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ORIGINAL ARTICLE

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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/m^2 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 hada 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

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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/m^2 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 $\geq 1500/\mu l$ and a platelet count of $\geq 100{,}000/\mu l$; 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 $\geq 50\%$ without evidence of congestive heart failure. Patients were not eligible if they had received a total doxorubicin dose of more than 300 mg/m^2 intravenous (i.v.) bolus or 400 mg/m^2 i.v. continuous infusion or if they had received a total mitoxantrone dose of more than 105 mg/m^2 i.v. bolus or 140 mg/m^2 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/m^2 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/m^2 increments of liposomal doxorubicin if the patient had received ≥ 300 mg/m^2 of anthracycline in the past. If not, then the cardiac scan was obtained once the patient had reached 300 mg/m^2 of anthracycline and every 100 mg/m^2 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 chemotherapeutic 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

Table 1 Patient characteristics

No. of patients	
Entered	11
Evaluable	11
Sex, female	11
Race, white	11
Age (years)	
Median	51
Range	39–71
Performance status	
0	3
1	8
No. of metastatic sites	
1	3
2	1
3	4
>3	3
Visceral dominant site	8
No. of prior chemotherapy regimens	
1	5
2	5
3	1
Prior therapy	
Hormonal	4
Radiation	7

and two others with evidence of stable disease. One patient had a hypersensitivity reaction with her first dose of the drug after less than 1 min of infusion and declined further treatment. The remaining six patients showed evidence of progression while on the drug. One of the patients who had a minor response had only received adjuvant chemotherapy. The other patient with a minor response had received taxane-based chemotherapy as first-line treatment for her metastatic disease. Of the 11 patients, 9 had died of progression of their metastatic disease at the time of this report. The median time to progression was 2 months (range 2 to 7 months). None of the patients was receiving treatment with Doxil at the time of this report.

Minimal toxicity together with the fact that no objective responses were observed in the first seven patients led to modification of the Doxil dose from 50 to 60 mg/m^2. However, no responses were seen in the four patients who were treated at the higher dose. This dose escalation did translate into an increase in toxicity. The toxicity observed in these four patients included grade 3 palmar-plantar erythrodysesthesia, grade 3 nausea, grade 3 fatigue, grade 4 neutropenia, and an episode of neutropenic fever.

Toxicity

Hematologic

Toxicity was evaluated for all patients. A total of 27 courses were administered. The median number of courses received was two (range one to five).

Hematologic toxicity was not a significant problem observed with this drug. Only one patient developed grade 4 neutropenia during the second course of chemotherapy. Of note is the fact that this patient was treated at the higher dose of 60 mg/m^2 and subsequently required a dose reduction. Another patient developed an episode of grade 3 neutropenia that was associated with fever. Other hematologic toxicities were not a major problem with only grade 1 thrombocytopenia and grade 1/2 anemia reported in 3 and 20 of all courses, respectively. The average nadir granulocyte count for all courses was 2500/μl and occurred at an average of 23 days.

Nonhematologic

Grade 3 or 4 nonhematologic toxicity was not a significant problem during any of the courses. Grade 3 palmar-plantar erythrodysesthesia was reported by three patients and grade 3 fatigue was reported by five patients. Other grade 3/4 toxicities experienced by patients during the trial included stomatitis in one patient, and nausea in one other patient. The patient who developed grade 3 stomatitis also developed neutropenic fever during the same course of treatment. This patient was initially treated at a dose of 60 mg/m^2 but did not develop any major toxicity until after the second course of chemotherapy. The patient was retreated at a 50% dose reduction but eventually developed grade 3 hand-foot syndrome. She had no change in her disease and was eventually taken off the study. The remaining toxic effects observed were mild with mostly grade 1 and 2. Most patients, however, did not receive the drug long enough to evaluate for other possible cumulative toxicity. There were no major dose delays related to therapy.

