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Invited review

Rationale for immunotherapy of renal cell carcinoma

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Summary. Metastasis to distant organs is the principal cause of death from renal cell carcinoma (RCC). No commonly accepted therapy is available for disseminated RCC at present. Immunotherapy is a mode of therapy that either interferes with the immune system or makes use of drugs that have been derived from soluble mediators of the immune system. Several lines of evidence suggest that combinations of genetically engineered cytokines (e.g. interleukin-2 and interferon alpha) may be particularly active in the treatment of advanced RCC. There are two major rationales for considering immunotherapy for RCC: (1) there is currently no other therapy available, and (2) there is hardly any innovative approach besides immunotherapy. Still, immunotherapy is far from being a standard therapy for disseminated RCC.

Key words: Renal cell carcinoma – Immunotherapy – Cytokines

The life expectancy of cancer patients is determined by the presence or absence of distant metastases in most human tumours. In renal cell carcinoma (RCC), the probability of surviving 10 years is more than 70% in the absence and 0% in the presence of tumour metastasis at time of initial diagnosis [8].

Approximately 15,000 patients will have newly diagnosed RCC in 1990 in the USA [198], the incidence being comparable to that in Europe. Among them, about 25%–52% will have occult metastatic disease at the time of diagnosis. The mere presence of tumour cells in the circulation is not a predictor of metastatic disease [77]. Of the patients with disseminated disease, 80% will die within 3 years after surgery [46]. In contrast, 65% of patients with local disease survive 10 years [46].

Currently, no commonly accepted therapy is available for metastatic RCC. Therapy for advanced RCC is a challenge for new therapeutic approaches because there is virtually no alternative. Major advances in immunology and molecular biology have led to a variety of new drugs and methods with potential anti-proliferative and/or cytotoxic activities which are being used in clinical phase I and II trials.

Current therapy

The primary treatment for RCC is radical nephrectomy with or without lymph node dissection. Tumour enucleation alone has been proven to be an inadequate therapy in patients with a normal contralateral kidney [15, 134, 135]. In advanced disease, results with either single-agent or combination chemotherapy have been disappointing in the past [29, 38, 196]. Results from recent clinical trials with either single-agent or combination chemotherapy have been summarized in Tables 1 and 2, respectively.

Yagoda [232] has recently reviewed the results of 39 chemotherapeutic agents administered in clinical trials for therapy of RCC. The overall result with more than 2,000 patients was an objective response rate of 8.77%. From these data, chemotherapy appears not to be a therapy of choice for advanced RCC.

One of the reasons for the failure of conventional approaches with chemotherapy might be the high rate of multi-drug-resistance (MDR) gene expression in human RCC. MDR gene expression was demonstrated in 80% of h-RCC specimens [63, 80], as reviewed by Klein et al. [111]. MDR genes code for a 170,000 dalton glycoprotein (P-glycoprotein) that serves as a transmembrane efflux pump for cytotoxic drugs and thereby makes chemotherapy ineffective in a variety of cancers [126]; P-glycoprotein, however, may be inhibited by several drugs that influence membrane-bound electrolyte pumps, e.g. verapamil [212], reserpin [100], quinidine [64, 213], amiodarone [64] or cephalosporin antibiotics [82]. Clinical trials with antagonists to P-glycoprotein have been conducted in multiple myeloma and Hodgkin's disease (for review see [83]). On the other hand, P-glycoprotein is not only found in cancer cells but also in normal, untransformed cells, specifically in the kidney [63].

Table 1. Selected clinical trials of single-agent chemotherapy of renal cell carcinoma

Drug	No. of evaluable patients	% OR	Source
Acivicin	27	1	[54]
L-Alanosine	36	1	[54]
Aminothiadiazole	46	1	[54]
AZQ (aziquone)	55	1	[202]
10-Deazaaminopterin	13	0	[190]
Demethoxydaunorubicin	19	0	[191]
2-Deoxy-5-fluorouridine	25	1	[47]
2-Deoxy-5-fluorouridine	45	2	[44]
2-Deoxy-5-fluorouridine	18	5	[223]
Elliptinium	14	0	[166]
IRCF-187 (razoxane)	40	0	[23]
Ifosfamide	9	0	[16]
Lonidamine	25	2	[226]
N-Methylformamide	14	0	[1]
Mitoxantrone	58	0	[72]
Vinblastine	21	1	[42]
Vinblastine	35	3	[54]

% OR = percentage objective responses

Table 2. Selected trials of combination chemotherapy for renal cell carcinoma

Drugs	No. of evaluable patients	% OR	Source
Cyclophosphamide + misonidazole	30	1	[78]
Dacarbazine + cyclophosphamide + cisplatin + doxorubicin + vindesin	16	1	[129]
Mitomycin C + metronidazole	12	3	[204]

Radiotherapy may be helpful for palliation [20, 177]. Brain metastases may be reduced in size by radiation [131]. Overall survival after radiation of skeletal metastases from RCC is approximately 12 months [20]. Hormone therapy (testosterone, progesterone, oestrogen, antagonists) has not improved the survival of patients [88, 217], although promising in vitro results have been demonstrated [32]. Surgery of solitary metastases may improve survival in less than 50% of the patients [51, 97].

