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Lack of activity of stealth liposomal doxorubicin in the treatment of patients with anthracycline-resistant breast cancer

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Abstract Purpose: We conducted a single-institution phase II clinical trial to determine the objective response rate, duration of response, time to progression, and overall survival in patients with anthracycline-resistant breast cancer treated with Doxil. Patients and methods: Patients with metastatic breast cancer were eligible if they had disease progression while receiving an anthracycline-containing regimen or developed evidence of metastatic disease during or within 6 months after the last cycle of an anthracycline-containing adjuvant regimen. Prior treatment with liposomal doxorubicin was not allowed. Patients received a dose of 50 mg/m² infused every 4 weeks via a peripheral vein or central line. Doxil was administered for a total of six cycles or until disease progression. Results: We treated 11 patients with stage IV breast cancer of whom two had never received chemotherapy for their metastatic disease. Most had a performance status of 1 and had visceral involvement as their dominant site of disease. All patients had received prior therapy with doxorubicin. No clinical evidence of congestive heart failure or cardiac toxicity was observed. The most common toxicities were nonhematologic and were mostly grade 1/2. These included fatigue, nausea, vomiting, and stomatitis. Significant myelosuppression was only observed in one patient. No complete or partial response was observed. There were two patients who had minimal response and two other patients who had evidence of stable disease. Conclusion: Doxil was well tolerated with minimal toxicity. However, the lack of antitumor activity in anthracycline-resistant breast cancer patients indicates that further evaluation in this patient population is not warranted.

Keywords Stealth liposomes · Doxil · Breast cancer · Anthracycline resistance

Introduction

The anthracycline antibiotic doxorubicin has a broad spectrum of antineoplastic action and is correspondingly in wide clinical use. In addition to its role in the treatment of breast cancer, doxorubicin is indicated in the treatment of Hodgkin’s disease and non-Hodgkin’s lymphoma, hepatocellular and gastric carcinoma, small-cell cancer of the lung, soft tissue and bone sarcomas, as well as cancer of the ovary, bladder, and thyroid. Unfortunately, toxicity limits the therapeutic activity of doxorubicin and may preclude adequate dosing.

Liposomal encapsulation of doxorubicin may reduce both the nonspecific drug delivery to normal tissues as well as the high peak plasma levels of free drug responsible for its toxicity. Stealth liposomal doxorubicin (Doxil) is a formulation in which the drug is encapsulated in liposomes that escape instant recognition and uptake by the mononuclear phagocyte system. As a result, the formulation has a long circulation time, and the liposomes can eventually become extravasated through the abnormally permeable vessels characteristic of many tumors. Once concentrated in tumors, the liposomes can deliver high levels of doxorubicin to malignant cells, without affecting normal tissue [1, 2, 3, 4].

Doxil has been studied extensively in patients with AIDS-related Kaposi’s sarcoma. There are well-documented cases of anthracycline failure in some Kaposi’s sarcoma patients who have subsequently responded to Doxil at a dose of 20 mg/m² every 3 weeks. In this population, 43 patients were identified as having progressed on prior chemotherapy with doxorubicin. Of these 43 patients, response rates to Doxil ranged from 27% to 52% depending on the method of measurement [5].
The treatment of anthracycline-resistant metastatic breast cancer remains a challenge despite the recent introduction of additional cytotoxic agents such as the taxanes. The need for new therapeutics is evident. The antitumor activity observed in breast cancer patients and in Kaposi’s sarcoma patients who had failed anthracyclines as well as a decreased toxicity profile led us to evaluate the activity of this drug in anthracycline-resistant breast cancer patients.

**Patients and methods**

**Eligibility criteria**

Patients were eligible for the study if they had histologic proof of breast carcinoma with evidence of progression of their metastatic disease. They were required to have either (1) evidence of metastatic disease while receiving an anthracycline-containing adjuvant therapy regimen or developed evidence of metastatic disease within 6 months after the last cycle of an anthracycline-containing adjuvant chemotherapy regimen, or (2) progressive disease after a minimum of one cycle of an anthracycline-containing regimen for advanced disease as a first-line or second-line treatment. The patients who had an initial response, either a partial or complete response, or stable disease on an anthracycline-containing regimen who then developed progressive disease while still receiving the same anthracycline-containing regimen were considered as demonstrating progressive disease and were eligible for study entry.

