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Clinical Trial Summary

TCNU in Advanced Renal Cancer

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

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INTRODUCTION

THE RESULTS of the treatment of advanced renal carcinoma remain universally poor [1]. Hormones do not play any role. All cytotoxic agents tested lack reasonable antitumour activity [1]. Finally also the largest phase II studies with immune modulating agents are disappointing. Therefore the EORTC Genito-Urinary Tract Cancer Cooperative Group set up a single agent phase II screening programme. Subsequently, five different drugs have been tested, but all failed to produce responses [2].

TCNU [1-(2-chloroethyl)-3-{2-(dimethylaminosulphonyl)ethyl}-1-nitrosourea] (E84070) is a newly developed water-soluble nitrosourea based on the endogenous aminoethanesulphonic acid taurine [3]. It was found very active in pre-clinical screening against a wide variety of murine and human tumour models, but also *in vitro* and *in vivo* against human tumours. In two phase I studies conducted in 1986, it showed activity not only against the different lung cancer cell types, but also against melanoma, stomach cancer and renal cell cancer. The dose-limiting toxicity was myelosuppression [4, 5]. Based on these data the drug was selected for phase II testing in non pre-treated advanced renal cell cancer patients.

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PATIENTS AND METHODS

Thirty-eight patients were registered in this study between August 1987 and September 1988. All patients entered were eligible. 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 should have been stopped 4 weeks before protocol entry, no second tumour, no brain metastases, no radiotherapy to any indicator lesion. White blood cell count was above 4×10^9/l, platelet count $>125 \times 10^9$/l with adequate cardiac, kidney and hepatic functions.

Pre-treatment studies included physical examination, blood cell counts, serum creatinine level, 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 [6].

TCNU was given in a dose of 130 mg/m^2 orally every 5 weeks and continued until the development of progressive disease or unacceptable toxicity. If at 5 weeks no full haematological recovery had taken place retreatment was postponed until full recovery was achieved.

Dose modifications for nadir values were as follows:

WBC × 10^9/l		Platelets × 10^9/l	Percentage of prior dosage
≥4	and	≥125	120
2–4	and/or	50–125	100
1–2	and/or	25–50	75
<1	and/or	<25	50

RESULTS

Of the 38 eligible patients, three patients were not evaluable and thus excluded from the results: one patient died, not cancer- or treatment-related, after one cycle, one was lost to follow-up after one cycle and one patient received less than 50% of the scheduled dosage.

Two patients were partially evaluable, one because he refused treatment after one cycle and one patient had grade IV myelotoxicity after one cycle. These patients are included in the toxicity analyses and excluded from the response analyses.

The remaining 33 patients were fully evaluable.

The median age of the 35 evaluable patients was 54 years (31–68). Seventeen patients (49%) had a performance status of 0, 18 patients (51%) had a performance status of 1. There were 21 males and 14 females.

Pretreatment consisted of surgery alone in 15, radiotherapy alone in two, immunotherapy in three, surgery + radiotherapy in five, surgery + radiotherapy + hormonal therapy in one, surgery + immunotherapy in two and no treatment at all in seven patients.

The marker lesions were situated in the primary in two, in the lung in 18, in regional or metastatic nodes in nine and the liver in six patients. Several patients had measurable lesions in multiple sites.

The 35 patients received between one and four cycles (mean 1.7, median 2) and a total of 61 cycles. No complete or partial responses were observed amongst the 33 patients evaluable for response. Early progression after one cycle was observed in 10 patients (30%). One patient died due to malignant disease after one cycle, while after two cycles eight patients (24%) had no change and 14 (42%) progression.

TCNU was subjectively reasonably well tolerated in the 35 evaluable patients, except for nausea and vomiting grade II and III which was observed in 17 (49%) and six patients (17%) respectively. Diarrhoea grade II was observed in one patient, as was transient lethargy in two patients.

However, the major toxicity was myelotoxicity: especially considerable thrombocytopenia with WHO ≥3 in 10 out of 32 patients (31%). The median platelet nadir was 80.5 × 10^9/l. Accompanying haemorrhages WHO 2 were observed in four, WHO 3 in two patients. The median WBC nadir was 3.2 × 10^9/l with WHO 3 toxicity in only four patients. Of the 21 patients who had more than one cycle the dosage was escalated in five (24%). However, in eight (38%) of the patients the dosage was adapted according to the protocol: delayed in three (14%), reduced in one (4%) and both reduced and postponed in four patients (17%). All four had platelet-related toxicity.

CONCLUSION

In view of the failure of TCNU to show any response in this large group of patients and the considerable myelotoxicity observed, the drug cannot be recommended for further use in advanced renal cancer.

REFERENCES

1. Denis L, Van Oosterom AT. Chemotherapy of metastatic renal cancer. *Semin Surg Oncol* 1988, **4**, 91–94.
2. Van Oosterom AT, Stoter G, Bono AV *et al.* Mitozolomide in advanced renal cancer. *Eur J Cancer Clin Oncol* 1989, **25**, 1249–1250.
3. Workman P. TCNU: a ray of hope for designer nitrosoureas? *Eur J Cancer Clin Oncol* 1987, **23**, 1823–1828.
4. Smyth JF, Macpherson JS, Warrington PS *et al.* Phase I study of TCNU, a novel nitrosourea. *Eur J Cancer Clin Oncol* 1987, **23**, 1845–1849.
5. Vibe-Petersen J, Bork E, Moller H, Hansen HH. A phase I clinical evaluation of 1-(2-chloroethyl)-3-{2-(dimethylaminosylphonyl)ethyl}-1-nitrosourea TCNU. *Eur J Cancer Clin Oncol* 1987, **23**, 1837–1843.
6. *WHO Handbook for Reporting Results of Cancer Treatment.* Geneva, WHO offset publication No. 48, 1979.