

Clinical Trials Summaries

Phase II Study of TCNU in Advanced Breast Cancer

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INTRODUCTION

TCNU (Tauromustine 1-(2-chloroethyl)-3-(2-(dimethylaninosulfonyl-ethyl)-1-nitrosourea) is a newly developed water soluble nitrosourea based on the endogenous aminoethane sulphonic acid taurine. In experimental tumours TCNU showed equal or better activity than other nitrosoureas [1]. In phase I trials activity was found in non-small cell lung cancer, melanoma and breast cancer [2, 3]. In these trials haematologic and gastrointestinal toxicity was dose limiting.

In the present phase II trial TCNU was given orally to women with advanced breast cancer.

PATIENTS AND METHODS

Fourteen institutions of the EORTC Early Clinical Trials Group participated in the trial.

Included in the study were women ≤ 75 years old with progressive, recurrent or metastatic breast cancer not amenable to surgery, radiotherapy or conventional chemotherapy and/or hormonal therapy. Lesions had to be measurable or evaluable, performance status (PS) ≤ 2 , life expectancy ≥ 2 months, WBC ≥ 4.0 and platelets $\geq 100 \times 10^9/l$. Normal kidney and liver function was also mandatory. Exclusion criteria were previous treatment with nitrosoureas, prior radiotherapy to the measurable lesion or hormonal therapy including endo-

crine ablation or chemotherapy during the previous 4 weeks (6 weeks for mitomycin C or extensive radiotherapy). Also all toxic manifestations of prior therapy should have resolved.

Informed consent was obtained according to regulations in the individual participating institutions.

TCNU was administered orally every 5 weeks at a dose of 90 mg/m² in heavily pretreated patients (>3 cytostatic agents and/or extensive radiotherapy) and at a dose of 110 mg/m² in minimally/moderately pretreated patients (≤ 3 cytostatic agents and/or minimal radiotherapy). The drug was supplied by AB LEO, Helsingborg, Sweden. Subsequent doses of TCNU were delayed by 1 week if toxicity persisted at the day of scheduled re-treatment. If WBC and platelet counts were <4.0 and $100 \times 10^9/l$ 7 weeks after the last dose patients went off study. The dose of TCNU was adjusted according to WBC and platelet nadir counts encountered during the previous cycle. Treatment was discontinued if there was disease progression after two courses or in case of a rapid progression at the time the 2nd course was planned. In case of remission, TCNU was continued until progressive disease or severe toxicity developed.

Assessment of response and toxic side-effects was performed according to WHO criteria [4].

RESULTS

Forty-nine patients entered the study. Of these, six were not fully evaluable due to: lost to follow

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up (1 patient), early death (2 patients), vomiting causing doubtful resorption of TCNU (1 patient), no delay after prior hormonal therapy (1 patient) and early discontinuation of treatment (1 patient).

The 43 evaluable patients had a median age of 57 years (range 31–74) and a median PS of 1 (range 0–2). All patients had previously received chemotherapy. The median number of prior drugs was 4 (range 1–7). Thirty-four patients also had had radiotherapy.

The initial dose of TCNU was 90 mg/m² in 37 and 110 mg/m² in six patients.

One course of TCNU was given to 27 patients, two courses to 19 patients and three patients received more than two courses (maximum 7). Eighteen patients went off study due to early PD and five due to prolonged myelosuppression. Response was observed in 2/43 patients = 5% (95% confidence limits: 1–16%).

The median WBC and platelet nadirs of the 1st and 2nd treatment course were 3.8 (range 0.8–10.4) and 105 (range 18–251) $\times 10^9/l$ and 3.5 (0.8–10.4) and 100 $\times 10^9/l$ (18–251), respectively.

WBC below 3.0, 2.0 and 1.0 $\times 10^9/l$ were observed in 39%, 12% and 2%, and platelet counts below 100, 50 and 25 $\times 10^9/l$ were found in 42%, 29% and 15%, respectively.

The limited number of cycles administered made it impossible to evaluate the cumulated toxicity of the drug.

The median day of nadir for WBC was day 21 (range 6–39) and for platelets day 28 (range 9–36).

Other toxicities consisted of nausea in 44%, vomiting in 42%, diarrhoea in 2%, haemorrhage in 2% and minor to moderate infections in 4%.

DISCUSSION

In this phase II study of TCNU in heavily pretreated patients with advanced breast cancer only two of 43 patients responded. The reasons for only less than 50% receiving two cycles of treatment were rapidly progressive disease or prolonged myelosuppression. We conclude that TCNU was not found useful as salvage therapy in this group of pretreated patients with breast cancer.

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