The basis for immunotherapy

Spontaneous regression of malignant tumours and/or metastases is a rare event. Such reports should be carefully analysed; the term "spontaneous" is not always used in its strict sense, e.g. tumour regression without any previous therapy. Rather, there are reports about "spontaneous" regression that describe tumour disappearance after previous therapy. To date, no convincing evidence for a role of the immune defense system in unexplained "spontaneous" tumor regression has been presented. In melanoma, lymphocytic infiltrations in regressing tumours have been observed [139] but their biological importance is not fully understood [115].

Some 60% of the reported cases of spontaneous regression have involved just four types of cancer: malignant melanoma, RCC, choriocarcinoma and neuroblastoma [193]. There are approximately 70 reports in the literature describing unexplained spontaneous regression of RCC metastases (for review see [55, 105]). Most of them are well documented, and 22 are histologically proven [105]. In the majority, the regressing metastases were located in the lungs. The frequency of spontaneous regression in h-RCC is estimated between 0.5% [45] and 7% [156] of all cases.

An antigen is operationally defined as a structure that is recognized by the immune system. Thus, antigens that are present on RCC but not on normal renal tissue may provide a target for the humoral and cellular immune defense. Most antigens on RCC have been demonstrated serologically. Several groups have raised murine monoclonal antibodies against h-RCC. With a few exceptions [188, 159], serologically defined antigens on h-RCC are not exclusively found on cancer cells but also on non-tranformed renal cells, especially on tubular epithelium cells [35, 36, 112, 128, 157, 158, 214, 220] (for review see [4]). Antigens expressed on normal renal cells may be modulated in renal cancer [39].

Other antigens found on RCCs include receptors for hormones like Vitamin 1,25 D_3 [149] or for carbohydrates [92]. Moreover, several leucocyte differentiation antigens have been demonstrated on h-RCC [17].

Serologically defined antigens on h-RCC have been used as targets for immunolocalization and monoclonal antibody-targeted radiotherapy in experimental animals [35–37] (for review see 70]). Monoclonal antibodies with specificity for both the tumour antigen and the antigen receptor of cytoxic T cells have been shown to enhance T-cell-mediated cytolysis greatly both in vitro [216] and in nude mice [231]. Monoclonal antibodies have been used in the therapy of leukaemias, lymphomas, gastrointestinal tumours and melanoma (for review see [65]). Phase II studies with monoclonal antibodies have not been reported in RCC.

Current concepts for immunotherapy

Attempts at immunotherapy of advanced RCC have been made for more than 15 years (for review see [138, 145]. Most of them employed non-specific immunostimulators and/or relatively crude preparations of mediators with immunostimulatory activity. In the past few years, numerous mediators of the immune response have been genetically engineered and made available in nearly unlimited quantities for clinical studies. In this review, we will focus on approaches that are currently under investigation.

Table 3. Clinical trials with active specific immunotherapy for renal cell carcinoma

Regimen	No. of evaluable patients	CR	PR	% OR	Source
autologous vaccine	119	6	4	8.4	[187]
homologous vaccine	35	2	2	5.7	[174]
autologous vaccine + *C. parvum*	29	0	8	27.5	[121]
autologous vaccine + *C. parvum* + cyclophosphamide	20	1	4	25.0	[185]
aggregated tumour antigen + *Candida albicans*	23	0	0	0	[68]
polymerized tumour antigen	111	16	n.r.	14.4	[207]

n.r. = not reported; CR = complete remission; PR = partial response

Three major approaches have been chosen in recent clinical trials for the immunotherapy of advanced RCC (for review see [52, 84, 170]): (1) active specific immunotherapy, (2) recombinant cytokines and (3) adoptive transfer of immunocompetent cells. Of these, active specific immunotherapy and therapy with recombinant cytokines either alone or in combination with adoptive transfer of immunocompetent cells have been used in clinical trials.

The majority of the studies reported here are phase I or II studies. Thus, what is summarized in this review is early evidence, not new standard therapy. In phase I studies, toxicity of a new drug is examined. Phase II studies focus on the effects of a new drug on the tumour [123]. Response to therapy is reported as summarized by Grossman and Buch [87]: a complete response (CR) is defined as a complete disappearance of all evident tumour. A partial response (PR) is defined as a $\geq 50\%$ decrease in the cross-sectional area (product of the largest diameter and its perpendicular diameter) of measurable tumour without progression into other tumour sites or the appearance of new lesions. The term objective response (OR) is used for the sum of complete and partial responses.

