cannot be reproduced by others? And can we afford to undertreat elderly patients on the pretext of using well-tolerated regimens? Should we not treat all patients satisfying similar criteria with an effective regimen, e.g. CHOP? If I were such a patient, my answer would be very clear!

But what about the non-qualifying patients? Many of these may still benefit from chemotherapy, even though less aggressive, but how should these patients be selected, and by what criteria should they be declared unfit? Evidently, this is not easy and non-measurable clinical factors, including the patient's and his/her relatives' willingness, as well as the doctor's bias in favour or against such therapy, may play important roles [10]. Nevertheless, we should not accept these unclear factors, but strive to define more exactly which criteria need be fulfilled for less aggressive, palliative treatment, and which criteria for no treatment. Anything else is an unsatisfactory solution, and will not help future generations of patients and doctors forced to take treatment decisions.

Finally, recent developments point out that even so-called well-tolerated regimens may have side-effects comparable to CHOP. In the Dutch CNOP versus CHOP study, similar toxicities and a better complete response rate and overall survival was found in the CHOP arm in 145 evaluable patients older than 60 years (Sonneveld, personal communication). Finally, the EORTC 20872 trial, comparing VMP to CHOP in elderly patients, was prematurely closed for ethical reasons at the recent Paris meeting of the EORTC lymphoma group because of unexpected imbalances in efficacy and tolerance of the two arms (Tirelli, personal communication). Of course, we have to wait for the published full reports to know exactly how to interpret this information. Nevertheless, for the time being, it seems clear that all patients fulfilling entry criteria such as required for a prospective study should receive CHOP or an equivalent regime, without dose reduction. Those that do not fulfil the criteria should be included in trials that try to better define objective reasons for not treating these patients at all, or for treating them with a tolerable and efficient therapy adapted to their situation.

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Renal Cell Cancer: is There Long-term Survival Advantage From Cytokine Treatment?

R.T.D. Oliver

INTRODUCTION

IN THE U.K. financial restrictions have limited widespread use of interleukin (IL)-2 and interferon (IFN-α). Elsewhere in the world, there is disbelief that there is a need for a randomised trial in metastatic renal cell cancer patients, comparing IFN-α and placebo, namely medroxyprogesterone acetate (MPA)[1]. The U.K. MRC trial has now recruited 107 cases and has successfully passed its first review by a data monitoring committee, suggesting that there is, as yet, no significant gain from the use of IFN-α.

This situation, taken with the previously published small Scandinavian randomised trial involving 60 patients who showed no gain [2], gives added encouragement for continued recruitment into this trial. The retrospective prognostic factor analysis, comparing patients receiving either chemotherapy or IFN-α, reported by Fossa and colleagues in this issue, (pp. 1310–1314) provides added support. Though they claim significant gain with IFN compared to chemotherapy, it is only seen in the minority of patients who survive for more than 12 months and who have good risk factors, as defined by low erythrocyte sedimentation

Correspondence to R.T.D. Oliver at the Department of Medical Oncology, Medical College, Royal London Hospital, London E1 1BB.
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rate (ESR), good WHO performance status and lack of weight loss, all of which were more frequent in patients receiving IFN.

There have been at least two other previous prognostic factor analyses which have compared retrospectively cytokine-treated and historical controls [3, 4]. Both provide evidence that there may be some advantage for cytokine treatment in patients with good risk metastatic disease. As neither used ESR, Fossa's study suggests there could be a case to pay more attention to this relatively simple marker of disease activity, which was first reported by Van Der Werf-Messing [5].

SPONTANEOUS REGRESSION AND CELLULAR THERAPY

Since the first reports of Eversons and Cole [6], demonstrating that renal cell cancer was one of the most frequent histological types of tumour associated with spontaneous unexplained regression of metastases, there has been continued discussion as to how much regressions seen in renal cell cancer treatment studies are true effects of treatment or whether they simply reflect the sort of selection demonstrated by Fossa and colleagues in their study. Despite this, few studies give information on whether their patients have been observed so as to exclude spontaneous regression [7]. As yet, there has only been one adequately controlled prospective randomised trial in 90 patients with metastatic disease, which compared autolymphocyte therapy (a complex process involving retransfusion of autologous lymphocytes after *in vitro* stimulation with a cytokine "soup") plus cimetidine with cimetine alone [8]. Although there was significantly better survival (64 versus 44% at 1 year), few have taken up this treatment partly because of its complexity and cost, but also because it was felt that publication was premature, as the numbers randomised were perhaps too small by today's standards, and follow-up too short to calculate 2-year survival. In addition the controls were not treated in an identical way to treatment groups, so that the placebo effect of leucophosesis and the extra attention from medical and nursing staff given to the patients who were randomised to treatment was not controlled for.

The only other randomised trial in metastatic renal cell cancer did not have an untreated control but compared IL-2 versus IL-2 plus lymphokine-activated cells. There was no difference in survival [9].

