Eur J Cancer Clin Oncol, Vol. 21, No. 9, pp. 1013–1014, 1985.
Printed in Great Britain.

0277-5379/85$3.00+0.00

Mitoxantrone in Advanced Bladder Carcinoma. A Phase II Study of the EORTC Genito-urinary Tract Cancer Cooperative Group*

ALLAN T. VAN OOSTEROM,†‡ SOPHIE D. FOSSÅ,§ JANNES H. MULDER,|| ALESSANDRO CALCIATI,¶ MARLEEN DE PAUW** and RICHARD SYLVESTER**

†*Department of Clinical Oncology, University Hospital Leiden, The Netherlands,* §*General Department, Norwegian Radium Hospital, Oslo, Norway,* ||*Rotterdam Radiotherapeutic Institute, Rotterdam, The Netherlands,* ¶*Department of Oncology, Ospedale S. Giovanni, Torino, Italy and* ***EORTC Data Center, Institut Jules Bordet, Blvd. de Waterloo,* 1000 *Brussels, Belgium*

Abstract—*Mitoxantrone at a dose of* 12 mg/m² *i.v. q* 3 weeks *failed to produce a response in* 28 *adequately treated patients with measurable advanced bladder cancer. The side-effects observed in this group of patients with a good performance status were generally mild. On the basis of this negative result the use of mitoxantrone in this disease cannot be recommended.*

INTRODUCTION

BLADDER cancer accounts for about 4% of new cancer cases each year. Application of radical surgery and/or radiotherapy will ultimately cure 65% of the patients. However, these modalities have not improved the prognosis of patients with muscle invasive bladder cancer and have only palliative value in disseminated disease. Further advances in these patient groups might reside in the utilization of chemotherapy. The two most active single drugs presently available are methotrexate and cisplatin [1]. Activity has also been reported with adriamycin [2, 3] and velban [4]. The need for active drugs in this disease has led the EORTC Genito-urinary Tract Cancer Cooperative Group to undertake a programme of phase II studies. Such a study using mitoxantrone as a single agent is reported here.

von Hoff reported the results of a phase I clinical trial in patients with advanced solid tumors given a single i.v. dose of mitoxantrone every 28 days. Leukopenia was the dose-limiting toxicity. The maximum dose tolerated appeared to be 14 mg/m² and the recommended dose for phase II trials was 12 mg/m² repeated at 3- or 4-week intervals [5].

MATERIALS AND METHODS

Ten institutions entered 29 patients with histologically proven progressive measurable advanced transitional cell carcinoma of the urinary tract in a phase II study using mitoxantrone.

The eligibility criteria were: age under 80 yr, WHO performance status $\leqslant 2$, white blood cell count (WBC) $\geqslant 4 \times 10^9/l$, platelet count $\geqslant 125 \times 10^6/l$ and normal cardiac, kidney and hepatic functions. Patients with second cancers, brain metastases or an irradiated lesion as the only indicator site were excluded. Previous treatment with adriamycin or other anthracyclines was a reason for exclusion. Pretreatment studies included physical examination, complete blood count, biochemical tests of renal and liver functions and chest X-ray. Computerized

Accepted 18 March 1985.

Other participants included: K. J. Roozendaal, OLVG, Amsterdam, The Netherlands; A. Verbaeys, University Hospital, Gent, Belgium; L. Denis, Free University Hospital, Brussels, Belgium; G. Stoter, Free University Hospital, Amsterdam, The Netherlands; T. Splinter, Erasmus University Hospital, Rotterdam, The Netherlands; R. Hall, Freeman Hospital, Newcastle, U.K.

*This investigation was supported by grant No. 5 UIOCA 11488-15 awarded by the National Cancer Institute, DHEW, Bethesda, MD, U.S.A.

‡To whom requests for reprints should be addressed.

tomography and ultrasound echography were accepted as means of measuring indicator lesions. This could include an unresectable primary if it was not previously irradiated.