Active specific immunotherapy

Active specific immunotherapy is based on the assumption that a specific T-cell response will be elicited upon immunization of patients with inactivated autologous tumour cells plus more or less well-defined adjuvants [185, 187]. Immunization is carried out usually in vitro although interesting results have recently been reported employing an in vitro immunization schedule [161].

Typically, immunization with autologous or homologous tumour vaccines is a therapy without the severe side-effects observed in other immunotherapy regimens. Autologous as well as allogeneic tumour antigen preparations have been used for immunizations [68, 152, 207]. Additionally, agents with unspecific immunostimulatory activity have been co-injected with the tumour cells. Adjuvants such as Corynebakterium parvum *(C. parvum)*, *Candida albicans* or tuberculin purified protein derivative (PPD) have been employed. In most cases, no clear evidence for their activity in vivo, e.g. from animal models, has been presented.

Clinical results are conflicting, ranging from approximately 25% objective response down to 0% (Table 3). Most likely, differences in the response rates are caused by patient selection and lack of knowledge on the exact mechanism of tumour cell rejection by T lymphocytes. Currently, the role of tumour antigen in rejection is being investigated [14, 56, 90, 194].

Heicappell et al. [90] introduced an animal model for active specific immunotherapy of metastases. In this model, a chemically induced lymphoma cell line (ESb) metastasizes to the liver, spleen and lymphonodes of mice that have received the tumour intradermally. All mice transplanted with the tumour succumb to metastatic disease within a short time. For therapy, irradiated autologous tumour cells are modified by a virus in vitro prior to immunization. Vaccination of mice bearing metastases after surgery of the primary tumour leads to the complete disappearance of metastases in the liver and spleen. Clearly, in this model tumour-specific T lymphocytes have been activated by the regimen chosen [222]. Clinical trials were set up based on these experimental results.

Subsequent studies on active specific immunotherapy will benefit from increasing knowledge on the mechanism of the T lymphocyte response to tumours in vivo.

Cytokines

Cytokines are molecules that have pleiotropic activity and were mostly discovered by their crucial role in the regulation of the immune response. Many have been detected during the past 10 years, the function of some of them still not being clearly defined. It appears as though

Table 4. Side-effects of tumor necrosis factor (TNF)

General side-effects	Haematological side-effects	Other side-effects
Chills	Leucopenia	Hypertriglyceridaemia
Fever	Thrombocytopenia	
Headache		
Rigour		
Nausea		
Vomiting		
Hypotension		
Water retention		

there is an intricate interplay among the cytokines. Many are produced by activated cells of the immune system. Genes for cytokines are expressed in relatively high frequency in non-lymphoid organs of healthy individuals [211]. Some cytokines have been shown to possess direct cytotoxocity towards human tumour cells (e.g. tumour necrosis factor, TNF), some are growth inhibitory but not cytotoxic [e.g. interferon (IFN)-α], some do not have direct effects on tumour cells [e.g. interleukin (IL)-2] and some do not interfere with tumour growth at all (granulocyte-macrophage colony stimulating factor, GM-CSF; [186]).

Most of the cytokines may now be produced in nearly unlimited amounts by recombinant DNA technology. Typically, recombinant cytokines have molecular weights in the range of 15–40 kDa. In vivo, they usually possess, a short half-life only. Thus, in order to maintain effective levels systemically, high doses of the respective cytokines have to be infused. Therapy with cytokines usually has typical and sometimes severe side-effects.

Tumour necrosis factor. TNF-α is a macrophage-derived protein [130] that may be cytotoxic or cytostatic for human tumour cells in vitro [205], among them RCC [91]. For non-malignant cells, e.g. fibroblasts, TNF may serve as a growth factor [49, 221].

Two species are known, designated as TNF-α and TNF-β. TNF-β is a lymphocyte-derived tumouricidal factor that was termed "lymphotoxin" earlier [85]. Almost exclusively, studies about therapy for RCC have been conducted with TNF-α. Human renal carcinomas are sensitive to TNF-mediated cytotoxicity and/or cytolysis in vitro [11]. Heicappell et al. have demonstrated that cells within a RCC may differ in their susceptibility to lysis by TNF-α [91].

In vivo, TNF-α causes haemorrhagic necrosis in some tumour models [31]. It is likely that this is related to the activity of TNF-α on the vascular endothelium and the coagulation cascade [13, 215]. Other effects may also contribute to the anti-tumour activity in vivo: infusion of TNF induces secretion of large amounts of IL-6 (interferon-β_2) in tumour-bearing mice [140] and patients receiving TNF therapy [21, 101]. Moreover, the cytotoxicity of peripheral blood leucocytes is enhanced after infusion of TNF [34]. Thus, it can be assumed that the in vivo efficacy is not solely based on a direct effect of TNF; rather, other cytokines or cellular elements of the immune system possibly contribute to the final destruction of tumours.

