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Clinical Trial Summaries

Mitozolomide in Advanced Renal Cancer

A Phase II Study in Previously Untreated Patients from the EORTC Genito-Urinary Tract Cancer Cooperative Group

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INTRODUCTION

THE RESULTS of treatment of advanced renal cell carcinoma have been universally poor. All commercially available cytotoxic agents have been tested but lack reasonable antitumour activity [1]. The EORTC Genito-Urinary Tract Cancer Cooperative Group therefore started a single-agent phase II screening programme. Subsequently four different drugs were tested but all failed to produce responses [2].

Mitozolomide (NSC 353451; CCRG 81010; M & B 39565) is a new agent, with structural similarities to the chloroethylnitrosoureas [3]. The drug was highly active in pre-clinical studies and during phase I assessment some evidence of activity was seen in ovarian cancer, lymphoma, testicular teratoma and nasopharyngeal carcinoma [4]. Subjective toxicity with Mitozolomide was minimal with the dose-limiting toxicity being myelosuppression. Based on these data the drug was selected for phase II testing in non-pretreated advanced renal cell cancer patients.

PATIENTS AND METHODS

Twenty-three patients were registered in this study between August 1986 and June 1987. Four patients were not eligible; two had prior chemotherapy, one had a performance status of WHO3 and one had a creatinine level of 133 μmol/l.

Patients were eligible if they satisfied the following strict criteria: histologically proven progressive measurable metastatic renal cell cancer, age ≤70 years, WHO performance status ≤1, no previous chemotherapy, hormonal therapy stopped for at least 6 weeks, no second tumour, no brain metastasis, no radiotherapy to any indicator lesion, white blood cell (WBC) count $\geq 4 \times 10^9$/l, platelet count $\geq 125 \times 10^9$/l with adequate cardiac, kidney and hepatic functions.

Pretreatment studies included physical examination, blood cell counts, serum creatinine analysis, liver function tests, chest X-ray and documentation of indicator lesions. Computerized tomography and ultrasound echography were accepted as means of measuring indicator lesions.

The evaluation of response and toxicity was performed using WHO criteria [5].

RESULTS

Of the 19 eligible patients one patient was lost to follow-up during the first cycle, while one patient died of cardiovascular disease before the second cycle. The remaining 17 patients were fully evaluable. The median age of the 19 eligible patients was 55 years (28–68); seven had a performance status

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of 0, 12 had a performance status of 1. There were eight males and 11 females.

Pretreatment consisted of surgery alone in 11, surgery + radiotherapy in three, surgery + radiotherapy and immunomodulation in two and no treatment at all in three.

The marker lesions were situated in the lung in 13, in the primary and metastatic nodes in two, nodes alone in three, in the liver in one. Several patients had measurable lesions in multiple sites.

The 17 patients received between one and five cycles (mean 2.0, median 1.8) and a total of 36 cycles. No complete or partial responses were observed. Early progression after one cycle and early death due to malignant disease after one cycle were reported in two patients each. After two cycles progression was observed in 10 patients and only three patients showed no change.

Mitozolomide was subjectively generally well tolerated in the 19 eligible patients. Nausea was reported in nine patients (47%), transient vomiting in three (16%), transient diarrhoea in one (5%) and tolerable diarrhoea in one (5%).

The major toxicity was myelotoxicity: the median platelet nadir was 77×10^9/l where WHO3 toxicity was observed in three patients, WHO4 in four. The median WBC nadir was 3.4×10^9/l with WHO3 toxicity in three patients and WHO4 in one patient, resulting in high fever and a moderate infection. Of the 12 patients who have received more than one cycle, the treatment regimen was changed in five patients (42%) for haematological toxicity: in two patients Mitozolomide was delayed and reduced, in two patients it was reduced and in one patient delayed.

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