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Short communication

Phase II study of a combination of mitomycin, doxorubicin and cisplatin in advanced sarcomas

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Summary. In all 63 patients were treated monthly with a combination of mitomycin, doxorubicin, and cisplatin, and 27 (43%) experienced objective regression of their advanced sarcomas during a 3-month trial. The observed regression rate is numerically higher than any previously observed at our institution.

Introduction

A previous study in this institution with cyclophosphamide, doxorubicin, and cisplatin in combination (CAP) produced objective tumor regression in approximately 36% of patients treated for advanced sarcomas [5]. The addition to this regimen of bleomycin given by continuous infusion over 3 days failed to improve these results, with 34% of patients experiencing objective tumor regression [6]. Both these studies gave results superior to those we had obtained with single agents and earlier drug combinations [2, 3]. Thus, we have continued to modifiy this CAP treatment base in our continuing efforts to improve the therapy of patients with advanced sarcomas.

The most recent effort in this series of phase II studies involving doxorubicin–cisplatin combinations involves the use of mitomycin as the alkylating agent component (MAP). Mitomycin was selected for antisarcoma trial in this combination because of its activity against solid tumors of various types and because of previous evidence in squamous cell carcinoma of the lung, another CAP-sensitive tumor, suggesting that MAP was specifically superior to CAP chemotherapy in that disease [4]. While mitomycin has not been extensively studied as a single agent against sarcomas in adults in this country, it has been in clinical use for this purpose in Japan for several years [1]; and it did have limited efficacy against osteosarcomas during early trials in children [7].

Materials and methods

Sixty-three patients between the ages of 17 and 76 years (median 42 years) with unresectable metastatic sarcomas were studied. Five others had been enrolled in the study, but three were found to be ineligible and two withdrew prior to receiving any treatment. Nineteen sarcomas were of skeletal origin, 31 arose from extremity or head and neck soft tissues or from the outer body wall, and the remaining 13 arose from soft tissues within the abdomen or thorax or from the retroperitoneal body wall. Each patient had measurable or evaluable disease, an expected survival of at least 2 months, and Eastern Cooperative Oncology Group performance status of 3 or better. Patients were required to have leukocyte counts of at least 4000/μl and platelet counts of at least 130 000/μl with no elevation of direct serum bilirubin and serum creatinine no greater than 1.5 mg/dl. No patient had active heart disease or infection and all had recovered from any previous surgery, radiation or chemotherapy. None of the patients had previously received any of the cytotoxic drugs used in this study. Among the 29 men and 34 women studied, 50 had received major tumor surgery and 20 had received radiation therapy; however, only one had received prior chemotherapy (high-dose methotrexate).

The MAP regimen was given on day 1 of each monthly treatment cycle and was continued for 3 consecutive months unless disease progression occurred earlier. The three drugs were given sequentially beginning with mitomycin (8 mg/m^2) by IV injection through a free-flowing saline infusion followed immediately by doxorubicin 40 mg/m^2 administered by a similar IV injection technique.

Cisplatin 60 mg/m^2 was then administered by 2-h IV infusion in 1 iter 0.45% saline with 25 g mannitol added. Following three courses of MAP a consolidation treatment program was begun. Alternating monthly courses of the following drugs were given by IV injection until disease progressed or became resectable, with the elimination of doxorubicin after a total dose of 520 mg/m^2 had been received: vincristine 1.2 mg/m^2 (max. dose 2 mg) on days 1 and 5; cyclophosphamide 250 mg/m^2 on days 1, 3, and 5; and dactinomycin 0.325 mg/m^2 on days 1 through 5; alternating with vincristine (as above); doxorubicin 50 mg/m^2 on day 3; and dacarbazine 250 mg/m^2 on days 1 through 5. Doses of all drugs were modified appropriately to alleviate any serious drug toxicity problems. Patients who experienced progression of disease during MAP treatment were withdrawn from the study, while those in whom disease progression occurred during the initial 18 months of consolidation treatment were offered further treatment with MAP.