There is a limited number of protocols employing TNF in the therapy for metastatic RCC (for review see [69, 96]). A number of phase I studies have been conducted with TNF as an infusion in a dose range of 40–280 μg/m^2, the maximum tolerated dose being approximately 100 μg/m^2 [40, 102, 201, 206, 229]. In other approaches TNF has been used with intra-lesional application [6].

Few phase II studies have been reported. No objective responses have been observed in trials with TNF given IM. Recombinant TNF has a half-life of only 20–30 min in humans [69]. Thus, it may well be that through IM injection sufficient serum levels of TNF cannot be achieved.

Eisenhauer and co-workers [53] treated 22 patients with 150 μg rh-TNF/m^2 IV for 5 days every other week. They observed one partial response and one complete response.

TNF is the most important mediator of endotoxin shock [142]. Thus, side-effects are closely related to the symptoms of endotoxin shock, e.g. fever, hypotension and water retention [192]. In general, the toxic side-effects of TNF are similar to those of IFNs and are summarized in Table 4. Side-effects were similar irrespective of the route of application (e.g. IM or IV).

In order to improve the efficacy of TNF, experimental protocols have been set up that combine TNF with chemotherapeutic drugs such as cyclophosphamide [118] or actinomycin D [25]. Otto and colleagues reported 43% objective responses in a series of 14 patients who had been treated with a combination of TNF and IFN-α [163].

New recombinant TNFs with reduced toxicity have recently been introduced [74]. Interestingly, evidence suggests that TNF-α and TNF-β may also be secreted by human tumour cells in culture [117]. Further studies are required to clarify the role of TNF in the host defence against tumours.

Interferons. The interferons are a family of three different immunoregulatory proteins, termed as alpha, beta and gamma. The molecules are differentiated by source: IFN-α from leucocytes, IFN-β from fibroblasts and IFN-γ from activated lymphocytes. IFN-α and IFN-β are genetically related, whereas IFN-γ is not related to either one.

Table 5. Clinical trials with recombinant interferon alpha

Regimen	No. of evaluable patients	CR	PR	% OR	Source
2×10^6 U/m^2 IM (daily)	15	0	0	0	[171]
20×10^6 U/m^2 IM (daily)	15	0	4	26.6	[171]
20×10^6 U/m^2 IM (daily)	26	1	7	30.7	[171]
30×10^6 U/m^2 SC 5 days, every 2–3 weeks	20	0	1	5.0	[108]
18×10^6 U/m^2 IM	42	0	7	16.6	[162]
18×10^6/m^2 IM 3×/week	30	0	3	10.0	[9]
3–36 $\times 10^6$/m^2 IM 10 weeks	22	0	5	22.7	[30]
3×10^6 (daily) 4 weeks	24	3	3	25.0	[71]
3–36 $\times 10^6$ IM (daily) 5 days/week for 14 weeks	19	CR + PR:	5	26.3	[60]
10^6 IU SC 3×/week	18	1	0	5.5	[98]
2×10^6 IU/m^2 SC 2×/week	51	n.r.	5	9.8	[148] IFN α_2b
30×10^6 IU/m^2 5 days, every 3 weeks	46	n.r.	3	6.5	[148] IFN α_2b
10×10^6 IU IM	18	1	1	11.0	[189] IFN α-$_2$C

Table 6. Clinical trials with recombinant interferon beta

Regimen	No. of evaluable patients	CR	PR	% OR	Source
0.01–150 $\times 10^6$ U/m^2 IV 2×/week	15	0	2	13.3	[178]
3–30 $\times 10^6$ U IV	16	0	1	6.2	[110]
45–990 $\times 10^6$ U IV 3×/week	21	1	3	19.0	[109]
90–720 $\times 10^6$ U IV 3×/week	15	0	0	0	[153]

In therapy for RCC, IFN-α has been used much more frequently than IFN-β or IFN-γ (for review see [119, 143, 152]. Early results with partially purified, non-recombinant preparations suggested activity against RCC especially with IFN-α (for review see [99, 119]). Summarized results indicate an average objective response rate in the range of 14%–15% for IFN-α (Table 5), approximately 11% for IFN-β (Table 6) and below 10% for IFN-γ (Table 7).

The appearance of antibodies against IFN-α has been reported after its IM injection [59]. IFN-α and IFN-β possess direct anti-proliferative activity towards tumour cells. Moreover, recombinant IFN-α stimulates natural killer (NK) cells in humans [95] and enhances the expression of major histocompatibility complex (MHC) antigens in human tumour cells [76]. IFN-γ apparently does not have a direct cytolytic effect on tumour cells. Rather, it activates cells of the immune system that are involved in the host response against tumours, e.g. monocytes and macrophages (for review see [2]). Moreover, tumour cell antigens such as the histocompatibility antigens may be modified by IFN-γ [195].

Thus, of the interferons used in therapy for RCC, IFN-α seems to be the most active one. Consequently, clinical trials have been set up in order to improve further its anti-tumour activity by combining it with other modalities.

