from 33.2% Tac-positive cells on day 3 to 3.4% on day 6. There was no change in the percentage of Tac-positive cells in the untreated control sample (42.9% on day 3, versus 46.1% on day 6).

Screening of cDNA libraries

Several genes have been isolated by screening cDNA libraries from resting and growing B-cells, as well as from Epstein-Barr virus (EBV)-transformed B-cell lines, including the interferon-inducible gene thymosin-ß4 (Fig. 3) and the gene designated EBV77 (Fig. 4), which is unique and not represented in GenBank.

CONCLUSION

These studies showed that human peripheral B-cells could be activated to growth either by phorbol ester and Ca-ionophor or by a cocultivation protocol using anti-IgM and several lymphokines. The first protocol was alpha interferon-sensitive and associated with loss of Tac-antigen expression but not the second. Several genes have been isolated from a cDNA library derived from growing B-cells, of which one was expressed with three transcripts, differentially regulated by EBV.

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The Use of Interferon in Renal Cell Carcinoma

Hyman B. Muss

Metastatic renal cell carcinoma remains an incurable disease and current modalities can only offer major palliation to a small percentage of patients. Since treatment is palliative, choice and type of therapy must be carefully considered and reconciled with patient desires. When possible, patients should be offered participation in a clinical trial. For patients choosing progestin therapy, treatment with interferon (IFN) or other biological response modifiers can be instituted at the time of progestin failure. Those patients who have slow tumour progression and maintain a high quality of life can be observed without continued progestin therapy. Although pretreatment characteristics predict response to biologicals, no pretreatment characteristic should preclude an individual patient from a trial of IFN therapy. Whether high-dose interleukin-2 (IL-2), IL-2/lymphocyte-activated killer cells, or IL-2/IFN are superior to IFN alone is uncertain, but clinical trials currently underway should help resolve these issues.
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INTRODUCTION

THE AMERICAN CANCER SOCIETY estimates that there will be almost 24,000 cases of renal cell carcinoma in the United States in 1990 resulting in over 10,000 deaths [1]. Although the aetiology of renal cell carcinoma is unknown and there is no effective screening strategy, approximately 50% of patients present with localized disease amenable to surgical cure. Patients with recurrent or metastatic disease have a poor prognosis with a mortality rate of 74% at 1 year and 96% at 3 years [2]. The most common metastatic sites include the lung (65% of patients), bone (40%), liver (14%), adrenals (8%), and peritoneum (8%) [2]. The phenomenon of spontaneous regression seen in almost 1% of patients [3, 4] and the array of paraneoplastic syndromes [5] including fever, cachexia, polycythaemia or anaemia, hypercalcaemia and hepatitis, all associated with renal carcinoma, suggest that several biological substances are secreted by these tumours. The following review will focus on the treatment of advanced or recurrent disease with biological therapy, mainly the interferons. In addition, the role of endocrine therapy and chemotherapy will be discussed.

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HORMONAL THERAPY AND CHEMOTHERAPY

Progestin therapy remains a popular modality in patients with metastatic disease. Original reports by Bloom [6] indicated a response rate with progestin of 16%, but a more recent review by Hrushesky and Murphy [7] suggests that the true objective response to endocrine therapy is less than 5%. Nevertheless, their ease of use, minimal side effects and potentially beneficial

anabolic effects (weight gain), make them a frequent choice in metastatic disease.

Chemotherapy has been generally ineffective [7-9]; numerous single agents have been studied with poor response rates. Vinblastine has been associated with a response rate of approximately 15%. More recently, continuous infusion floxuridine (FUdR) given continuously or in a chronobiologically-defined manner has demonstrated response rates of 15% to 20%.

Combination chemotherapy and chemoendocrine therapy have not proven superior to single-agent treatment and many regimens have been associated with substantial toxicity [10,11].

INTERFERON

Interferon (IFN) has been the most extensively investigated agent in patients with metastatic disease with more than 1,000 patients evaluated in numerous clinical trials [12]. Early trials utilized leucocyte IFN prepared from whole blood leucocytes (Cantell preparations) or from viral stimulation of a human lymphoma cell line (lymphoblastoid IFN). More recently recombinant DNA technology has led to the large-scale production of recombinant IFNs including interferon alfa-2a (Roferon®, Hoffman-LaRoche), interferon alfa-2b (Intron A®, Schering-Plough), and recombinant interferons beta and gamma. The response rates associated with these different preparations are presented in Table 1. Cantell IFN has been

Table 1. Response to IFN by type

Type of IFN	No. of studies*	Evaluable patients	% CR + PR	95% CI
Cantell	5	138	20	14-28
Lymphoblastoid	8	277	17	12-22
Alfa-2a	8	325	15	12-20
Alfa-2b	3	163	10	6-16
Beta	2	38	18	8-34
Gamma	7	214	10	6-15

*Modified from Muss [12]. CR = complete response; PR = partial response.

associated with slightly higher response rates but the 95% confidence interval for response (95% CI) [13] for each preparation suggests that there are no significant differences. Moreover, the response rates presented are based on data from numerous studies which differ in patient selection, dose and schedule, and response criteria. It is the author's opinion that major differences in the IFNs do not exist as far as their ability to cause tumour shrinkage.

