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Letter to the Editor

4′Deoxydoxorubicin in Advanced Renal Cancer

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

ALLAN T. VAN OOSTEROM,*†† ALDO V. BONO,† STAN B. KAYE,‡ TED A.W. SPLINTER,§ ALESSANDRO CALCIATI,‖ SOPHIE D. FOSSÅ,¶ MARLEEN DE PAUW** and RICHARD SYLVESTER**

**Department of Clinical Oncology, University Hospital, Leiden, The Netherlands; †Ospedale Civile, Varese, Italy; ‡Gartnavel Hospital, University of Glasgow, U.K.; §Dept. of Oncology and Urology, University Hospital Dijkzigt, Rotterdam, The Netherlands; ‖Ospedale San Giovanni, Torino, Italy; ¶Department of Medical Oncology and Radiotherapy, Norwegian Radium Hospital, Oslo, Norway and **EORTC Data Center, Institut Jules Bordet, rue Héger-Bordet, 1000 Brussels, Belgium*

THE results of treatment of advanced renal cell cancer have been universally poor. All commercially available cytotoxic agents have been tested but lack reasonable anti-tumor activity. The EORTC Genito-Urinary Tract Cancer Cooperative Group started therefore a single agent phase II screening program. Subsequently methylglyoxal-bis-guanyl hydrazone, vindesine and mitoxantrone were tested, but all failed to produce responses [1–3].

4′Deoxydoxorubicin (4′deoxyDX) is a derivative of doxorubicin and has shown significant activity against a variety of experimental tumor systems [4]. In animal models 4′deoxyDX has been shown to be appreciably less cardiotoxic than doxorubicin [5]. Phase I studies showed myelosuppression to be dose-limiting, and i.v. administration of 30 mg/m^2 on an every-3-week-schedule was proposed for phase II trials [6].

Patients with histologically proven, progressive, measurable advanced renal cell cancer were to be given 4′deoxydoxorubicin (30 mg/m^2) i.v. once every 3 weeks, if they satisfied the following strict eligibility criteria: age < 65 yr, WHO performance status ≤ 1, no previous chemotherapy, hormonal therapy stopped for at least 6 weeks, no second tumor, no brain metastasis, no radiotherapy to any indicator lesion, white blood cell (WBC) count $> 4 \times 10^9$/l, platelet count $> 125 \times 10^9$/l with adequate cardiac, kidney and hepatic function. The evaluation of response and toxicity was performed using WHO criteria [7].

Between October 1983 and July 1984 10 institutions have entered 33 patients.

Three of the entered patients proved to be ineligible: one was too old, one had prior chemotherapy and one had wrong histology. Of the 30 eligible patients two died within a week of the first treatment, one due to rapid progressive disease, one unrelated. One patient who refused further treatment after one cycle is evaluable only for toxicity. Of the 27 fully evaluable patients the median age was 58 (32–66 yr), 13 had a performance status 0, 14 had a performance status 1, and there were 24 males and 3 females.

Fourteen patients had been pretreated with surgery alone, 9 with surgery and hormonal or immunomodulation, and 3 with surgery + radiotherapy + hormonal or immunomodulations. One patient had no prior treatment at all. In 18/27 patients marker lesions were situated in the lung, 3 had regional metastatic nodes, 5 had liver metastases and one had a large local recurrence. Several patients had measurable lesions in multiple sites.

The 27 fully evaluable patients received between 1 and 10 courses (mean, 3.3; median, 2.3). No complete or partial responses were observed. In 12 patients the disease remained stable, in 12 progression was reported and 3 had rapidly progressive disease after one course, so no second course was given.

4′Deoxydoxorubicin was generally very well tolerated. A total of 28 patients received 91 treatment cycles and are evaluable for toxicity. Of the non-hematological side-effects nausea and vomiting were the most common adverse effects occurring

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Other participants included: C. Bollack, CHU de Strasbourg, France, and W.G. Jones, Cookridge Hospital, Leeds, U.K.
††To whom requests for reprints should be addressed at: Department of Clinical Oncology, Antwerp University Hospital, B2520 Edegem, Belgium.
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in 43% (12/28) of the patients. Moderate alopecia was reported in 18% (5/28), slight oral toxicity was observed in 11% (3/28) and consisted only of soreness. A grade I phlebitis was noted in 3 patients (11%). No patients developed congestive heart failure, but in 1 patient a significant decline from 70 to 50% in the left ventricular ejection fraction (LVEF) at rest was observed after 9 treatment cycles of 4'DeoxyDX.

The only hematological toxicity observed was leukopenia. The white blood cell nadirs available for 85 cycles were grade 3 in 5 (6%), grade 2 in 13 (15%) and grade 1 in 16 cycles (19%). The platelet nadirs were always $> 100 \times 10^9/l$. Dose reduction had to be performed for 2 patients in 1 cycle and in 1 patient for 3 cycles.

The patients entered into this study permitted an optimal chance for 4'DeoxyDX to show its activity since all patients had a good performance status and no prior cytotoxic treatment. The majority of the indicator lesions were present in the lung and lymphnodes. No responses were observed in this group of advanced renal cancer patients. The dose given in this group of patients however, should perhaps have been a little higher since only in 40% of the cycles leucocytes dropped and no platelet nadir under $100 \times 10^9/l$ was observed. The total lack of activity does not raise much hope for a better outcome had the drug been given in a higher dose. All other toxicities observed were very mild in agreement with other recently published studies with 4'DeoxyDX [8,9] in which also no activity was shown. If further studies will be pursued the observation of cardiotoxicity in 1 patient after 9 courses (total 270 mg/m^2) must lead to careful cardiotoxicity monitoring of all patients entered.

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