Table 7. Clinical trials with interferon gamma

Regimen	No. of evaluable patients	CR	PR	% OR	Source
8–12 × 10^6 U/m^2 IM or IV for 4 weeks continuously	32	n.r.	n.r.	9.3	[175]
40 × 10^6 U/m^2 bolus IV intermittent 5 day/14 day	30	n.r.	n.r.	20.0	[175]
0.25–1.0 mg/m^2 IM daily	14	0	1	7.1	[172]
0.01–0.05 mg/m^2 IV	16	0	1	6.2	[172]
30–3,000 μg/m^2	41	1	3	9.7	[73]
0.25 × 10^6 U/m^2 IV continuous 5 days	24	0	0	0.0	[120]

Table 8. Clinical trials with recombinant interferon alpha (IFN) in combination with vinblastine

Regimen	No. of evaluable patients	CR	PR	% OR	Source
IFN: 36 × 10^6 IU IM 2/week Vin: 0.1–0.15 mg/kg IV every 2–3 weeks	18	0	6	33.3	[67]
IFN: 18–30 × 10^6 IU IM Vin: 0.1 mg/kg IV every 3 weeks	12	0	3	25.0	[67]
IFN: 18 × 10^6 IU IM 3×/week Vin: 0.1 mg/kg IV every 3 weeks	34	n.r.	2	11.7	[9]
IFN: 18 × 10^6 IU 3×/week Vin: 0.1 mg/kg IV every 3 weeks	18	0	2	11.1	[24]
IFN: 18 × 10^6 IU IM 3×/week Vin: 0.1 mg/kg IV every 3 weeks	25	n.r.	0	16.0	[93]
IFN: 3 × 10^6 IU/m^2 Vin: 0.1 mg/kg IV every 3 weeks	18	1	7	44.4	[33]
IFN: 18–36 × 10^6 IU 2×/week Vin: 0.1–0.15 mg/kg 2–3×/week	57	1	11	21.0	[66]
IFN: 18 × 10^6 IU 3×/week IM Vin: 0.075–0.15 mg/kg IV every 3 weeks	7	0	3	42.8	[107]
IFN: 10–20 × 10^6 IU IM 3×/week Vin: 0.075–0.15 mg/kg IV every 3 weeks	40	1	16	42.5	[12]
IFN: 18 × 10^6 IU 3×/week IM Vin: 0.1 mg/kg IV every 3 weeks	20	0	2	10.0	[197]

Table 9. Clinical trials with recombinant interferon alpha (IFN) in combination with other drugs

Drug	No. of evaluable patients	CR	PR	% OR	Source
IFN-α + IFN-γ	24	0	6	25.0	[75]
IFN-α + IFN-γ	10	0	5	50.0	[173]
IFN-α + cyclophosphamide	25	0	1	4.0	[224]
IFN-α + vinblastine + tamoxifen	24	0	1	4.1	[48]
IFN-α + medroxyprogesterone acetate	93	3	3	5.3	[167]

Table 10. Current classification of interleukins (IL)

Name	Source	Activity	Reference
IL-1	Monocytes, endothelium, epithelium	Mediator of inflammation; endogenous pyrogen	[50]
IL-2	T cells	T-cell growth factor	[154, 155]
IL-3	Activated T lymphocytes	Multi-CSF; histamine release from basophils; eosinophil maturation; B-cell differentiation	[154, 155]
IL-4	Activated T lymphocytes, bone marrow stroma	B-cell stimulating factor (BSF-1); activation of neutrophils; activation of IL-2-stimulated LAK cells induction of IgE	[154, 155]
IL-5	Activated T cells	T-cell replacing factor (TRF); B-cell growth factor II; growth and differentiation of eosinophils; enhancement of IgA production	[154, 155]
IL-6	Monocytes, lymphocytes, fibroblasts, tumour cells, endothelium, normal spleen, normal liver, normal kidney	B-cell stimulating factor (BSF-2); interferon β_2; hybridoma growth factor; hepatocyte stimulating factor; induction of acute phase proteins; activation of NK cells	[18]
IL-7	Bone marrow, stroma	Pre-B-cell growth factor; T-cell activation	[81]
IL-8	Leucocytes, monocytes	Granulocyte chemotactic peptide	[147]
IL-9	T lymphocytes	T-cell growth factor	[218]
IL-10	T helper cells	Cytokine synthesis inhibiting factor	[22]

CSF = colony stimulating factor; NK = natural killer; LAK = lymphocyte activated killer

Most groups used a combination with vinblastine, the rationale being that vinblastine is one of the chemotherapeutic drugs that had a marginal effect in RC.

A typical regimen consists of 3 injections (IM) of 18×10^6 IU/m^2 IFN-α per week plus 0.1 mg/kg vinblastine IV every 3 weeks. The results of 10 clinical trials with a total of 249 patients indicate a 22% objective response (Table 8). Of the other combinations used in clinical trials, the combination of IFN-α and IFN-γ was particularly successful, with an objective response rate of 25% in a small number of patients (Table 9). Side-effects of IFN-α/β therapy include fatigue, fever, chills, myalgias, headache and diarrhoea [151].