It is unclear whether a dose-response relationship exists for IFN therapy. Initial trials of Cantell IFN used a low dosage because of the difficulty of IFN preparation. Both Cantell IFN and lymphoblastoid IFN were only partially purified and it is possible that other lymphokines were also responsible for some of the anti-tumour effect. Although controversy continues to exist, a dose of 5-10 million units (MU) given at least three times per week appears to result in the best therapeutic index [14]. Only three trials have addressed the dose-response issue in a randomized study: two suggested that a high-dose regimen was superior [15, 16] while a third showed no difference between low- and high-dose treatment [17]. The route of administration has not been associated with response, with intramuscular and subcutaneous administration being as effective as intravenous treatment. Response to IFN is generally noted within 1 to 3 months after starting therapy but may not be seen for 6 months or longer. The median duration of response is approximately 6 months; however, as many as one-third of those who achieve complete or partial remission have durations exceeding 1 year. Partial responses are most frequent, but complete responses are noted in as many as 25% of responding patients.

In vitro, IFN is capable of potentiating a wide variety of anti-neoplastic agents including vinblastine [18]. Almost 200 patients have been treated with combinations of IFN and vinblastine, with IFN doses ranging from 3 to 36 MU given intramuscularly or s.c. three times weekly and vinblastine doses between 0.075 and 0.15 mg/kg given every 3 weeks. The response to this combination approximates 25% — higher than the response to IFN alone — but preliminary data from a large randomized trial comparing IFN alone to IFN plus vinblastine show no benefit for the more toxic combination [19]. IFN has also been combined with cyclophosphamide, doxorubicin, medroxyprogesterone and aspirin without any evidence of superiority over IFN alone. Moreover, the addition of aspirin to IFN did not ameliorate the flu-like toxicity associated with therapy [20].

Patients with resected renal cell carcinoma and lymph node involvement, penetration into the perirenal (Gerota's) fascia or involvement of the renal vein, have a failure rate exceeding 50%. Recently, randomized clinical trials comparing post-operative IFN to no treatment have been instituted and the results of these trials will provide data concerning the efficacy of adjuvant IFN. At present, adjuvant IFN should not be given to high-risk patients unless done as part of a clinical trial.

IFN toxicity is universal with a flu-like syndrome consisting of malaise, fever, chills or muscle aches occurring in almost all patients; such side effects are dose-related, but are rarely severe at dosage less than 10 MU daily. Tachyphylaxis occurs with continued treatment; in addition, two case reports suggest that corticosteroids may almost completely abolish IFN toxicity without blocking response [21, 22].

The role of anti-IFN antibodies in relation to response is unclear [23]. The appearance of neutralizing antibodies has been associated with disease progression and decreased toxicity in some studies but not others. Published data indicate that recombinant interferon alfa-2b is associated with less antibody production than interferon alfa-2a [24], but patients in clinical trials utilizing interferon alfa-2a have generally received higher IFN doses. Measuring antibody levels (if available) in patients who have amelioration of toxicity and disease progression while taking IFN might be beneficial as such patients might be changed to alternative preparations or given a higher dosage of their current preparation.

INTERLEUKIN-2

The demonstration by Rosenberg and colleagues [25] that interleukin-2 (IL-2) combined with lymphokine activated killer cells (LAK) could cause tumour regression in a wide variety of refractory malignancies led to the development of numerous

clinical trials using IL-2 alone or with other biological response modifiers. Rosenberg and his colleagues at the National Cancer Institute (NCI) indicated that as many as 35% of patients with renal cell carcinoma treated with IL-2/LAK achieved remission; approximately one-third of responders achieved complete remission with a median duration greater than 18 months [26]. Using an identical protocol, a working group sponsored by the NCI noted a response rate to IL-2/LAK of 16% [27]. Subsequently, other workers using different doses and schedules of IL-2/LAK have confirmed its activity in renal cancer with an overall response rate of 20-25% [26, 28-32] (Table 2). The initial dose and schedule of IL-2/LAK therapy

Table 2. Response to IL-2/LAK therapy

Author	Year*	*n*	CR+PR	%	95% CI
Rosenberg *et al.*†	1989 [26]	72	8 + 17	35	24-47
Fisher *et al.*†	1988 [28]	32	2 + 3	16	5-33
Philip *et al.*	1989 [29]	15	0 + 3	20	4-48
Mittleman *et al.*	1989 [30]	12	0 + 1	8	2-38
Negrier *et al.*	1989 [31]	51	5 + 9	27	16-42
Stahel *et al.*	1989 [32]	14	0 + 3	21	5-51

*References in [ ]. †Same dose and schedule. CR = complete response; PR = partial response.

used by Rosenberg and colleagues required hospitalization and close monitoring, was costly and resulted in the need for intensive care for the majority of patients, including intubation in approximately 5%. Other regimens using continuous infusions of IL-2 with LAK have led to similar results as the NCI working group, with diminished toxicity [31].

