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Letter to the Editor

Cyclophosphamide, Adriamycin and Cisplatin Combination Chemotherapy in Advanced Bladder Carcinoma: an EORTC Phase II Study*

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THE PURPOSE of this study was two-fold: first, to determine the objective tumour response rate and toxicity of Cyclo, Adria and *cis*-Pt combination chemotherapy in patients with advanced transitional cell carcinoma of the bladder and second, to see if the treatment results warrant general application of chemotherapy in patients with advanced bladder carcinoma. Fifty-two patients were entered in this study of which a total of 10 patients could not be evaluated for the effect of treatment. Five patients were ineligible and five patients were eligible but not evaluable for tumour response: one because he developed signs of brain metastases in the second week after the start of treatment, one because the single tumour parameter, a skeletal metastasis, was irradiated before the response to chemotherapy could be determined, one because of treatment-induced renal failure after the first course and two others because the Karnofsky index decreased to 40 per cent after the first course. One patient had a complete nodal regression after one course of treatment and subsequently refused further chemotherapy. Although the tumour response rate was originally defined in terms of those patients who had received at least two consecutive courses, this patient is included in the final analysis. Consequently, 42 patients were evaluable for tumour response. The patients were treated with a combination of Cyclo, Adria and *cis*-Pt. Dosages of the agents were 400, 40 and 40 mg/m^2, respectively, intravenously in a bolus on day 1 and repeated once every 3 weeks. Intravenous pre- and post-hydration with normal saline was given to all patients. Mannitol and diuretics were generally not used. If tumour progression was evident immediately before the third course, the treatment was discontinued. In the case of response after two courses, the therapy was continued until disease progression or toxicity precluded further therapy.

Complete response (CR) denotes total clinical disappearance of all known disease. Partial response (PR) of soft tumour lesions indicates a 50 per cent or more decrease in the sum of the products of the diameters of all measurable lesions. Partial response in bone metastases was defined as a partial decrease in the size of the lesion and/or recalcification. No change (NC) is an estimated decrease of less than 50 per cent or increase of less than 25 per cent. Progressive disease (Prog.) is an estimated increase of 25 per cent or more or appearance of any new lesion. In patients with more than one indicator lesion the poorest response designation prevailed. It was mandatory that the duration of response was at least four weeks

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from first appearance of response. Extramural review of the records of all those patients who responded (CR + PR) was arranged at the end of the study.

The overall response (CR + PR) was 40 per cent. Patient characteristics and response data are given in Table 1. If tumour regression occurred, this was obvious after the second course, apart from one patient with skeletal metastasis, who showed a regression after the administration of the third course. The overall survival from the start of treatment to follow-up or death as a result of metastatic disease was calculated. Although the median survival time of the responders (CR + PR) (11 months) was significantly longer ($P = 0.0001$) than that of progressors (3 months), the difference in median survival time of responsers and those patients with no change during treatment (9.5 months) was not significant (log rank test).

The main reason for discontinuation of treatment was gastrointestinal toxicity, as a result of which the median number of courses per patient was only 3. In the responders the median number of courses was 5, with a range from 1 to 12 courses. Alopecia was noted in all patients. As the development of uremia is common in patients with advanced bladder carcinoma, it was not always possible to differentiate accurately between tumour growth related- and primary *cis*-Pt-induced renal failure. Treatment-induced nephrotoxicity was suggestive in 3 out of 52 patients: one developed significant renal failure immediately after the first chemotherapy course and in the others a clinically significant increase in serum creatinine level was observed after the third and fifth course of treatment respectively. Leukopenia and thrombocytopenia did not represent serious problems in any of the patients.

Yagoda demonstrated that *cis*-Pt-containing regimens do not appear to be more effective than *cis*-Pt alone. Our tumour response rate of 40 per cent is very close to the mean response rate (CR + PR) of 35 per cent with a 95 per cent confidence limit of 28–43 that Yagoda calculated for *cis*-Pt alone [1].

It is important to note that a urologist will see many patients with advanced bladder carcinoma but without measurable tumour disease. Moreover, many patients with advanced disease are in a poor general condition (Karnofsky index below 60%). As the gastrointestinal toxicity of our schedule and, presumably, of all other effective *cis*-Pt schedules will be considerable in these patients with advanced disease, we do not advocate *cis*-Pt chemotherapy in patients having no measurable indicator lesion. In particular, as long as the responders (CR, PR) do not survive significantly longer than patients with 'no change', only a limited group of patients will have any benefit of chemotherapy. We would like to suggest the restriction of chemotherapy to patients with measurable disease and to treat them with *cis*-Pt alone according to the treatment strategy described in this paper.

Table 1. *Patients' characteristics and response data*

Registered: 52	Ineligible: 5	Non-evaluable: 5		Evaluable: 42
Response category	CR	PR	NC	Prog.
Response rate (%)	12	28	48	12
Age (years)	64(50–76)	65(39–76)	65(43–74)	61(49–63)
Males (%)	60	75	75	80
Karnofsky	100(90–100)	90(60–100)	100(60–100)	75(70–100)
Prior radiation (%)	80	67	50	40
Prior chemotherapy (%)	0	25	20	20

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