Interleukins. The interleukins are a class of cytokines that activate and regulate growth and/or differentiation of leucocytes (for review see [154, 155]. Ten different interleukins numbered 1 to 10 were known at the time of completion of this review; the number is steadily increasing. The genes for interleukins 1 to 10 have been molecularly cloned; thus, they are available in nearly unlimited quantities. The interleukins, their sources and targets are depicted in Table 10. For immunotherapy of cancer, IL-2 is the major interleukin involved in preclinical and clinical studies. In the future, IL-4 and IL-6 may gain importance in that respect, too.

Interleukin-2 (IL-2) is a T helper lymphocyte-derived hormone that induces proliferation of antigen-triggered cytotoxic T lymphocytes but does not affect non-lymphoid cells, e.g. tumour cells of epithelial origin, directly. IL-2 has been used in therapy for RCC alone [199, 200] or in combination with adoptively transferred peripheral [62, 181, 227] or tumour-infiltrating T lymphocytes [10, 210]. Upon activation with IL-2, a certain subset of peripheral lymphocytes may acquire the ability to non-specifically lyse fresh autologous tumour targets but not normal cells; this apparently heterogenous sub-population of peripheral lymphocytes is termed lymphocyte activated killer cells (LAK cells; for review see [160]). Synergy of IL-1 with IL-2 in the induction of LAK cells has been described recently [43].

Based on these findings three major therapeutic approaches have been developed: adoptive transfer of LAK cells; adoptive transfer of tumour infiltrating lymphocytes (TIL); infusion of IL-2 alone. A typical regimen for LAK cell therapy consists of bolus infusions of 10^5 U of IL-2 per kg every 8 h for 5 consecutive days. Infusion of IL-2 initially causes a considerable decrease in the absolute number of peripheral lymphocytes within 24 h [200]. After discontinuation of IL-2 infusion a 2–10-fold increase of lymphocyte numbers – as compared with pre-therapy baseline values – usually occurs within 24 h [200]. Other

Table 11. Clinical trials with recombinant interleukin (IL-2) plus lymphokine-activated killer (LAK) cells

Regimen	No. of evaluable patients	CR	PR	% OR	Source
39×10^3 U/24 h continuous 5 days/week MNC + periodate + IL-2/48–72 h	13	0	6	46.1	[225]
10^5 U/kg every 8 h days 1–5 days 8–12 leukapheresis, days 12–16 10^5 U/kg every 8 h + LAK cells	32	2	3	15.6	[62]
5-day cycles constant infusion 3×10^6 U/m^2 IV + LAK cells	20	0	2	10.0	[227]
3×10^6 U/m^2 continuous IV 5 days days 8–10 leukapheresis, days 13–17 LAK cells + IL-2	8	1	0	12.5	[208]
days 1–5 IL-2 10^5 U/kg every 8 h days 8–12 leukapheresis days 12, 13, 15 LAK cells IL-2 every 8 h	36	4	8	33.3	[181]
days 1–5 IL-2 10^5 U/kg days 8–12 leukapheresis days 12, 13, 15 LAK cells	35	2	3	14.2	[132]
days 1–5 IL-2 10^5 U/kg every 8 h days 8–12 leukapheresis days 12, 13, 15 LAK cells every 8 h	11	0	1	9.0	[136]

effects of IL-2 infusions include an increase in the number of IL-2 receptor positive lymphocytes and LAK cells. Moreover, the NK activity of peripheral blood lymphocytes is increased [208]. From day 8 patients are subjected to one leukapheresis per day for 5 days. Leucocytes are harvested and expanded in IL-2 in vitro for 4 days. From day 12 to day 15 patients receive IL-2 plus LAK cells that have been expanded in vitro. Ziegelbaum and co-workers have demonstrated that in vitro LAK cells from patients with RCC can be induced [233]. Rosenberg and co-workers report objective response rates in the range of 20%–30% in a large series of patients with RCC [179, 181]. Their results have been reproduced by a multi-centre study group [132]. The overall result with this protocol in the seven clinical trials reviewed here is 21% objective responses (Table 11). In regressing metastatic lesions a leucocyte infiltrate can be found predominantly consisting of macrophages as well as CD4 and CD8 positive lymphocytes in equal proportions [184].

