European Journal of Cancer Vol. 31A, No. 1, pp. 130–131, 1995

0959–8049/95 $9.50+0.00

0959-8049(94)00375-0

Phase II Study of Cystemustine in Advanced Renal Cancer

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PATIENTS WITH recurrent or metastatic disease of renal cell carcinoma have a poor prognosis. They are a natural choice for clinical trials designed to evaluate potential therapeutic modalities, but most cytotoxic drugs are usually ineffective in these patients [1, 2]. Nevertheless, some nitrosourea analogues have limited clinical activity, with a low response rate of 15% [3, 4]. Cystemustine is a chemically synthesised metabolite of 2-chloroethyl nitroso carbamoylcystamine [5], a newly developed water-soluble nitrosourea (1985). This alkylating agent was found to be very active in preclinical screening against a wide variety of murine tumour models [6]. It was found to cross the blood–brain barrier at a cytotoxic concentration, and also showed reduced bone marrow toxicity (the dose limiting toxicity of chloroethyl nitrosoureas). In a phase I and phase II study conducted in 1989 [7], it showed activity against melanoma, glioma, and different types of adenocarcinomas. Based on these data, the drug was selected by the EORTC Clinical Screening Group [8] for phase II testing in advanced renal cell cancer patients.

56 patients were registered in this study between January 1990 and June 1992. All but 2 patients were eligible, 1 patient because of a single lesion previously irradiated, and 1 because of poor medical risk of non-malignant disease. The patients met (male: 43, female: 11) the following strict criteria: age <70 years (median: 58); histologically proven measurable metastatic renal cell cancer, with lesions having been in progession for at least 1 month; WHO performance status ≤2; no previous chemotherapy (except vinblastine in combination with interferon = 12); no radiotherapy to any indicator lesion, nor radiotherapy to more than one-third of haematopoietic bone marrow within 6 weeks before protocol entry. The pretreatment check-up included physical examination, chest X-ray, bone scintigraphy, and documentation of indicator lesions (tomography and echography). While blood cell count was above 4×10^9/l, platelet count $>120 \times 10^9$/l, with adequate cardiac and hepatic functions (bilirubin <35 μmol/l, creatinine <180 μmol/l). All patients provided written consent for their participation in the study.

As recommended, the first group of patients received cystemustine at a starting dose of 60 mg/m^2 (group 1). Thereafter, this well-tolerated dosage was considered to be too low and a second group received a dose of 90 mg/m^2 for the first three cycles, followed by 60 mg/m^2 for further cycles (group 2). Cystemustine was given intravenously as a bolus infusion of 100 ml 5% dextrose. The treatment plan consisted of one administration every 2 weeks for four cycles. In patients without disease progression 2 weeks later, cystemustine was continued up to 4 months after the beginning of treatment (stable disease) or until the development of progressive disease or unacceptable toxicity in case of objective response. Evaluation of the results was performed using WHO criteria [9, 10]. The response was evaluated after a minimum period of four cycles. Dose modifications for day 15, according to blood count values, were performed and the patient was withdrawn from the study if no full haematological recovery was observed after three consecutive weekly reports.

The 54 patients received a median number of 5 cycles (range: 1–11) in group 1 and a median of 4 (1–8) in group 2 (total of 256 cycles). The median total dose received was 284 mg/m^2 (59–658) in group 1, and 321 mg/m^2 (87–518) in group 2. Of the 54 eligible patients, 1 patient was lost to follow-up after 1 cycle and the case was deemed to be a failure in responding to treatment.

Response to treatment

In group 1 (60 mg/m^2), 1 complete response (CR) was observed amongst the 27 eligible patients (3.7%); 8 had no changes (29.6%); there were 16 progressions (59%) and 1 early progression ≤2 cycles (3.7%). The single CR occurred after 8 cycles in a patient who had not been previously treated who had lumboaortic lymph nodes and multiple lung metastases, and survived 33 months. In group 2 (90, then 60 mg/m^2), no change was observed in 10 patients (37%); there was progression in 17 patients (63%) including 4 early progressions (15%). No response was observed.