Cardiac

All patients had previously received therapy with an anthracycline, in this case, doxorubicin. Four patients received prior therapy with doxorubicin in the adjuvant setting while seven patients received it for their metastatic disease. The median cumulative dose for all patients of free and liposomal doxorubicin was 240 mg/m^2 (range 120 to 338 mg/m^2) and 120 mg/m^2 (range 0.6 to 200 mg/m^2), respectively. The total median cumulative dose for both free and liposomal doxorubicin combined was 360 mg/m^2 (range 150.6 to 500 mg/m^2). The average left ventricular ejection fraction for all patients was 62% at baseline. A total of ten patients underwent serial cardiac scans with an average ejection fraction of 61% upon completion of the study. One patient had a drop in ejection fraction of 13% and another had a drop of 17%, both after two courses of chemotherapy. The total cumulative dose of doxorubicin, free and liposomal, was 330 and 400 mg/m^2, for each one of these patients, respectively. Neither one of the patients had a prior history of cardiac disease. Both patients still retained an ejection fraction above 50% without any cardiac symptoms or signs of congestive heart failure.

Discussion

Doxil has been evaluated and approved in the treatment of malignancies such as Kaposi's sarcoma and ovarian cancer. The drug has demonstrated activity in patients with Kaposi's sarcoma refractory to doxorubicin and ovarian cancer patients who have failed platinum- and taxane-based chemotherapy [5, 8]. While doxorubicin is cleared rapidly from the serum, a prolonged pharmacokinetic profile of Doxil is achieved by virtue of its formulation as pegylated liposomal doxorubicin. As a result, prolonged systemic circulation is achieved, with higher concentrations of the drug in areas of increased vascularity such as tumor tissue. Efficacy might be enhanced by this selective concentration of doxorubicin within tumor tissue. This altered pharmacokinetic profile provides a plausible explanation for responses to Doxil seen in patients with tumor progression while receiving doxorubicin therapy.

Having demonstrated the clinical response achieved with Doxil in patients with Kaposi's sarcoma refractory to doxorubicin, it was considered logical to evaluate the clinical response to Doxil in patients with anthracycline-resistant breast cancer. This rationale was also supported by a study reported by Ranson et al. [9] in which the efficacy of Doxil was evaluated in breast cancer patients. In that study, patients with metastatic breast cancer who had never received chemotherapy for their disease or had not received an anthracycline were treated with doses of Doxil that ranged from 45 to 60 mg/m^2. An objective response rate of 31% was reported.

In contrast to the study of Ranson et al., our patient population was considered to be at high-risk because of their known resistance to anthracyclines. This could explain the difference in response rate between the two studies. Early termination of the study was undertaken since responses were not seen in 11 consecutive patients, nor in another similar study reported in abstract form by Smith et al. [10]. In that study, 17 patients with anthracycline-resistant (recurred within 6 months of last dose) metastatic breast cancer were treated with 30 mg/m^2 of Doxil every 3 weeks. All patients had received more than 200 mg/m^2 but less than 500 mg/m^2 of doxorubicin. Four patients had stable disease but no confirmed responses were seen. The authors concluded that the lack of activity could have been related to a decreased dose intensity and that perhaps increasing the dose to 50 mg/m^2 would enhance the activity of the drug. Our study used a dose of 50 mg/m^2 of Doxil every 4 weeks and no objective responses were observed. The dose of Doxil was increased to 60 mg/m^2 in the last four patients, but this increase in dose intensity translated into an increase in toxicity without additional antitumor activity. Assuming that there is an increase in concentration of free doxorubicin in tumor tissue, then this mechanism alone does not seem to be sufficient to overcome the resistance developed by tumor cells once they have been exposed to free doxorubicin.

The role of Doxil in breast cancer patients continues to be defined. Perhaps, the drug will be of greater value when combined with other agents with different toxicity profiles and mechanisms of action. For example, one possibility would be the use of Doxil in combination with trastuzumab in Her2/neu-positive patients as a way to minimize the risk of cardiac toxicity. Clinical studies are currently ongoing to help define the role of Doxil in the constantly increasing armamentarium of drugs to treat breast cancer.

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