year [1]. It occurs more commonly in men, and has a peak incidence around 60–70 years, although can occur at any age. The incidence is increasing [2]. If confined to the kidney, surgical resection is the treatment of choice, and cure can result. However, most patients with metastatic disease survive less than 1 year [3], and chemotherapeutic or hormonal approaches are generally ineffective.

The natural history of renal cancer characteristically manifests an indolent course, with long periods of stable disease. In addition, the 'spontaneous regression' of metastases has often been reported in the literature, and Evenson & Cole [4] made the observation that renal cancer appeared to have the highest incidence of this controversial and intriguing phenomenon. The actual frequency of spontaneous regression in renal tumours is not known, but estimates put it at around 0.3% [5]. A higher frequency has been reported following nephrectomy in patients with established metastatic disease [6]. The existence of spontaneous regression has been put forward as evidence that a form of innate 'host factor' or immunological response may be involved in its pathogenesis. Such a hypothesis is supported by the increase in renal cancer cases observed in patients receiving long-term immunosuppressive therapy for organ transplantation [7].

The immune response

The *'immune surveillance'* hypothesis was first conceptualized at the beginning of the century by Paul Ehrlich. He suggested that the malignant transformation of a cell was a frequent occurrence, and that the transformed 'rogue' cells were recognized as foreign to the body and destroyed by its immune system. In this model, transformed cells develop into overt tumours as a consequence of either somehow losing their immunogenicity, or because of a defect in the host's immune system. Such an elegant and simple hypothesis has been difficult to substantiate; it has been observed that nude mice (lacking a thymus and therefore immunodeficient) do not appear to be more susceptible to cancers than immunocompetent mice. Furthermore, the majority of malignancies developing in organ transplant patients receiving immunosuppressants like cyclosporin involve the immune system, and do not generally manifest as the more common solid tumours.

Despite these caveats, it can be demonstrated that a host immune response is produced and directed against tumour cells, although is often *ineffective*. The generation of a co-ordinated immune response to an antigenic stimulation like cancer is extremely complex and requires the interaction of several cell types. Figure 1 outlines the essential components and interactions of the human immune response; for a more detailed description, the reader is referred to Kuby [8]. In the humoral response, the T_H cell (lymphocytes displaying the CD4 membrane glycoprotein; *helper* T-lymphocytes) interacts with an antigen committed B-lymphocyte, which has presented its antigen on the cell membrane (via endocytic processing) to the T_H cell in association with a class II MHC (major histocompatibility complex) molecule. Secretion of a number of cytokines by the T_H cell, including IL-2, IL-4, IL-5, IL-6, and interferon-γ then occurs. Cytokines are low molecular weight proteins which bind with very high affinity to specific target cell receptors, eliciting biochemical changes responsible for signal transduction that results in an altered pattern of gene expression in the target cells. These cytokines have the effect of stimulating differentiation and proliferation of the B-lymphocyte into B-memory lymphocytes, and into plasma cells which secrete antibody. Following T_H cell interaction with an antigen – class II MHC molecule on an antigen presenting cell, the cytokine IL-2 is secreted and binds to a newly expressed receptor on the T_H cell. In this situation, such autostimulation results in proliferation and clonal expansion of T_H cells, which are specific for the initiator antigen.