CYTOKINE COMBINATIONS

Table 1 provides a review of recent publications which enable a comparison to be made between single-agent and combination IFN, IL-2 alone and combined with 5-fluorouracil (5FU).

Table 1. *Recent cytokine trials in metastatic renal cell cancer*

	No. of cases	Response (CR + PR)	Response duration (months)	Alive at 2 years
IFN-α [25]	159	1 + 10%	12.2	21%
CIV IL-2 [12]	193	4 + 11%	11.0	23%
LDSC IL-2 [19, 26, 27]	61	5 + 10%	NA	NA
IL-2 + IFN [11]	185	4 + 15%	8.1	19%
IL-2/IFN/5-FU [17, 18]	51	14 + 37%	NA	NA

CR, complete response; PR, partial response; IFN-α, interferon-α; CIV, continuous intravenous infusion; IL-2, interleukin-2; LDSC, low-dose subcutaneous; 5-FU, 5-fluorouracil; NA, not applicable.

Although the results of the three-drug 5-FU-containing combination are quite impressive, with a 51% response rate, it must be remembered that there is no information on 5FU and IFN alone, and the German group who developed this regimen were also the first to report on subcutaneous IL-2 and IFN, and produced a 35% response [10] compared to their current overview of 19% [11].

As shown in Table 1 there is such a small benefit (15 versus 19%) between the single-agent data for IL-2 [12] and the effect seen from IL-2 in combination with IFN (almost certainly a reflection that better prognostic patients were selected for combination [12]), that it can be concluded that the single-agent treatment is to be preferred. Although most trials of IL-2 have only given treatment for 6–8 weeks, IFN has usually been given indefinitely if response continues. However, the result of a recent pilot trial reported by Abratt and colleagues [13], who treated 12 good risk patients for only 8 weeks and achieved 17% response, has provided the first indication that it may only be necessary to use IFN for a short-term induction period, like IL-2. If this can be confirmed, it is likely that IFN will become the treatment of choice, but only if it really is better than placebo in the current ongoing MRC trial. Although MPA is thought these days to have no effect, anecdotal observations that this drug can induce impotence (Oliver, unpublished), similar to that caused by any other endocrine treatment used for treating prostate cancer, does raise the question as to whether any of the renal cell cancer responses to MPA, initially reported by Bloom [14], could have been due to endocrine-induced hypothalmic changes. There is now some evidence that the hormone treatment used in prostate cancer, i.e. surgical castration or gonadotrophin-releasing hormone (GNRH) analogues, can induce regeneration of the thymus [15, 16]. It is possible that there may be a case to re-examine the role of endocrine treatments further if the trial comparing MPA and IFN demonstrates no difference.

Despite these provisos, with three centres now having reported encouragingly better results than previously published using the 5FU/IFN/IL-2 regimen [17–19], it will probably be necessary to develop a mechanism whereby it can be included as a third arm in the MRC trial, while still retaining the "placebo" MPA arm.

THE ROLE OF NEPHRECTOMY IN PATIENTS PRESENTING WITH METASTASES

With the proportion of metastatic renal cell cancer patients receiving IL-2 treatment without having had a prior nephrectomy declining from 24 to 12% in the last 5 years in the Eurocetus trials [12], it is clear that the message that nephrectomised patients have a higher response to cytokine treatment has become widely disseminated. There have been two recent developments which suggest that there may be a case for re-considering the need for nephrectomy before entry to cytokine trials. Firstly, there is an increasing number of series demonstrating that initial use of cytokines before surgery may improve prognostication, and does not reduce the chances of response [20, 21]. Secondly, new information on the biology of trauma-induced repair cytokines [22] has provided an explanation for the old observation of Rous [23] that trauma can induce acceleration of metastasis. In breast cancer, there is some evidence that it may even occur after needle biopsy during the unopposed oestrogenic phase of the menstrual cycle [24]. The current proposal of the MRC Renal Cell Cancer Working Party to investigate this in a separate study which will run in parallel with the IFN versus MPA protocol, with randomisation of metastatic renal cell cancer patients

presenting with the primary tumour unresected to surgery or no surgery before definitive treatment of metastases, could provide important information in respect of this issue.

CONCLUSION

The impressively high responses reported in two pilot trials of the combination of 5FU, IFN-α and IL-2 are provoking considerable excitement that a regimen may have been developed which is better than any previously reported. However, the long history of excessive enthusiasm for new regimens developed in specialist referral centres for renal cell cancer, which has been dashed when large numbers of unselected cases representative of the disease as a whole are treated, warns that caution is still required, and certainly does not justify discontinuation of the current MRC trial to compare IFN and MPA. However, it does encourage the incorporation of the new combination as a third arm in the study to increase recruitment, which though healthy with 107 cases already recruited, is still only including a minute proportion of the potentially eligible patients. The proposal to also run a parallel study investigating the value of elective surgery before cytokine treatment in patients with metastases should also stimulate more interest.

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