Mitoxantrone 12 mg/m² was administered in a 100-ml 5% dextrose solution given intravenously in 30 min, repeated every 3 weeks. However, treatment was deferred until blood counts returned to pretreatment values with a maximum postponement of 3 weeks. A dose reduction by 10 and 25% respectively was applied on day 29 if blood counts showed WHO haematologic toxicity of grades I and II respectively.

The evaluation of response and toxicity was performed using WHO criteria [6].

RESULTS

Evaluability

One of the 29 patients proved to be ineligible because all indicator lesions had been irradiated.

Patient characteristics

The median age of the 28 evaluable patients was 64 yr (range 41–76 yr); seven had a performance status 0, 11 had a performance status of 1 and ten had a performance status of 2. There were 23 males and five females.

Prior treatment consisted of: surgery only in five, irradiation only in five, chemotherapy only with cisplatin and methotrexate in four, surgery plus radiotherapy in three, surgery plus cisplatin-containing combination chemotherapy in six, radiotherapy plus cisplatin–methotrexate chemotherapy in one, and surgery plus irradiation plus chemotherapy (cisplatin based combinations) in two. Two patients received no prior treatment.

In summary, 15 patients had no prior chemotherapy and 13 had prior chemotherapy with cisplatin-containing combinations.

The indicator lesions followed were the primary in two, lung metastases in 14, primary and lung in one, regional nodes in two, metastatic nodes in two, primary plus liver in one, metastatic nodes plus liver in two, skin in three, lung plus metastatic nodes in one and primary plus liver plus soft tissue in one.

Response to treatment

The 28 fully evaluable patients received between one and six courses (mean 2.3; median 2). In four patients early progression after one cycle was observed. In 18 patients progression after two cycles was observed and the treatment stopped. In six patients no change was observed lasting from 2 to 5 months.

Toxicity of the treatment

Mitoxantrone was generally well tolerated. All 28 patients were evaluable for toxicity and received a total of 65 cycles. No treatment-related reduction nor postponement of cycles had to be performed. Dose escalation with 2 mg/m² could be performed in three patients who had WHO grade O for white blood cells and platelets at nadir.

Of the non-haematological side-effects transient nausea and vomiting were the most common, occurring in 61% (17/28 patients). Mild alopecia was observed in 21% (6/28 patients). Major infection due to leucopenia was observed in one patient, a moderate infection in two patients.

Concerning haematological side-effects, the worst grades included white blood cells grade IV plus platelets grade III in two patients, white blood cells grade III and platelets grade II in one patient, and white blood cells grade IV and platelets grade II in one patient.

DISCUSSION

No response to mitoxantrone in this group of advanced bladder cancer patients was observed, although 15 patients had no prior chemotherapy. We therefore must conclude that mitoxantrone cannot be recommended for inclusion in combination chemotherapy in advanced bladder cancer.

REFERENCES

1. Stoter G, Williams SD, Einhorn LH. Single-agent activity in advanced bladder cancer. In: Pinedo HM, ed. *Cancer Chemotherapy Annual 3*. Amsterdam, Excerpta Medica, 1981, 324.
2. Yagoda A. Future implications of phase II chemotherapy trials in ninety five patients with measurable advanced bladder cancer. *Cancer Res* 1977, **37**, 2775.
3. Pavone-Macaluso M. Chemotherapy of bladder tumors. *Urol Res* 1978, **6**, 259.
4. Blumenreich MS, Yagoda A, Natale RB, Watson RC. Phase II trial of vinblastine sulfate for metastatic urothelial tract tumors. *Cancer* 1982, **50**, 435.
5. Von Hoff DD, Pollard E, Kuhn J, Murray E, Coltman CA. Phase I clinical investigation of 1,4-dihydroxy-5,8-bis(((2)(2-hydroxyethyl)amino-ethyl-amino)(-9,10 anthracenedione dihydrochloride) NSC 301739) a new anthracenedione. *Cancer Res* 1980, **40**, 1516–1518.
6. *WHO Handbook for Reporting Results of Cancer Treatment*. Geneva, WHO offset publication No. 48, WHO, 1979, 1–32.