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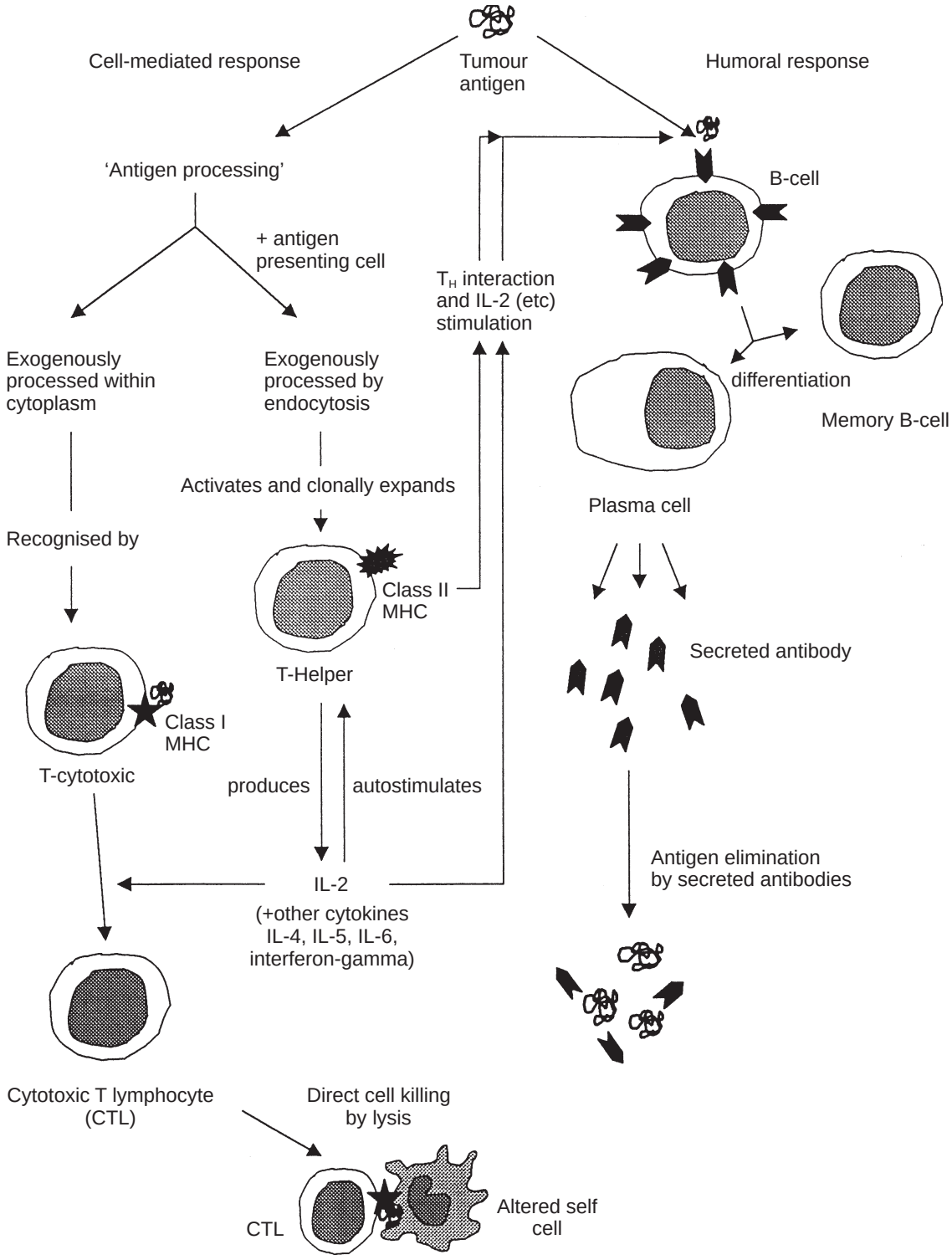

Figure 1 Overview of the humoral and cell-mediated immune response.

The activated T_H cells are then crucial in the generation of both humoral and cell mediated responses.

In the cell-mediated response, the presence of IL-2 secreted by the T_H cells induces T_C cells (cells displaying CD8; *cytotoxic* T-lymphocytes) into becoming cytotoxic T lymphocytes (CTLs) which are able to mediate cell membrane damage and lysis to altered self cells. Other secreted cytokines enable the differentiation of a number of other nonspecific effector cells. IL-2 and interferon-γ activate macrophages, thus enhancing the phagocytic

activity of these cells against ingested pathogens and tumour cells. These cytokines also enhance the activity of the natural killer (NK) cell.

There are several types of cancer for which the approach to treatment involves augmentation or supplementation of the natural defence mechanisms described above. However, the complexity of the cytokine network makes it very difficult to know precisely how intervention with a specific cytokine may affect the production of other cytokines, as there are demonstrated antagonistic as well as synergistic relationships within this network. In metastatic renal cancer, treatment with purified human leucocyte interferon-α (IFA), was reported to have antitumour effects in the early 1980s [9]; however, it was not until the various cytokine genes were cloned before large-scale production and sizeable clinical trials were possible.

Interferon-α (IFA)

Although large quantities of purified recombinant preparations of the interferons α, β, and γ are commercially available, most clinical trials in renal cancer have involved IFA. Given by subcutaneous injection, the dose of IFA is limited by side-effects which involve many organ systems, in addition to toxicities thought to be specific to the immune system. An acute phase of toxicity occurs in the immediate postinjection period and may consist of fevers/chills, nausea, myalgia/arthralgia and malaise. Attempts to abrogate these toxicities include premedication with paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen. Toxicities associated with chronic administration consist of fatigue, anorexia, weight loss, depression, lack of concentration, diarrhoea, low blood pressure and mild haematological and hepatic abnormalities. Very high doses (up to 100 000 mega units (MIU)) have been shown to be profoundly toxic and can be fatal, but such doses are not required to achieve therapeutic benefits. Most patients currently treated with IFA for metastatic renal cancer receive 3–10 MIU, thrice weekly by subcutaneous injection. IFA is currently licensed in the U.K. for use in a variety of malignancies.