Partial regression of disease was defined as at least 50% reduction in the product of the longest perpendicular di-

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ameters of the lesions measured without the appearance of any new lesions, or for nonmeasurable (evaluable) lesions a definite decrease in tumor size agreed dupon by two investigators. Complete tumor regression was defined as the total disappearance of all tumor. Disease progression was defined as an increase by at least 25% in the product of the longest perpendicular diameters of measured lesions or the appearance of any new lesion, or for evaluable disease a definite increase in tumor size or the appearance of new lesions.

Results

Of the 63 patients 27 (43%)[1] achieved objective regression of disease, all regressions occurring during the initial 3-months MAP treatment phase. A patient with splenic angiosarcoma later achieved complete regression during the consolidation phase. Twelve other patients (19% experienced no significant change in tumor size for at least 2 months, and 24 patients (38%) experienced progression of disease (23 patients) or refused to continue treatment (1 patient) within 2 months after beginning MAP treatment. By histological subtypes objective tumor regression was achieved in 2 of 7 patients with leiomyosarcoma, 6 of 11 with malignant fibrous histiocytoma, 5 of 11 with osteosarcoma, 4 of 8 with fibrosarcoma, 1 of 3 with neurofibrosarcomas, 3 of 4 with angiosarcoma, 2 of 3 with liposarcoma, 2 of 3 with synovial sarcoma, 1 of 2 with Ewing's sarcoma, 1 of 2 with undifferentiated small cell sarcoma, 1 of 1 with lymphangiosarcoma and none of 3 with chondrosarcoma. One patient each with epithelioid sarcoma, cystosarcoma phylloides, hemangiopericytoma, and undifferentiated sarcoma of soft tissues failed to achieve objective tumor regression.

Myelosuppression was present regularly, with a median leukocyte nadir of 2150/μl (700–13 600, $n=58$) and median platelet nadir of 125 000/μl (20 000–388 000, $n=57$) during the MAP treatment phase. Among the 60 patients who returned for evaluation of MAP toxicity 53 had alopecia, 50 experienced vomiting (20 severe), and 17 developed stomatitis (2 severe). One patient developed pneumonitis and died following an episode of severe leukopenia (total WBC count 400/μl) during the consolidation phase of her chemotherapy; and another patient was reported to have died of sepsis during the consolidation phase of treatment, but no other information was available. Median survival (Kaplan-Meier estimate) following the first course of MAP treatment was 276 days (range 17–730+ days), and at the time of this report 18 patients were still surviving. Patients who experienced disease progression before completing three courses of MAP chemotherapy have not responded favorably to our consolidation treatment program given as secondary treatment or to other systemic secondary treatments. In fact, we have observed only one patient who has responded favorably to secondary chemotherapy (vincristine-cyclophosphamide-dactinomycin) after MAP failure.

Discussion

The 43% objective sarcoma regression rate observed in this study with a combination of mitomycin, doxorubicin, and cisplatin is numerically higher than any result previously observed here during chemotherapy trials in patients with advanced sarcomas. Median survival, however, and long-term survival prospects in this group of patients remain about the same as those observed in our most recent prior studies. Since our studies have been done sequentially no ciritical comparisons can be made.

Of interest in the present study is the observation that all 27 patients who experienced objective tumor regression did so during the initial 3-month MAP treatment phase. Thus, continued use of the three-drug (MAP) induction regimen might be preferable to obligatory crossover after 3 months to a consolidation regimen, as practiced in the the current study. The further observation that only one patient has experienced objective tumor regression during other systemic treatment efforts after failure of MAP chemotherapy indicates that efforts at effective study of new phase II agents in such previously treated patients may be futile. To define the relative clinical efficacy of the MAP regimen against advanced sarcomas, a phase III comparison of this regimen with doxorubicin alone is planned.

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[1] The 95% confidence interval for true regression probability (unadjusted for multiple examinations of the data) is 0.30–056