No more than two prior chemotherapy regimens for metastatic disease were allowed. All patients were required to have evidence of measurable disease. Patients were required to have a life expectancy of at least 12 weeks, to have a performance status of  ≤ 2 on the Zubrod scale [6], and to be at least 18 years of age. Patients were not eligible for this study if they had received prior therapy with liposomal doxorubicin. Other eligibility criteria included: adequate bone marrow function, defined as an absolute granulocyte count of ≥1500/µl and a platelet count of ≥100,000/µl; adequate liver and renal function, defined as a bilirubin concentration <1.2 mg/dl and serum creatinine concentration <2.0 mg/dl; and a cardiac ejection fraction ≥50% without evidence of congestive heart failure. Patients were not eligible if they had received a total doxorubicin dose of more than 300 mg/m² intravenously (i.v.) bolus or 400 mg/ m² i.v. continuous infusion or if they had received a total mitoxantrone dose of more than 105 mg/m² i.v. bolus or 140 mg/m² i.v. continuous infusion.

**Treatment plan and evaluation**

Prior to study entry, patients underwent a complete history and physical examination, including evaluation of performance status and weight, and documentation of all prior anticancer treatments and any residual side effects from prior therapies. Appropriate baseline studies were obtained to fully define the extent and severity of existing or suspected malignant and non-malignant disease. All patients had a baseline cardiac evaluation with an electrocardiogram and an isotope cardiac scan to determine the left ventricular ejection fraction. Laboratory data included a complete blood cell count with differential and platelet counts, urinalysis, blood chemistry studies, and in patients of childbearing potential a serum pregnancy test.

All patients were registered with the M. D. Anderson Cancer Center data management office. All gave written, informed consent. Patients received a fixed dose of 50 mg/m² of Doxil infused i.v. over 2.5 h on day 1 via a peripheral vein or central line. Each cycle was repeated every 28 days on an outpatient basis. The patients were treated until there was unacceptable toxicity or evidence of progression of their disease. The patients were also allowed to go off treatment at the investigator’s discretion. Dose adjustments were made according to the system showing the greatest degree of toxicity. Toxicities were graded using the NCI Common Toxicity Criteria.

Patients were followed up with complete blood cell counts, differential counts, and platelet counts prior to each dose of Doxil. Blood chemistry studies were repeated before each course or as frequently as needed to define drug toxicity. Serum tumor markers were repeated every three courses if levels were initially elevated. Appropriate radiologic assessments to follow measurable and evaluable disease were performed after every three courses unless the clinical situation required assessment sooner. An isotope cardiac scan was performed every 100 mg/m² increments of liposomal doxorubicin if the patient had received ≥300 mg/m² of anthracycline in the past. If not, then the cardiac scan was obtained once the patient had reached 300 mg/m² of anthracycline and every 100 mg/ m² thereafter.

Tumor lesions were measured in centimeters prior to each course of therapy. For bidimensionally measurable lesions, size was reported as the product of the longest diameter and its perpendicular. Measurements were made and recorded either by the physician or by the oncology research nurse under the physician’s supervision. An estimate of overall objective and subjective response was made and recorded prior to each course. Standard response criteria were applied [7].

The patients were removed from the study if any of the following occurred: (1) evidence of increasing disease after three courses of therapy at doses sufficient to produce some evidence of toxicity or other biologic effect; (2) the development of unacceptable toxicity; or (3) a decline in left ventricular ejection fraction to <45% or a decrease to 20% under baseline.

**Statistical analysis**

A total of 35 evaluable patients were to be entered into the study in order to estimate response rate with standard error of approximately 0.07. An interim analysis was scheduled to be performed after entering 14 patients, but the study was terminated early at the request of Alza Pharmaceuticals since no responses had been observed in any of the 11 eligible patients.

**Results**

**Patient characteristics**

Between May 1997 and December 1998, 11 eligible patients were registered in this study. Demographic and clinical characteristics of all patients are listed in Table 1. The median age was 51 years and the median Zubrod performance status was 1. The median number of metastatic sites was three (range one to five). Most patients had visceral involvement as their dominant site of disease. Five patients had received one prior chemotherapy regimen and six had received two or more chemotherapeutic regimens. Two of the patients had only received prior adjuvant chemotherapy. Four patients had received prior hormonal therapy, 7 had prior radiation therapy, and 11 had prior breast surgery.

**Responses**

There were no partial or complete responses reported in this study. There were two patients with minor responses