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Short communication

Phase-II trial of 4-demethoxydaunorubicin (DMDR) for advanced hypernephroma

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Summary. *A phase-II trial of 4-demethoxydaunorubicin (4-DMDR) was performed in 21 patients with advanced renal cell carcinoma. The drug had demonstrated a broader spectrum of activity with less cardiotoxicity in preclinical evaluation than the parent compound daunorubicin. The starting dose was 12.5 mg/m², with escalations to 15 and 17.5 mg/m² in the absence of toxicity. Myelosuppression was the primary toxicity and cardiac toxicity was not seen in four patients who received four or more doses of DMDR. No responses were seen in 19 adequately treated patients, including 14 who had received no prior therapy.*

Introduction

4-Demethoxydaunorubicin (DMDR), a derivative of daunorubicin that lacks a methoxy group in position 4, has demonstrated significant therapeutic activity against the P388 and L1210 leukemias, and against the solid tumors MS-2 and sarcoma 180 [2, 5, 6]. In rats, dogs, and rabbits, less cardiotoxicity was noted in chronic toxicity tests; even at lethal doses, dogs or rabbits did not experience any myocardial damage [5]. In phase-I trials, myelosuppression the dose-limiting toxic effect; the degree of granulocytopenia was greater than that of thrombocytopenia [3, 4]. A phase-II disease-oriented trial of DMDR was undertaken at Memorial Hospital and North Shore University Hospital in patients with advanced measurable renal cancer.

Materials and methods

Twenty-one patients with pathologically confirmed metastatic hypernephroma received DMDR. Patient entry required adequate hematological parameters (WBC > 4,000 cells/mm³; platelets > 150,000 cells/mm³), Karnofsky performance status (PS) ≥ 50%, bilirubin < 2.0 mg%, BUN < 30 mg%, creatinine < 1.5 mg%, and bidimensionally measurable lesions. Patients with cardiac disease falling in AHA class III or greater were excluded. Prior hormones and cytotoxic drugs were discontinued at least 3 weeks before therapy, except for nitrosoureas and methothrexate/vinblastine, which were stopped at 6, 2, and 2 weeks before, respectively. All patients had a complete history and physical examination with measurement of the two longest perpendicular diameters of palpable lesions by two independent investigators. Prior to each dose, a CBC, SMA-12, and 5′ nucleotidase were obtained. Chest X-rays were performed every 6 weeks, or every 3 weeks if used to evaluate disease. In selected cases, liver and bone radionuclide scans and computerized transaxial tomograms (CT scans) were performed initially and repeated at 6-week intervals to evaluate disease parameters. All x-rays and scans were evaluated independently (RCW). Electrocardiograms were repeated after the third dose and then prior to every second dose. Gated cardiac blood pool scans were performed prior to entry if clinically indicated, or after the fourth dose. Most patients obtained an ABC 7, 10, and 14 days after each dose.

An adequate trial was defined as one dose with myelosuppression (WBC < 2,500 cells/mm³, platelets < 125,000) and /or rapid disease progression (> 50% increase in the size of measurable lesions), or two doses with progression. Response criteria included: partial remission (PR): 50% decrease in the summed products of perpendicular diameters of all measurable lesions for 1 month; minor response (MR): 25%–49% decrease in measurable lesions for 1 month; stabilization of disease (STAB): 25% change in tumor size for 3 months; and progression (PROG): 25% increase.

The drug was administered IV every 3 weeks over 10 min, at a starting dose of 12.5 mg/m². If significant myelotoxicity did not occur doses were increased by increments of 2.5 mg/m². One patient who had malignant hepatomegaly and abnormal renal function and in whom pharmacokinetic tests were performed was initially treated with 6 mg/m² but subsequently received 12.5 mg/m². Of 13 patients who started at 12.5 mg/m², 3 had the dose escalated to 15 mg/m², and 5 to 17 mg/m²; two patients required dose reduction and three had no change in dosage. Of the seven patients entered at 15 mg/m², five received the same dose in subsequent courses and two had the doses reduced to 12.5 mg/m² because of toxicity.

There were 15 male and six female patients: the median age was 56 years (range, 46–72) and the median PS 80% (range, 60–90). While 15 (60%) patients had not received prior cytotoxic chemotherapy, three had been treated with one drug and three with two or more drugs. Although three patients had received bisantrene, a guanidino-substituted anthracene derivative, none had had other anthracycline therapy. There was a history of prior irradiation in three cases, but in none to an indicator lesion. Other therapies included hormones in three cases and immunotherapy in 1. The median time from symptoms to diagnosis was 1 month (range, 0–19), and from diagnosis to protocol 2 months (range, 0–84). The primary indicator lesions were: pulmonary masses in nine cases; abdominal masses evaluated by CT scan in five; abdomi-

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nal/subcutaneous masses in two; malignant hepatomegaly in two; and lymph nodes in two. On review, one patient was classified as having only evaluable disease, e.g., osseous metastases. Secondary parameters included abnormal CT scans in five cases, subcutaneous masses in one, and lymph nodes metastases in one.

Results

There were no (95% confidence limits, 0–12%) responses in 19 adequately treated cases, 14 (95% confidence limits, 0–16%) of whom had had no prior cytotoxic chemotherapy. One patient had stabilization of disease for 6 months and a second demonstrated no change in an abdominal mass after four doses (2.5 months) but relapsed with central nervous system metastases. It is of note that one patient responded subsequently to interferon.

The median number of doses was three (range 1–5): one patient had one dose; six had two; eight had three; and six had four to eight doses. Ten patients experienced no symptomatic toxicity. Nausea occurred in 10 (47%) cases, mild vomiting in nine (43%), fatigue in two, diarrhea in one, anorexia lasting 1–2 days following each dose in three (16%), and partial alopecia in two. One patient developed a radiation recall reaction in a site that had been previously irradiated 7 years prior to DMDR. There was no evidence of electrocardiographic (ECG) changes or renal dysfunction in four patients who received total doses of 50–108 mg/m^2 (total 88–172 mg). Abnormalities in liver function were not observed.

In all, 20 patients were evaluable for hematological toxicity. Myelosuppression was observed in 18 cases; leukopenia (< 3,000 cells/mm^3) occurred in 17, and thrombocytopenia (< 125,000 cells/mm^3) in seven. WBC and platelet nadirs were observed on day 10, with recovery by day 14. Evidence of a cumulative effect on platelets was noted after three doses, resulting in postponement of DMDR administration for 7–14 days.

One patient who had an occasional atrial premature contraction initially did not experience new ECG abnormalities after three doses of DMDR. Five patients who received four or more doses were evaluated for cardiac toxicity. Two had serial gated pool cardiac scans with no evidence of cardiac dysfunction. A third, who developed nonspecific ST-T wave changes at submaximal levels of exercise in the pretreatment study after five doses of bisantrene, showed no change on a repeat stress test done after four doses of DMDR. A fourth showed nonspecific 3-mm ST upsloping in V_5 after seven doses and a fifth relapsed in the central nervous system and could not undergo cardiac scanning.

Discussion

In the present study, no responses occurred in 19 adequately treated patients, 14 of whom were unpretreated. Although newer analogs of anthracyclines are being sought, results of the present trial, combined with experience with the anthracyclines doxorubicin and 4-epi-doxorubicin [1], suggest a limited role for this class of compounds in treatment of patients with advanced hypernephroma.

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