The discovery that IL-2 stimulated the production of other lymphokines, including tumour necrosis factor and gamma IFN, as well as its demonstrated efficacy in conjunction with LAK, led to trials using IL-2 as a single agent. An overview of trials utilizing IL-2 as a single agent in metastatic renal cancer is

Table 3. Response to single agent IL-2 therapy

Author	Year*	*n*	CR+PR	%	95% CI
Rosenberg *et al.*	1989 [26]	54	4 + 8	22	12-36
Sosman *et al.*	1988 [33]	17	0 + 3	18	4-43
Negrier *et al.*	1989 [31]	32	2 + 4	19	7-36
Bukowski *et al.*	1990 [34]	41	1 + 4	12	4-26
Abrams *et al.*	1990 [35]	16	0	0	0-21
Fujioka *et al.*	1990 [36]	14	1	7	1-34

*References in [ ]. CR = complete response; PR = partial response.

presented in Table 3 [26, 31, 33-36]. The results of these trials suggest that IL-2 therapy has a steep dose-response relationship and that IL-2 regimens similar in efficacy to IL-2/LAK require hospitalization and intensive monitoring. Randomized trials comparing IL-2 and IL-2/LAK are in progress; preliminary data suggest a superior response with IL-2/LAK without improvement in survival [27].

The demonstration of *in vitro* synergy between IFNs, IL-2, and other biologicals stimulated other clinical trials in renal cancer. Initial results utilizing combinations of IL-2 and IFN as well as other biologicals suggest similar efficacy to either single agent IL-2 or IFN [37]. The results of recently published trials using this combination are presented in Table 4 [26, 38-42].

Table 4. Response to IL-2/IFN therapy

Author	Year*	IFN	*n*	CR+PR	%	95% CI
Rosenberg *et al.*	1989 [26]	α2a	46	4 + 11	33	20-48
Kirgel *et al.*	1990 [38]	ß	22	1 + 5	27	11-50
Figlin *et al.*	1990 [39]	α2a	22	0 + 7	32	14-55
Bartsch *et al.*	1990 [40]	α2b	19	0 + 3	16	3-40
Lindemann *et al.*	1990 [41]	α2a	24	1 + 0	4	1-21
Lipton *et al.*	1990 [42]	α2a	12	3 + 3	50	21-79

*References in [ ]. CR = complete response; PR = partial response.

Toxicity for IL-2/IFN combinations has generally exceeded that of IFN treatment alone but has generally been much less than with regimens using high doses of IL-2. Many of the current IL-2/IFN regimens can be safely administered on an out-patient basis.

It is not certain whether IL-2 alone, IL-2/LAK or IL-2/IFN is superior to IFN therapy. Although initial response rates have generally been higher for high-dose IL-2 or IL-2/LAK, patient selection for such trials has been extremely rigorous; entry criteria have required excellent performance status, minimal tumour burden and, frequently, nephrectomy. In addition, recent reports have suggested that the durability of remission is superior for patients treated with IL-2-containing regimens [26]. Although this may be the case, approximately one-third of patients who achieve remission with IFN alone have durations of response exceeding 1 year. Since patient selection may be a crucial factor in predicting treatment outcome as well as treatment tolerance, further randomized trials will be necessary to resolve this issue.

PATIENT SELECTION FOR BIOLOGICAL THERAPY

The likelihood of response to therapy with IFN as well as other biologicals can be predicted by pretreatment characteristics (Table 5). Response to IFN does not appear to

Table 5. Patient selection for biological therapy: host/treatment characteristics and response

Patient characteristics	Effect on response
Age	None
Gender	None
Disease-free interval	None
Prior treatment	Equivocal - probably none
Performance status	Better status at entry = higher response
Nephrectomy	Higher response
Site	Lung metastases are most responsive
Dose	Equivocal - intermediate dose has best therapeutic index
Anti-IFN antibodies	Equivocal - may be important in patients receiving interferon alfa-2a

be correlated with age, gender, disease-free interval or prior treatment. The effect of prior chemotherapy or radiation on response is unclear but they do not appear to have major impact if the patient has good performance status. Patients with normal performance status or who are minimally symptomatic, and with isolated or dominant pulmonary metastases have a higher probability for a good response. Nephrectomy appears to be associated with a higher response rate; however, most patients in published trials have had nephrectomy prior to study entry. The response rate for patients with nephrectomy compared to those without nephrectomy was 17% and 12%, respectively, in a previous review [12].

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