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Mitomycin C (MCC) in Advanced Soft Tissue Sarcoma: a Phase II Study of the EORTC Soft Tissue and Bone Sarcoma Group

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Abstract—*Mitomycin C at a dose of* 12 mg/m² *i.v. q* 3 weeks *was administered to* 34 *patients with measurable progressive advanced soft tissue sarcomas. No objective response was observed although in one of the* 12 *patients with overall stabilisation of disease a partial response was reported in lung lesions. The side-effects observed in this group of patients were generally mild. On the basis of this result the application of mitomycin C in this disease cannot be recommended.*

INTRODUCTION

THE TREATMENT of advanced soft tissue sarcomas in adults remains disappointing. This can be attributed mainly to the lack of effective drugs. Adriamycin alone has a repeatedly confirmed response rate of more than 25% [1, 2]. Several new and established drugs, claimed to be effective, were recently tested by the EORTC Soft Tissue and Bone Sarcoma Group but failed to show significant activity [2-7].

Mitomycin C, a bi- or trifunctional alkylating agent, has been studied clinically for more than 20 yr, but it is only recently that information has been generated allowing its more general application. In earlier studies it was used in a daily low-dose schedule in which severe bone marrow toxicity was encountered. Using this regimen in children [8] and adults [9, 10], some activity in sarcoma has been reported. The reawakening of interest in mitomycin C came about with the introduction of a single high-dose schedule [11] which, when applied alone or in combination, has shown considerable activity in several tumor types [12-14]. Therefore a phase II study with mitomycin C in advanced soft tissue sarcoma, resistant to standard treatment, was initiated.

MATERIALS AND METHODS

Twelve institutions entered 45 patients with histologically proven progressive, measurable advanced soft tissue sarcoma into a phase II study using mitomycin C. The eligibility criteria were: age between 15 and 75 yr, WHO performance status $\leqslant 2$, white blood cell count (WBC) $\geqslant 4 \times 10^9/l$, platelet count $\geqslant 125 \times 10^9/l$ and adequate cardiac, kidney and hepatic function. Patients with second malignancies, brain metastases or an irradiated lesion as the only indicator site were excluded.

Pretreatment studies included physical examination, complete blood count, biochemical tests of renal and liver function and chest X-ray. Computerized tomography and ultrasound echography were accepted as means of measuring indicator lesions.

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Mitomycin C, 12 mg/m², was administered by i.v. bolus every 3 weeks, intervals increased after 2, 4 and 6 courses. Treatment was deferred until blood counts returned to pretreatment values with a maximum postponement of 3 weeks. Blood counts were obtained weekly and if WBC $\leqslant 1.5 \times 10^9$/l and/or platelets $\leqslant 50 \times 10^9$/l were observed between courses the next dose was reduced by 25%.

The evaluation of response and toxicity was performed using WHO criteria [15].

RESULTS

Evaluability

Four of the patients entered proved to be ineligible, two had inadequate histopathology and two had a performance status of 3. Of the 41 eligible patients, seven were inevaluable: four refused the treatment or were lost to follow-up, two had inadequate treatment and one died of malignant disease within 3 weeks of starting the treatment.

Patient characteristics

Of the 34 evaluable patients the median age was 59 yr (range 22-71 yr); ten had a performance status 0, 16 had a status of 1 and eight had a status of 2. There were 11 males and 23 females. All patients received previous chemotherapy: four as adjuvant, 30 for advanced disease. The number of prior drugs were one in 20 patients, two in five patients, three in one, four in five, five in one and six in two patients. Thirty-one had received adriamycin, and five 4′-epiadriamycin; of the other drugs DTIC had been administered in eight, cyclophosphamide in seven and vincristine in seven. Previous radiotherapy had been administered to ten of the 34 patients. The parameters followed were loco-regional disease only in eight patients, distant metastases only in 22 and loco-regional + distant metastases in four patients. In 22 patients the parameters followed included lung metastases.

Response to treatment

The 34 fully evaluable patients received between 2 and 7 courses (mean 3; median 2). In 12 patients the disease remained stable for a median of 17 (range 10-36) weeks. It must be mentioned that the protocol asked for disease progression in the 6 weeks prior to entry. In one of the 12 stable disease patients lung metastases decreased by more than 70% while the disease loco-regionally remained stable. In 22 patients the disease progressed.

Toxicity of the treatment

Mitomycin C was generally well tolerated. All 34 patients are evaluable for toxicity and received 93 treatment cycles.

