to research in breast cancer [10] and other hormone associated tumours. This work will not be fruitful until there is more cooperation between steroid biochemists, endocrinologists, oncologists and neurosurgeons. At present, for practical purposes, gestrinone [11], a potent antiprogesterone drug without antiglucocorticoid effects, is the best choice in treating men and postmenopausal women with inoperable meningiomas. I have four patients in whom such tumours have not grown for up to 3 years, but have also not shrunk. Gestrinone has few side-effects and can be used long-term; however, it is not the final answer. If meningiomas prove to be homogeneous in progesterone binding activity then a radiolabelled antiprogesterone drug may be the answer, but such speculation is premature until a more scientific basis for treatment is established.

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Eur J Cancer, Vol. 26, No. 8, pp. 860–862, 1990.
Printed in Great Britain

0277–5379/90 $3.00 + 0.00

Is the Outlook Changing for Patients with Renal Cell Cancer?

THERE HAVE been radical changes in the treatment of renal cell cancer that have led clinicians to reassess their management policies for this condition. Before the mid-1980s the main treatments for metastatic renal cell cancer were hormonal and chemotherapeutic, with surgery as an option for those rare patients with solitary metastases [1]. Hormonal therapies developed from the empirical observations of the effects of orchiectomy upon renal cell cancer in hamsters. However, the initial observation that medroxyprogesterone acetate produced regression of metastatic disease in approximately 30% of patients [2] was not confirmed and the true response rate is less than 5% [3–5]. Other hormonal agents, including flutamide and tamoxifen, have been used with response rates of between 5 and 10% [6, 7]. Hormonal therapies are attractive because of their relative lack of toxicity compared with chemotherapy. Vinblastine and lomustine are probably the most effective of the agents used but the true order of response is low at less than 10%. Combinations increase toxicity but not efficacy [8–10]. Newer cytotoxic drugs have almost as little effect on the course of disease as more established therapies [11–13].

This comparative lack of response to conventional therapies has resulted in a continued search for new treatments and in this context the role of immunotherapy has been investigated with enthusiasm. The first report of the effects of the interferons in renal cell carcinoma came in 1983. Human leucocyte interferon was used to treat 19 patients, 5 of whom had partial responses [14]. Similar response rates have been seen with lymphoblastoid and recombinant interferon alpha [15, 16]. An overview of 1532 patients treated with alpha interferon showed complete response in 32 (2%) and partial response in 219 (14%) [17]. The median duration of complete response was 8 months. Several different treatment schedules have been investigated but there is no advantage with high doses of interferon and a considerable disadvantage in terms of toxicity. Beta interferon has been used in 18 patients and 2 partial responses were reported [18]. Gamma interferon has greater *in vitro* antitumour activity than alpha or beta interferon and clinical trials with this agent started optimistically. However, only 1 complete and 10 partial responses were seen in 121 patients, showing no advantage with gamma compared with alpha or beta interferon [17]. Interferons combined with chemotherapy are not synergistic [19, 20].

At the United States National Cancer Institute, a new form of treatment with interleukin 2 and lymphokine activated killer

(LAK) cells, known as adoptive immunotherapy, has been developed. An early report suggested that our nihilistic views about the outlook for patients with metastatic renal cell cancer should radically change [21]. Is this true? Interleukin 2 is a chemically defined lymphokine originally described as a T-cell growth factor that leads to increased chemotaxis and cytotoxicity in T-cell subsets bearing the CD4 surface marker. Interleukin 2 induces the release of other lymphokines, such as gamma interferon and tumour necrosis factor, and activates a variety of cytotoxic cells. Interleukin 2 alone or in combination with LAK cells decreased the size of pulmonary and hepatic metastases from experimental tumours [22]. In these studies the combination of both agents produced maximal effect. In 1983 clinical trials began in patients with disseminated malignancy. Encouraging response rates were described in solid tumours unresponsive to conventional therapies and the most responsive was renal cell carcinoma [21]. There have been 13 (8%) complete and 31 (18%) partial responses in 169 patients treated with either interleukin 2 alone or interleukin 2 with LAK cells [23–28]. Those patients who are likely to respond are those with good performance status and small bulk disease and who are without cerebral or bone metastases. Responses are thought to be more durable than those achieved with other cytokines. In the largest series of patients, the duration of complete response ranged from 6 to over 34 months and partial responses from 1 to over 36 months [25]. Although overall response rates may not differ greatly from that for alpha interferon, response duration is longer, confirming early enthusiasm.

The toxicities of treatment are considerable and seen in virtually every patient. This toxicity is due to a vascular leak syndrome in which lymphoid cells and other peripheral blood components migrate into extravascular tissues [29]. The most commonly observed feature of this syndrome is fluid retention manifesting as pulmonary or cerebral oedema; fevers, nausea, vomiting, eosinophilia, myxoedema, anaemia, ascites and myocardial infarction are also reported [21, 30–32]. Any description of the toxicity of treatment should be considered with regard to the toxicities of standard treatment and the overall prognosis of metastatic renal cancer, which is for a median survival of 9 months. In an attempt to reduce toxicity, interleukin 2 has been given without LAK cells or as a continuous infusion [33]. Although this schedule is said to be less toxic, the claim is contentious.

Newer approaches aimed at improving the response rate to interleukin 2 have been examined. The activity of tumour infiltrating lymphocytes extracted from resected tumours, expanded *in vitro* with interleukin 2 and then reinfused into patients has been investigated. 2 partial responses were seen in 7 patients [34], but the advantages of this approach compared with conventional methods of administering interleukin 2 are not yet clear. Other cytokines are thought to act synergistically with interleukin 2 and future trials will investigate interleukin 2 combined with tumour necrosis factor and alpha interferon. Studies with interleukin 2 have been carried out in the presence of gross bulk disease. It may be that cytokine treatment is more effective when there is minimal residual disease, interleukin 2 being given in the adjuvant setting.

Critics of cytokine therapy have stated that responses to treatment are difficult to evaluate in a disease with a natural history of spontaneous regression of metastases. However, such regressions are rare and highlight the importance of biological therapies. In the largest series of patients in whom spontaneous remissions have been investigated, 2 of 115 patients had complete remissions and 2 partial remissions of pulmonary metastases after nephrectomy [35]. This response rate is lower than that seen with interleukin 2.

So the prospects for patients with renal cell carcinoma have improved as a result of the advances of the past 5 years. Response rates are not as high as first reported. However, durable cures and partial responses can be achieved with interleukin 2 in a small proportion of patients and these remissions last significantly longer than those achieved with other treatments. It is hoped that there will be refinements in cytokine therapy. Treatment needs to be less toxic, although this may not be possible. Randomized trials are required to compare interleukin 2 with standard treatment and to investigate seqential treatments in combination with other cytokines. Clinicians should be aware of the changing outlook for renal cell cancer and refer patients to specialist centres for treatment.

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