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Clinical Trials Summaries

A Phase II Study of 4-Epi-Adriamycin in Advanced Urothelial Transitional Cell Cancer

EORTC-GU Group Protocol 30867

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INTRODUCTION

CISPLATIN and methotrexate (MTX) are currently the two most active cytostatic agents in the treatment of bladder cancer [1]. There is, however, a need to identify drugs with cytotoxic activity in bladder cancer which are tolerable even in patients with impaired renal function. Adriamycin (ADM) is recognized as such an active drug [1], and 4-epi-adriamycin (epi-ADM) has been developed as its less toxic analogue [2].

Therefore the EORTC GU Group performed a phase II study of epi-ADM in advanced urothelial cancer (EORTC Protocol 30867).

PATIENTS AND METHODS

Forty patients with advanced bidimensionally measurable urothelial transitional cell cancer entered a phase II study evaluating epi-ADM. Conditions for eligibility included: age less than 80 years, WHO performance status ≤ 2, adequate renal, hepatic and cardiac functions, no previous chemotherapy with the drug selected or with ADM or other ADM analogues.

TREATMENT

Epi-ADM (90 mg/m^2) was given as a bolus injection on day 1 every 3 weeks. Treatment was postponed for 1 week if the white blood cell count was $\leq 4 \times 10^9$/l and/or platelets $< 100 \times 10^9$/l on day 22. Treatment postponement was followed by a 25% reduction of the subsequent dose. Nadir values of leucocytes $< 2.0 \times 10^9$/l and/or platelets $< 75 \times 10^9$/l ($< 50 \times 10^9$/l) also resulted in a dose reduction of 25% (50%) of the subsequent dose.

At least two cycles were given before response evaluation unless progressive disease (PD) occurred within the first 6 weeks (early progression). Patients with no change (NC) or partial remission (PR) were to be treated until a progressive cumulative dose of 1000 mg/m^2 of epi-ADM was given or unacceptable toxicity occurred.

Toxicity

The blood cell counts, hepatic and renal function were monitored on day 1 of each treatment cycle. Blood cell counts were also evaluated on day 15. Subjective toxicity was graded according to the WHO recommendations.

RESULTS

Forty patients were entered in this study by 11 institutions. Of these 40 patients, two were excluded from further analysis, since one received only 72% of the scheduled dose and another did not receive the treatment due to a rapid increase in serum creatinine after he was registered to the trial. Therefore, only 38 patients were evaluable, of whom 37 for toxicity and 33 for response. Their characteristics are shown in Table 1.

Five patients are evaluable for toxicity but not

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Table 1. *Patient details*

Evaluable for response/toxicity	38
Females/males	10/28
Median age (years) (range)	71 (40–79)
Previous treatment	
None	16
Surgery only	7
Radiotherapy ± surgery	3
Chemotherapy ± radiotherapy ± surgery	12
Site of indicator lesion	
Primary tumour	15
Lung ± other	14
Lymph nodes	6
Liver	1
Skin	1
Other*	1
Performance status	
0	10
1	15
2	13

*Other = mass in the abdominal wall not connected directly with vesical wall.

for response. In four patients, treatment was discontinued after one cycle due to major toxicity [3] or greatly impaired performance status [1]. One patient was lost for further follow-up after one cycle.

Of the 33 patients evaluable for response, one was not evaluable for toxicity due to a too short interval between previous cisplatin-based chemotherapy and entry into the study.

No complete responses were observed. Five of the 33 patients had a PR (15%) (95% confidence interval: 5–32%) (primary tumour: 1, lung metastases: 1, metastatic lymph nodes: 3). Four of the responding patients had not received prior chemotherapy whereas the fifth patient had been treated with cisplatin and methotrexate. Seventeen patients had NC and 11 patients progressed.

Nine of the 37 patients evaluable for toxicity developed grade 3/4 leukopenia, and three patients had grade 1/2 thrombocytopenia (nadir values). Fourteen patients (38%) experienced grade 2/3 gastrointestinal side-effects in spite of standard antiemetic treatment. Nausea (grade 1) was frequently seen and tended to last for 1–2 weeks after the injection. A 65-year-old male patient developed severe, possibly drug-related, cardiotoxicity after 11 cycles. In 14 patients treatment could not be continued according to the protocol due to unacceptable side-effects or decreasing performance status.

DISCUSSION

Epi-ADM in the used dose is marginally active in advanced urothelial transitional cell cancer, comparable to adriamycin [1].

Niijima *et al.* [3] obtained a 20% response rate in patients with advanced bladder cancer and a 14% response rate in patients with renal pelvic and ureteral tumours. Gad-El-Mawla *et al.* [4] reported a 60% response rate in patients with bilharzial bladder cancer when using epi-ADM 80 mg/m^2 every 3rd week. Tripi *et al.* observed two long-lasting CRs in 19 bladder cancer patients given epi-ADM 75 mg/m^2 every 3rd week [5]. The overall conclusion is that epi-ADM is as effective as ADM in advanced urothelial cancer.

The frequency of a haematological toxicity in this study was similar to that reported by Ganzina *et al.* [2] for the same dose of epi-ADM. As also observed by Tripi *et al.* [5], cardiotoxicity may occasionally develop during epi-ADM treatment.

Larger doses of epi-ADM might have yielded a higher response rate. However, it seems unlikely that the doses of epi-ADM could be increased to a much larger extent in this population of elderly patients with advanced bladder cancer. This is mainly due to the subjective toxicity and morbidity (slight but long-lasting nausea, vomiting, asthenia).

In conclusion, 4-epi-adriamycin (90 mg/m^2) given every 3 weeks has limited activity in advanced bladder cancer comparable to that of adriamycin.

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