All patients given LAK cells and IL-2 in a bolus regimen (3×10^5 U/kg every 8 h) had to be treated in an intensive care unit because of live-threatening toxic side-effects [132], most severely with high dose IL-2 therapy. The most predominant side-effect of IL-2 therapy was a "vascular leakage syndrome" that leads to fluid retention in the extracellular space [183]. The major clinical manifestation of fluid extravasation was pulmonary oedema [132]. In experimental animals, the vascular leakage syndrome could effectively be treated by administration of IL-1 [168]. Neurological side-effects were somnolence or agitation in about a third of the patients. Moreover, 73% of the patients after LAK-cell therapy developed a severe anaemia that required blood transfusion. Other side-effects included metabolic changes, i.e. elevation of liver enzymes, hypocholesterinaemia [230] or hypothyreosis [89], cardiac depression [122] and impairment of renal function [113]. Toxic side-effects of IL-2 therapy have been found to be dose-dependent and reversible after its discontinuation [41]. For therapy with LAK cells and IL-2, detailed guidelines have been issued after completing a multi-centre study [132]. New regimens with diminished toxicity are currently under investigation [113, 208].

An improved approach for the adoptive transfer of in vitro activated lymphocytes has been introduced by Belldegrun et al. [10]: instead of expanding human peripheral blood lymphocytes they isolated and expanded tumour-infiltrating lymphocytes (TIL) from a h-RCC specimen. These cells are presumably sensitized to the tumour in vivo and have been shown to possess a 50–100 times stronger lytic activity than LAK cells [180]. Based on cell membrane antigens 95% of IL-2 expanded TIL have been found to possess the phenotype of cytotoxic T lymphocytes [210]. Kradin and co-workers recently reported preliminary results with TIL therapy in RCC [114]. In their series of 7 patients, 2 had objective tumour response after therapy. The protocol consisted of infusion of IL-2 ($1\text{–}3 \times 10^6$ U/m^2 per 24 h) on days 1–5, days 8–12 and days 15–17. TIL were infused every 2nd day during

Table 12. Clinical trials with recombinant interleukin (IL-2) as single agent therapy

Regimen	No. of evaluable patients	CR	PR	% OR	Source
1×10^6 U IV or SC for 21–240 days	13	2	1	23.0	[137]
3×10^6 U/m^2 5 days IV every 2nd week for 5 weeks	10	1	2	33.3	[103]
3–10 $\times 10^6$ U/m^2 IV (daily) 1/week for 6 weeks	16	0	1	6.2	[169]
1–3 $\times 10^6$ U/m^2 IV (daily) 4 days/week for 4 weeks	17	0	3	17.6	[199, 200]
$5 \times 10^5 - 5 \times 10^6$ SC daily 5 days/week	14	0	0	0	[228]
3–6 $\times 10^6$/m^2 IV bolus daily 5 days/week for 4 weeks 3–6 $\times 10^6$/m^2	12	0	1	7.4	[228]
10^5 U/kg IV every 8 h IV bolus daily days 1–5, days 12–16	16	0	0	0	[1]
42.5 $\times 10^6$ U total dose	18	1	2	16.6	[164]
10 $\times 10^6$ U/m^2 bolus IV 2×/week	41	1	2	7.0	[27]

Table 13. Clinical trials with recombinant interleukin (IL-2) in combination with other drugs

Regimen	No. of evaluable patients	OR	Source
IL-2 + vinblastine	12	4 (33%)	[5]
IL-2 + cyclophosphamide	11	0 (0%)	[124]
IL-2 + IFN-α_{2a}	15	4 (26.6%)	[27]
IL-2 + IFN-α_{2a}	14	3 (21%)	[133]
IL-2 + IFN-α_{2a}	19	4 (21%)	[144]
IL-2 + IFN-α_{2a}	12	6 (50%)	[127]
IL-2 + IFN-α_{2a}	22	7 (32%)	[61]
IL-2 + IFN-α_{2a}	24	1 (4%)	[125]
IL-2 + IFN-α_{2b}	14	5 (36%)	[3]
IL-2 + IFN-α_{2b}	19	3 (19%)	[7]
IL-2 + IFN-β	24	6 (25.0%)	[116]
IL-2 + IFN-γ	10	0 (0%)	[176]

IL-2 therapy. Therapy was applied on a general rather than an intensive care ward. Unlike Rosenberg and colleagues [180] they did not use cyclophosphamide in the TIL protocol. Side-effects of TIL therapy were generally milder than with LAK cell therapy. Side effects in patients treated with a high dose of IL-2 (3×10^6 U/m^2 per 24 h) consisted of fever and rigour (89%), desquamating skin rash (89%), thrombophlebitis (100%) and nausea (57%).

It has been argued that bolus infusion of high doses of IL-2 as used by Rosenberg and co-workers is necessary in order to maintain the activity of the LAK cells infused. Thompson and co-workers have demonstrated that – in addition to LAK cells – continuous infusion of IL-2 yields a better biological activity than bolus injection every 8 h [209]. Herberman [94] was able to show that infusion of adherence-purified LAK cells reduces the amount of IL-2 needed to maintain activity in vivo considerably.