Prior to randomised trials, the overall response rates (incidence of observed tumour regression) to IFA in renal cancer were reported to be of the order 10–12%, with complete responses observed in less than 2% of patients [10]. Responses were slow to develop, and were seen most frequently in patients having had a nephrectomy, and who were relatively fit with few metastatic sites (lung metastases being the 'best' site). In a group of 159 nonrandomised patients treated with IFA in a single cancer centre, median survival was reported as 11.4 months [11].

Data from randomised trials in renal cancer are required to fully evaluate the possible advantages of IFA, and it is particularly important to compare with no treatment (or 'best supportive care') in renal cancer, given the potential for side-effects. The first reported randomised study did not actually demonstrate an advantage for IFA over a relatively nontoxic hormonal therapy (medroxyprogesterone acetate; MPA) [12]. However, this trial was small (60 patients total) and was not empowered to make any significant statistical comparisons between the two treatments. In addition, 15/30 patients receiving MPA crossed over to IFA following the development of progressive disease.

A larger trial in metastatic renal cancer randomised 197 patients to receive either interferon-γ or placebo injections [13]. Interferon-γ was chosen because of laboratory data which hinted at greater activity for this cytokine than either IFA or interferon-β. However, this trial found no significant difference in survival for patients receiving interferon-γ, when compared with placebo. Once again though, it was not large enough to detect small, potentially significant differences in survival. In addition, previous smaller nonrandomised trials had also failed to hint at a clinically relevant advantage for interferon-γ; Wirth [10] reported a response rate of 12% culled from 234 patients over four separate trials.

A recent pivotal trial from the MRC (trial RE01) compared IFA and MPA in 335 patients with metastatic renal cancer [14]. Here, patients were randomised to receive IFA 10 MIU thrice weekly for 12 weeks by subcutaneous injection, or MPA 300 mg day^{-1} for the same duration. A survival advantage for IFA (1 year survival 43% *vs* 31%, median survival 8.5 months *vs* 6 months) was seen which translated into a 28% reduction in the risk of death (hazard ratio 0.72; 95% CI 0.55–0.94, $P=0.017$). Although side-effects were more common in patients receiving IFA, these differences were not as obvious at the end of the 12 week treatment period, which may suggest that patients adapt and develop improved tolerance to chronically administered immunotherapy.

Similar improvements in progression-free survival for IFA have also been reported by Pyrhonen and colleagues [15] who randomised 160 patients to receive either IFA in combination with vinblastine (a cytotoxic agent), or to treatment with vinblastine alone. Prior experience with vinblastine has shown very low activity in renal cancer, in common with most other cytotoxics [16], and therefore the control arm here could be considered as little more than placebo. The results of these two studies suggest that IFA has a beneficial effect on survival for metastatic renal cancer when compared with placebo. However, this increased survival due to immunotherapy needs to be weighed against the side-effects and subsequent detrimental effect on the patients' quality of life.

Interleukin-2 (IL-2)

Recombinant interleukin-2 (rIL-2) was first produced in 1983 [17], and was subsequently found to be a potent immunostimulant. Significant responses were observed in selected human tumours [18] and laboratory studies suggested that a dose–response relationship existed [19]. Because of this, the initial clinical trials used high-dose intravenous bolus administration schedules.

A 255-patient database of renal cancer patients treated with rIL-2 in seven phase II studies submitted to the U.S. Food and Drug Administration (FDA) has recently been updated [20]. In these studies, patients received 0.6 or 0.72 MIU kg^{-1} rIL-2 by 15 min bolus infusion every 8 h for up to 14 consecutive doses over 5 days. Patients tolerating this treatment could receive further courses of rIL-2 following rest periods. Overall, antitumour efficacy was very encouraging, with an overall response rate of 15%, and complete responses seen in 7%. However, the duration of such responses was the most encouraging feature, with a median response duration of 54 months (range 3–104+), and complete responses lasting for a median of 20 months (range 3–97+). Median survival for the group as a whole was 16.3 months. The earlier results of these studies were used to gain FDA approval in 1992 for the use of rIL-2 in the treatment of metastatic renal cell cancer in the USA.

Unfortunately, bolus intravenous administration was found to be associated with severe toxicity. Many of the side-effects seen were unexpected, and unlike those observed with conventional chemotherapy. A capillary leak syndrome resulted in a variety of serious, life-threatening conditions such as pulmonary oedema, multi-organ failure, and renal/hepatic dysfunction. Fatalities were not uncommon, and many patients became critically ill, requiring intensive care nursing. Despite this, clinicians were sufficiently encouraged by both the complete responses observed and the relatively long duration of such responses, and ways to abrogate these side-effects became an important objective.