Toxicity (*Table* 1)

In both groups, cystemustine was subjectively well-tolerated in the 54 eligible patients, except for nausea and vomiting grade 2 and grade 3 which were observed in 8 patients (15%) and 4 patients (7.4%), respectively. Several grade 2 side effects were observed in 6 patients of group 2: asthaenia (3 patients), haemorrhage (1), fever (1), alopecia (1). The major toxicity was haematological, especially thrombocytopenia, with platelet nadirs grade 3–4 in 2 of 27 patients (7.4%) in group 1 (median platelet nadir: 143×10^9/l; range: 14–538) and 7 of 27 patients (26%) in group 2 (median: 87×10^9/l; range 16–413). Accompanying grade 2 haemorrhage occurred in 1 patient. Granulocyte nadir grade 3 was observed in 2 patients (7.4%) in group 1 (median: 2.7; range: 0.8–10) and in 6 patients (22.2%) in group 2 (median: 1.8

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Contributions were also received from the Hôpital Universitaire Saint-Pierre, Brussels and the Institut Jean Godinot, Reims, France.
Revised 23 Aug. 1994; accepted 7 Sep. 1994.

Table 1. Toxicity (maximal toxicity per patient)

	Group 1 (60 mg/m²) n = 27				Group 2 (90 × 3 mg/m² then 60 mg/m²) n = 27			
WHO Grade	1	2	3	4	1	2	3	4
Leucocytes (10^9/l)	6	6	—	—	7	7	3 (11%)	1 (3.7%)
Neutrophils (10^9/l)	6	3	2 (7.4%)	—	5	4	4 (14.8%)	2 (7.4%)
Platelets (10^9/l)	3	2	1 (3.7%)	1 (3.7%)	3	4	5 (18.5%)	2 (7.4%)
Nausea/vomiting	5	6	1 (3.7%)	—	8	2	3 (11%)	—
Diarrhoea	1	—	—	—	2	—	—	—
Fever	—	—	—	—	—	1	—	—
Haemorrhage	—	—	—	—	1	1	—	—
Infection	1	—	—	—	—	—	—	—
Neurotoxicity	2	—	—	—	—	—	—	—
Hypotension	1	—	—	—	—	—	—	—
Asthaenia	1	—	—	—	1	3	—	—
Alopecia	1	—	—	—	—	1	—	—
Hot flushes	—	—	—	—	2	—	—	—

n = number of patients.

× 10^9/l; range: 0.07–9.59). For 31 cycles (12.1%) of a total of 256 cycles in the two groups, the dosage and schedule of treatment were modified according to the protocol. Haemoglobin nadir grade 3–4 was observed only in 5 patients of group 2 (median: 6.2 mmol/l; range: 2.7–8.8).

In conclusion, the present study reveals that the new nitrosourea cystemustine, scheduled either for 60 mg/m² or 90 × 3 mg/m² then 60 mg/m² every 2 weeks, has minimal activity in advanced renal cancer with only 1 response amongst 54 eligible patients. The drug is less toxic than other nitrosoureas (lomustine, fotemustine) with minor clinical side-effects, and acceptable myelotoxicity, but with the same mild antitumour efficacy. Thus cystemustine cannot be recommended for further use in renal cancer at these schedules of administration.

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European Journal of Cancer Vol. 31A, No. 1, pp. 131–132, 1995

0959–8049/95 $9.50+0.00

0959-8049(94)00410-2

Cladribine and Tumour Lysis Syndrome

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CLADRIBINE (2-CHLORODEOXYADENOSINE, 2-CDA) is an adenosine analogue with a broad spectrum of activity among lymphoproliferative disorders [1]. Recent reports on the occurrence of tumour lysis syndrome after treatment with cladribine [2,3] drew our attention to a similar case which further cautions against its use.

A 29-year old Caucasian man presented with a 10-year history of cutaneous T-cell lymphoma treated elsewhere with chemotherapy, alpha interferon, radiotherapy, phototherapy and plasmapheresis. He was ill and pyrexic at 39°C with pachydermia, itching erythema, lymph oedema, generalised lymphadenopathy, liver and spleen enlargement. White blood cells were 13 × 10^9/l with 73% lymphocytes CD3 and CD4 positive. Platelets were 395× 10^9/l. The LDH was 953 U/l. Bone marrow and skin biopsies showed massive infiltration by abnormal CD3 positive lymphocytes. Ultrasound revealed retroperitoneal lymphadenopathy, hepatosplenomegaly, kidney infiltration and ascites. Electrolyte and creatinine were within normal limits.

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Received 7 Jul. 1994; accepted 28 Sep. 1994.