Of the non-hematological side-effects, transient nausea and vomiting were the most common, occurring in 50% (17/34) of the patients. Alopecia was complete in one patient, patchy in two and minimal in three. A major infection related to leucopenia was reported in one patient, a moderate infection in two patients. Drug extravasation leading to skin necrosis necessitating a graft occurred in one patient. Grade 3 cardiac toxicity, responding to medical management, was observed after 6 courses in a patient heavily pretreated with anthracyclines.

Hematological side-effects were mild. Only 8 courses had to be modified, mostly due to leucopenia. The increasing intervals between treatments based on the knowledge of the cumulative myelotoxicity of mitomycin C proved to be well scheduled.

DISCUSSION

Only one partial response of lung metastases (but with no overall response in that patient) was observed in 34 evaluable progressive patients with advanced soft tissue sarcomas despite the fact that this particular group of patients was not heavily pretreated. Thus data suggesting significant activity of mitomycin C in this disease could not be confirmed. We must conclude that mitomycin C cannot be recommended for inclusion in combination chemotherapy for soft tissue sarcomas. The search for other active drugs in this disease must continue.

REFERENCES

1. Benjamin RS, Wiernik PH, Bachur NR. Adriamycin: a new effective agent in the therapy of disseminated sarcomas. *Med Pediatr Oncol* 1975, **1**, 63-76.
2. Bramwell VHC, Mouridsen HT, Mulder JH *et al.* Carminomycin versus adriamycin in advanced soft tissue sarcomas: an EORTC randomised phase II study. *Eur J Cancer Clin Oncol* 1983, **19**, 1097-1104.
3. Bramwell VHC, Brugarolas A, Mouridsen HT *et al.* Phase II study of cisplatin in Cyvadic-resistant soft tissue sarcoma *Eur J Cancer* 1979, **15**, 1511-1513.
4. Mouridsen HT, Bramwell VHC, Lacave J *et al.* Treatment of advanced soft tissue sarcomas with chlorozotocin: a phase II trial of the EORTC Soft Tissue and Bone Sarcoma Group. *Cancer Treat Rep* 1981, **65**, 509-511.

5. Bramwell VHC, van Oosterom AT, Mouridsen HT *et al.* *N*-(Phosphonacetyl)-L-aspartate (PALA) in advanced soft tissue sarcoma: a phase II trial of the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer Clin Oncol* 1982, **18,** 81-84.
6. Buesa JM, Mouridsen HT, Santoro A *et al.* Treatment of advanced soft tissue sarcomas with low-dose methotrexate: a phase II trial by the EORTC Soft Tissue and Bone Sarcoma Group. *Cancer Treat Rep* 1984, **68,** 683-684.
7. Somers R, Rouëssé J, van Oosterom AT, Thomas D. Phase II study of elliptinium in metastatic soft tissue sarcoma. *Eur J Cancer Clin Oncol* In press.
8. Gutierrez ML. Mitomycin C in childhood cancer. In: Carter SK, Crooke ST, eds. *Mitomycin C: Current Status and New Developments.* New York, Academic Press, 1979, 213-217.
9. Wasserman TH, Comis RL, Goldsmith M *et al.* Tabular analysis of the clinical chemotherapy of solid tumors. *Cancer Chemother Rep* 1975, **6,** 399-419.
10. Godfrey TE, Wilbur DW. Clinical experience with mitomycin C in large infrequent doses. *Cancer* 1972, **29,** 1647-1652.
11. Baker LH, Caoili EM, Izbicki RM, Opipari MI, Vaitkevicius VK. Comparative study of mitomycin C and porphyromycin. *Proc ASCO* 1974, **15,** 182.
12. van Oosterom AT, Powles TJ, Hamersma E, Smith IE, Engelsman E. Phase II study of mitomycin C in advanced breast cancer. In: Mouridsen HT, Palshof T, eds. *Breast Cancer Experimental and Clinical Aspects* (Suppl. to *Eur J Cancer Clin Oncol*). Oxford, Pergamon Press, 1980, 275-277.
13. Comis RL, Carter SK. A review of chemotherapy in gastric cancer. *Cancer* 1974, **34,** 1576-1586.
14. MacDonald JS, Schein PS, Woolley PV *et al.* 5-Fluoro-uracil, Doxorubicin and mitomycin (FAM) combination chemotherapy for advanced gastric cancer. *Ann Intern Med* 1980, **93,** 533-536.
15. *WHO Handbook for Reporting Results of Cancer Treatment.* WHO offset publication. Geneva, World Health Organization, 1979.