Administering rIL-2 by continuous intravenous infusion seems to reduce the need for intensive care support during treatment, without negatively impacting on the durability of remissions [21]. However, this approach has not been directly compared with intravenous bolus therapy, and there is some data suggesting that rIL-2 should not be delivered by continuous infusion because of inactivation in the giving set tubing [22].

The use of lower intravenous bolus doses has been the subject of a prospective, randomised trial, which is not yet mature enough for definitive conclusions to be made regarding survival [23)] In this study, patients were randomised to receive 0.72 or 0.072 MIU kg^{-1} rIL-2 by 15 min bolus injection, 8 hourly. With 116 and 112 patients randomised in each arm, significantly less toxicity was experienced by patients in the low-dose arm. However, there is a suggestion that the high dose arm is associated with a superior short-term response rate (19% *vs* 10%). Longer-term follow-up may reveal if these differences are significant.

A number of subcutaneous schedules have been developed to deliver low doses (0.8–6 MIU day^{-1}) of IL-2 [24–27]. Similar preclinical immunomodulatory effects have been demonstrated with both subcutaneous and intravenous low-dose IL-2. Studies indicate that the chronic administration of low-dose rIL-2 induces anti-tumour immunomodulatory effects comparable with those obtained with high-dose rIL-2 with a significant decrease in systemic toxicity [24]. The definitive dose of 'low-dose' rIL-2 is unclear, but is now generally accepted to be less than 6 mIU day^{-1}.

In another approach to rIL-2 therapy, Huland and coworkers reported the experience of 116 patients with pulmonary or mediastianal metastases from renal carcinoma treated with inhaled IL-2 [28]. Toxicity was minimal, consisting mainly of cough, despite the high doses (up to 36 MIU day^{-1}) administered. Some patients received concurrent systemic rIL-2 or IFA in addition. Many significant responses were observed in pulmonary metastases, and disease stabilization was seen in over 50% patients. The authors concluded that the lack of serious toxicities enabled long-term administration of IL-2 (up to 4 years in some cases) and that disease stabilization was associated with prolonged survival.

Combined interleukin-2 and interferon-α therapy

As stated previously, the complexity of the cytokine network makes it very difficult to know precisely how one cytokine will affect the production of other cytokines. Theoretically, several cytokines could enhance the efficacy of IL-2, whereas others could be antagonistic. IFA appears to be able to activate cytotoxic function by stimulating host lymphocytes and macrophages, and upregulating MHC class I antigen expression on tumour cells, thus increasing CTL activity. However, it may also inhibit rIL-2-mediated lymphocyte activation [29].

The first phase II study of subcutaneous rIL-2 plus IFA in cancer patients was initiated by Atzpodien & Kirchner in the late 80 s [30, 31]. Treatment consisted of a 2 day rIL-2 pulse followed by a 5 day rIL-2 schedule for 6 weeks in addition to IFA 2–3 times weekly over the same period. Doses of rIL-2 were 14.4–18 MIU m^{-2} day^{-1} induction pulses, and 3.6–4.8 MIU m^{-2} day^{-1} thereafter. Doses of IFA were 3–6 MIU m^{-2}. Of 32 renal cancer patients treated, four complete responses (CR) and six partial responses (PR, >50% reduction in tumour volume) were

observed, for an overall response rate of 31%. Moreover, a further 13 patients had stable disease, and the median duration of the complete responses was 19 months. Side-effects were graded as mild or moderate in the majority of patients, and no deaths due to therapy occurred. This ease of administration contrasted favourably with bolus intravenous administration or rIL-2, and was certainly acceptable as out-patient therapy.

Dutcher and colleagues initiated a corroborative phase II study of subcutaneous rIL-2 plus IFA in metastatic renal cell cancer in 1992 [32]. Here, a simpler schedule was utilized, with comparable doses of both cytokines. Treatment consisted of rIL-2 5 MIU m^{-2} on days 1–5, plus IFA 5 MIU m^{-2} on days 1,3 and 5 with both cytokines administered for 4 weeks with a 2 week break. Repeated cycles were allowed, and 50 patients were treated, of which eight (17%) responded with two complete responses. Response duration was 12 months (range 1–56+).