LAK-cell therapy according to the protocol as proposed by Rosenberg and co-workers can be applied in highly specialized centers only. All patients have to be subjected to intensive care. Moreover, a clinical laboratory is required that is experienced enough to handle large amounts of blood cells safely. Consequently, attempts have been made to modify IL-2/LAK-cell therapy in a way that allows for widespread application. It could be shown that in humans infusion of IL-2 alone was capable of inducing LAK cells in vivo [41, 165]. Thus, attempts have been made to induce LAK cells in vivo rather than in vitro. Six clinical trials have been reported with different regimens of IL-2 infusion alone. Results (Table 12) indicate approximately 11% objective responses. Moreover, with continuous infusion of IL-2 fewer infectious complications were observed as compared with IL-2 plus LAK cells [203]. In a review of 34 clinical trials it has recently been suggested that the objective response was dependent on dose intensity of IL-2, e.g. dose per unit time, whereas LAK cells did not seem to be critical for the overall response [19]. In order to improve the results, IL-2 has been combined with other immunomodulators or chemotherapeutic drugs [26] (summarized in Table 13). Encouraging results (approximately 20%–25% objective response) have been specifically reported from clinical trials with combined IL-2 and IfN-α [3, 61, 125, 127, 133, 144] or IFN-β [116] therapy. In contrast, no responses were seen in a small series of patients treated with IL-2 and IFN-γ in combination [176]. Moreover, IFN/IL-2 therapy has been applied SC with good results on an out-patient basis [3, 80].

IL-2 is part of a network of humoral immunoregulatory agents. Thus, attempts have been made to improve the

Table 14. Summary of clinical trials for therapy of renal cell carcinoma

Therapy	Number of patients	% OR
IL-2 + IFN-α	139	23.5
IFN-α + vinblastine	249	22.0
IL-2 in combination (chemo + IFNs)	196	21.9
IL-2 + LAK cells	155	20.6
IFN-α	346	14.4
Active specific immunotherapy	337	12.7
IL-2 alone	157	10.8
IFN-α + other drugs	176	10.7
IFN-β	67	10.4
IFN-γ	157	9.5
TNF	28	7.1
Combination chemotherapy (selected regimens)	58	6.8
Single-agent chemotherapy (selected regimens)	500	3.6

efficacy of IL-2 therapy. IL-4 has been shown to enhance further the anti-tumour active of IL-2-activated TIL [106]. Infusion of IL-2 raises the levels of circulating TNF and IL-6 in patients [101, 104]. Thus, the anti-tumour effect of IL-2 infusion may not exclusively be caused by IL-2.

Perspectives

The rationale for immunotherapy of RCC is based on the fact that there is no other therapy for advanced cases. Chemotherapy, hormonal therapy and radiotherapy have not been effective.

For new immunological approaches, the availability of a valid pre-clinical screen is very important [219]. Immunotherapeutic approaches interfere with the regulation of the immune system. Thus, a meaningful pre-clinical screen would most likely be an in vivo rather than an in vitro system. Moreover, an animal model should include the most important aspect of therapy for human cancer, the metastatic spread of cells from the primary tumour. For RCC, a nude mouse model is available that – upon orthotopic tumour inoculation – metastasizes to the same organs as in humans [150]. This model has been successfully used as a pre-clinical screen for anti-metastatic immunotherapy [28]. Interestingly, the approach that is one of the most promising in experimental RCC therapy – LAK-cell therapy plus IL-2 – is based on a solid foundation of experimental data in a mouse model [86]. In contrast, most reports on new chemotherapy regimens for RCC do not include a statement on the rationale of the respective approach. New therapies for advanced RCC should always be based on experimental data rather than just on the availability of new drugs.

Super-additive (synergistic) effects have been observed with combinations of cytokines. Based on these findings, in vivo studies have been initiated [173]. The combination of IL-2 and IFN-α seems to be particularly active in RCC in terms of objective responses (Table 14). Furthermore, combinations of adoptive transfer, chemotherapy and cytokines are currently being investigated in animal experiments [182]. The efficacy of active specific immunotherapy or therapy with interleukins can be improved by chemotherapeutic drugs; cyclophosphamide and adriamycin have been used in this respect (for review see [141]).

Hybrid cytokines, e.g. hybrid IFNs-α, have been constructed by recombinant DNA technology. Some have been shown to possess greately improved anti-proliferative activity in vitro [58]. Furthermore, "artificial cytokines", hybrids of different cytokines, e.g. IFN-γ and TNF-β, have recently been developed [57].

In the future, the experimental therapy for RCC will benefit from increasing knowledge of the immune system and its regulation. Clearly, knowledge of the biology of tumour metastasis from RCC is a prerequisite for developing innovation approaches to the cure of advanced RCC.

At this time, innovative approaches come from two directions: firstly, attempts are being made to overcome the chemoresistance of RCC by drugs that interfere with the MDR gene product P-glycoprotein; the second line of innovative approaches comes from immunology. There is a rapid gain of knowledge on the immune system and its activation against tumours. In the therapy for advanced RCC these results should be used for the benefit of patients who with conventional approaches would not have a chance ot survive more than a few months.

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