PANEL DISCUSSION

Question from the floor: Dr Eriksson, with carcinoid tumours and liver metastases you often have leucopenia. Does that influence your schedule of interferon administration?

Eriksson (Sweden): I don't think that many of our patients have leucopenia as a consequence of liver metastasis. We do, of course, see a reduction in leucocyte counts and we use this to adjust the dose, but it is not a big problem.

Question from the floor: In how many patients did you have to add somatostatin and for how long did you have to give it? Also, did you see rebound phenomena when you stopped somatostatin?

Eriksson (Sweden): We have not seen any rebound phenomena on stopping somatostatin. We have tried to use the drugs separately to be able to say how many respond to interferon, and how many respond to somatostatin, but we now have 60 patients who either failed on somatostatin and were then given alpha interferon, or who failed on alpha interferon and then received somatostatin. It is in this group that the results look the most promising because there is at least an additive effect of these two agents. With this combination, we have high response rates of around 60% in patients with carcinoid tumours.

Question from the floor: Dr Muss, for how long should we continue interferon treatment in renal cell carcinoma patients?

Muss (U.S.A.): I'm not certain but I would continue interferon indefinitely if the patient was not experiencing substantial toxicity.

Question from the floor: In our clinic, we have 29 cases of advanced renal cell carcinoma; the four responders have pulmonary and/or retroperitoneal metastases but none of them with bone metastases. Is there any explanation for the lack of response in bone metastases?

Muss (U.S.A.); I think that it must have something to do with tumour heterogeneity. For all biological response modifiers, the literature suggests that most responses are in the lung, including the majority of long-term responders, although there are some patients with response in liver, bone and soft tissue, such as lymph nodes. I don't think it is just a phenomenon related to differences in measurement of response; I think there is a real biological difference in lung lesions.

Freund (Germany): Dr Atzpodien, you have also shown that patients with pulmonary metastases respond better.

Atzpodien (Germany): When employing the combination of IL-2 and alpha interferon, we have seen a lot of regression of metastatic lung disease but we have also observed good partial regressions of both bone and liver lesions; so at least, the combination of IL-2 and alpha interferon may work in the bone and the liver, although responses here are much more rare than in metastatic lung disease.

Freund (Germany): Maybe it would be a good idea to evaluate bone metastases by NMR in order to improve the accuracy of measurement.

Question from the floor: Dr Muss and Dr Atzpodien, listening to your data one gets the impression that you have an overall response of around 30% with the alpha-2 interferon, and the same type of response seems to be the case with IL-2 and with gamma interferon. So is there any difference between these three cytokines?

Atzpodien (Germany): I think it is much too early to really tell about the differences in therapeutic efficacy of these various cytokines. However, what you *can* tell is the difference in systemic toxicity and safety and tolerance, and I think this is really very important in these patients with metastatic disease. I think we really need to do randomized trials to compare therapeutic efficacy of various treatment regimens and these are currently underway.

Muss (U.S.A.): I personally do not believe there have been great differences among the cytokines in terms of therapeutic efficacy. Response difference among cytokines might be statistically significant if you had a study with 1000 patients per arm, but they probably would not be clinically significant.

Question from the floor: Do you have evidence that patients that are refractory to one of the interferons or one of the biologicals are responsive to another?

Atzpodien (Germany): In our current trials, we have quite a few patients who were in progressive disease after receiving alpha interferon alone; after they were switched to the IL-2/interferon combination, we did see some responses in these patients. So it seems that there is no common immune resistance mechanism. It probably also depends on the dose and the type of regimen used.

Muss (U.S.A.): I agree with Dr Atzpodien. I think it may depend on the type of interferon. Interferon alfa-2b is not associated with a high frequency of anti-interferon neutralizing antibodies, while some other interferons are. In some studies, patients have been reported who were initially responders, and then when their toxicity diminished, their disease progressed at the same time. If one found antibodies in patients like that, you could either change preparations or perhaps give larger doses and obtain further response.

Question from the floor: In the last three years, the combination of cimetidine and coumarin has been proposed for the treatment of metastatic renal cell carcinoma. Would you like to comment on that and the possibility of interferon/coumarin combinations, for example?

Muss (U.S.A.): I think some of those studies were done by Dr Marshall and colleagues in Kentucky and they were originally positive [1]. There has since been a recent publication of a study that tried to duplicate the coumarin/cimetidine data but did not show responses [2]. If someone did verify the initial response rates, it would be reasonable to combine this therapy with something like interferon and see if it was better.

Ludwig (Austria): We are presently carrying out a randomized study in Austria comparing interferon with interferon plus cimetidine and coumarin, and the last interim analysis did not show any significant difference between the two groups.

Question from the floor: Do you see any role for an adjuvant administration of interferon for patients with renal cell cancer with further high risk of metastatic disease?

Muss (U.S.A.): In patients with Stage III disease, with disease that has penetrated through Gerota's fascia, disease with extensive nodal involvement, for example, I think it is reasonable to test interferon as adjuvant therapy. There are several trials ongoing in the United States, both with interferon alfa-2a and interferon alfa-2b, comparing 6 months of adjuvant therapy versus observation. I think we will probably have an answer to that question within a year or two.

Question from the floor: Which dose do you recommend in metastatic renal cell carcinoma, and if you achieve a response do you go on with the same dose or reduce the dose?

Muss (U.S.A.): I would suggest a dose of 10 MU three times a week subcutaneously and, depending on toxicity and patient tolerance, I would keep patients on therapy.

References

1. Marshall ME, Mendelsohn L, Butler K *et al.* Treatment of metastatic renal cell carcinoma with coumarin (1, 2-benzopyrone) and cimetidine: A pilot study. *J Clin Oncol* 1987, **5**, 862-866.

2. Dexeus FH, Logothetis CJ, Sella A *et al.* Phase II study of coumarin and cimetidine in patients with metastatic renal cell carcinoma. *J Clin Oncol* 1990, **8**, 325-329.