However, there were concerns that although response rates appeared comparable with high-dose intravenous bolus treatment, the duration of response appeared to be shorter with the lower doses delivered. A randomised phase II trial of high dose rIL-2 and high dose rIL-2 plus IFA had previously demonstrated that the addition of IFA to high dose rIL-2 did not improve efficacy [33]. In addition, Clark and coworkers have since reported that very low doses of both cytokines (1 MIU m^{-2} day^{-1} for 12 weeks of both IL-2 and IFA) is ineffective, with no responses observed in 19 patients selected for their perceived inability to tolerate intravenous IL-2 [34].

Perhaps the definitive study comparing combined cytokine therapy with single cytokine treatment was carried out by the Groupe Francais d'Immunotherapie. This trial (the 'CRECY'trial) not only set out to compare single agent rIL-2 with the combination of rIL-2 plus IFA but also intended to compare both of these treatments with IFA alone in a three-way randomization [35]. In this multicentre randomised trial, 425 patients were allocated treatment with either (i) a continuous intravenous infusion regimen of rIL-2 18 MIU m^{-2} day^{-1} (ii) 10 weeks of subcutaneous IFA 18 MIU day^{-1} three times a week or (iii) rIL-2 as in (i) in addition to a reduced dose of IFA, 6 MIU day^{-1} three times a week, for the 10 weeks of treatment. Following a response assessment after 10 weeks of therapy, patients could receive maintenance therapy or cross over to the other cytokine (i.e. groups i and ii). Patients receiving rIL-2 were required to have a central venous catheter inserted for the duration of therapy. Efficacy was in favour of the combination arm in that response rates for the three arms were (i) 6.5% (ii) 7.5% and (iii) 18.6% ($P<0.01$). In addition, the 1 years event free survival for the groups were 15%, 12% and 20% ($P=0.01$). Despite this, the overall survival rates were not found to be significantly different for any treatment arm (median survival 12, 13 and 17 months, $P=0.55$). With respect to tolerability, side-effects were seen more frequently in the group receiving continuous infusional rIL-2.

Chemoimmunotherapy

Despite the low activity generally for chemotherapy in renal cell carcinoma, preclinical synergy has been demonstrated for 5-fluorouracil (an antimetabolite which has been available since the 1950s) and interferon [36]. A phase I/II trial of combination chemoimmunotherapy was reported in 1995 by Atzpodien and colleagues, wherein 24 patients with progressive metastatic renal cancer were treated with a regimen containing rIL-2, IFA, 5FU, vinblastine and 13-cis-retinoic acid for 8 weeks [37]. The doses and schedule are shown in Table 1. This pilot study produced an overall response rate of 42%, with four complete responses and six partial responses at a variety of metastatic sites. Significant cytokine-related side-effects were seen in only 4–8% of treatment cycles, although 20% of treated patients did develop a peripheral neuropathy, likely to be secondary to vinblastine.

In a subsequent study, this group reported a 39% response rate in 120 patients receiving only 5-FU in combination with rIL-2 and IFA at the same doses as in Table 1 [38]. Again, significant efficacy was demonstrated, and 13 complete remissions were observed, which were durable. The majority of patients had only mild constitutional symptoms such as fever, chills, and malaise which confirmed the suitability of this regimen as an outpatient treatment. In another study 78 patients were randomised

Table 1 Chemoimmunotherapy regimens.

(a) Ref [37]			
rIL-2	10 MIU m^{-2} 2xday	days 3–5	weeks 1+4
	5 MIU m^{-2} 2xday	days 1,3,5	weeks 2+3
IFA	6 MIU m^{-2}	days 1	weeks 1+4
	6 MIU m^{-2}	days 1,3,5	weeks 2+3
	9 MIU m^{-2}	days 1,3,5	weeks 5–8
5-FU	1g m^{-2}	day 1	weeks 5–8
Vinblastine	6 mg m^{-2}	day 1	weeks 5–8
13-cis retinoid	35 mg m^{-2}	day 1–7	weeks 1–8
(b) Ref [41]			
rIL-2	10 MIU m^{-2} 2xday	day 1	weeks 1+4
	5 MIU m^{-2} 2xday	days 1,3,5	weeks 2+3
IFA	6 MIU m^{-2}	days 3–5	weeks 1+4
	6 MIU m^{-2}	days 1,3,5	weeks 2+3
	9 MIU m^{-2}	days 1,3,5	weeks 5–8
5-FU	750 mg m^{-2}	day 1	weeks 5–8
(c) Ref [42]			
rIL-2	9 MIU	days 1–6	weeks 1,3,5,7
IFA	6 MIU m^{-2}	days 1,3,5	weeks 1,3,5,7
5-FU	600 mg m^{-2} day^{-1} c.i.	days 1–5	weeks 1,5

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