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An EORTC Phase II Study of Methyl-glyoxal Bis-guanylhydrazone in Advanced Renal Cell Cancer*

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Abstract—*In a phase II study of methyl-glyoxal bis-guanylhydrazone (methyl-GAG) in patients with bi-dimensionally measurable metastases of renal cell cancer, 30 patients were given 500 mg/m² weekly for at least 4 treatment cycles and were evaluable for response. Three patients (10%) achieved partial remission (PR) with a duration of 8–12 weeks; in 11 patients the disease was assessed as stable; and in 16 there was progression. A total of 40 patients were evaluable for toxicity. Nausea and vomiting occurred in 17 (43%), neuropathy, myopathy or myalgia in 8 (21%) and mucositis in 6 (14%). In addition to 3 patients taken off treatment before 4 treatment cycles, toxicity precluded further treatment in 3 others after 5, 6 and 7 cycles respectively. Methyl-GAG has minimal activity in renal cell cancer and, in this dose schedule, causes appreciable toxicity.*

INTRODUCTION

THE RESULTS of treatment of advanced renal cell carcinoma have been universally poor. The regression of metastases following nephrectomy is unusual and surgery has little or no effect on survival [1]. Hormonal therapy has proved disappointing [2] and recent reports only confirm the lack of response [3]. Suggestions that immunocompetence might be of particular relevance in this tumour continue to encourage the application of tissue specific and nonspecific immunotherapy alone and in combination with chemotherapy [4–6], but the value of this modality has yet to be established. A variety of chemotherapeutic agents have been tested. None has shown appreciable activity. The highest claimed response rate has been 25% for vinblastine [2, 7].

Methyl-glyoxal bis-guanylhydrazone (methyl-GAG) was first synthesised in 1958 and was used in the treatment of leukaemias in the early 1960's [8, 9]. It has an anti-proliferative effect on cancer cells, reflecting its principal properties: selective binding to mitochondria, causing structural and functional damage and inhibition of polyamine, especially spermidine, synthesis [10, 11]. Given on a daily basis, methyl-GAG produced quite marked toxicity with mucositis, nausea, vomiting and myelosuppression. More recently, it was suggested that weekly infusions of the drug caused less toxicity and preliminary reports indicated that solid tumours, including metastatic renal cancer, might show response to such treatment [12]. On this basis, the EORTC Urological Group formulated a phase II study of methyl-GAG in patients with advanced renal cancer in order to determine the objective tumour response rate in patients with bidimensionally measurable metastases.

MATERIALS AND METHODS

It was required that patients should be under 75 yr of age, have a Karnofsky performance index above 60 and have given informed con-

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sent. The presence of bidimensionally measurable metastatic lesions of histologically or cytologically proven renal cell carcinoma was also a requirement. Patients receiving concurrent treatment and those with second malignancies or brain metastases were excluded. Normal renal function and blood cell counts were requirements for eligibility.

Pre-treatment evaluation included history and physical examination, blood counts, standard biochemical screen, urine analysis and chest X-ray. Intravenous pyelography, skeletal X-rays, radionuclide liver and bone scans, ultrasonic echography and computerised axial tomography were carried out if indicated.

Follow-up studies included blood counts and urea and creatinine analyses. Investigations necessary for the assessment of indicator lesions were repeated at the discretion of the investigators, but were required in all patients one week after the fourth or seventh and final cycles of methyl-GAG.

The dose of methyl-GAG was 500 mg/m^2 i.v. weekly. The drug was dissolved in water for injection (100 mg in 1 ml), diluted in 250 ml of 5% glucose and administered by infusing intravenously over 30 min. Dose modifications were not allowed, but if depression of blood counts (WBC $< 3 \times 10^9$/l or platelets $< 100 \times 10^9$/l) or rise in serum creatinine ($>$ 1.5 mg/100 ml) occurred, delay in treatment to a maximum of 3 weeks was permissible.

Response criteria were: complete remission (CR): disappearance of all evidence of disease for no less than 4 weeks; partial remission (PR): $>$ 50% decrease in the product of the two largest perpendicular diameters of all measurable lesions for no less than 4 weeks, with no new lesions developing; stable disease: $<$ 50% decrease or $<$ 25% increase in measurable disease, with no new lesions developing; progression: $>$ 25% increase in measurable disease or development of new lesions.

Patients were considered evaluable for response if they had been treated with a minimum of 4 treatment cycles. Patients receiving less treatment for various reasons who otherwise fulfilled study criteria were considered evaluable for toxicity.

Patient characteristics

Forty-five patients were entered into the study. Five were not evaluable because of ineligibility (4 patients) and incomplete data (1 patient).

Ten patients received less than 4 treatment cycles. Of these, 2 refused further treatment, 3 showed severe toxicity, 1 developed brain metastases and there were 4 early deaths (3 due to the malignant disease and 1 due to pulmonary embolism). Hence, 40 patients were evaluable for toxicity and 30 for response. The age range was 33–73 yr (mean 55 yr) and the male : female ratio was 2 : 1. Nephrectomy had been carried out in 75% and other previous treatment included radiotherapy (16%), chemotherapy (17%) and hormonal therapy (24%). The indicator lesions were predominantly pulmonary metastases.

RESULTS

Of the 30 fully evaluable patients, 3(10%) achieved PR, 11 showed stabilisation and 16 showed disease progression. The 3 PR were recorded after 4, 6 and 7 cycles respectively, with duration of 8–12 weeks. The indicator lessions in these cases were supraclavicular lymph nodes in two and a mediastinal metastasis in one.

Toxicity was considerable. In addition to the 3 patients who went off study before the fourth cycle, another 3 patients had to stop treatment because of severe neuropathy, vasculitis and arthralgia. The principal side effects were: anorexia, nausea and vomiting (43%), moderate or severe in 19% of all patients; neuropathy, myopathy and myalgia (21%), moderate or severe in 19% of all patients; mucositis (14%); skin reactions (12%); leucopenia (9%); and diarrhoea (9%). Delay in chemotherapy because of leucopenia was necessary in only 3 cases.

DISCUSSION

In this phase II study no CR was recorded and PR occurred in only 10% of the evaluable patients. One group (SWOG) [13] have recorded 1 CR and 2 PR in 23 patients (14 previously untreated) given methyl-GAG in a weekly dose of 500 mg/m^2 with 100 mg/m^2 dose escalations. Responses were seen both within 4 and after 4 treatment cycles. Mucositis (43%) was the commonest side-effect, with nausea and vomiting (26%) the next most frequent. Todd *et al.* [14] had 1 CR and 3 PR among 18 evaluable patients. The dose of methyl-GAG was 500 mg/m^2 with 50 mg/m^2 escalations, and all responses occurred within 4 weeks. The incidence of side-effects was high, with nausea and vomiting in 70%, mucositis in 45% and myalgias in 45%.

Zeffren *et al.* [15], adopting flexible dose escalation and de-escalation, recently observed

no CR or PR in 30 patients and noted considerable toxicity with weakness, fatigue and lethargy in 63% and mucositis in 37%. In the present study, toxicity was frequent, though considered to be severe in only the minority. The nature of the side-effects in studies to date has been broadly similar. If the results of our study are added to the previous ones, only 10 remissions (CR + PR) have been seen in a total of 101 patients.

It may be concluded that methyl-GAG has no role to play in the treatment of advanced renal cell cancer because of its minor activity and appreciable toxicity.

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