Cancer Chemother Pharmacol (2002) 50: 6–8
DOI 10.1007/s00280-002-0464-0

ORIGINAL ARTICLE

**Daniel J. Booser · Francisco J. Esteva · Edgardo Rivera
Vicente Valero · Laura Esparza-Guerra
Waldemar Priebe · Gabriel N. Hortobagyi**

Phase II study of liposomal annamycin in the treatment of doxorubicin-resistant breast cancer

Received: 18 December 2001 / Accepted: 14 March 2002 / Published online: 21 May 2002

Abstract Liposomal annamycin (L-AN) has shown antitumor activity in preclinical studies. It may selectively target tumors and bypass MDR-1 resistance. A total of 13 women with doxorubicin-resistant breast cancer were treated on this phase II study. The median number of prior chemotherapy regimens was two, and six patients had two or more organ sites of involvement. L-AN was administered at 190–250 mg/m^2 as an i.v. infusion over 1–2 h every 3 weeks. No responses were observed. Of the 13 patients, 12 had clear deterioration and new tumor growth after one or two courses. The 13th patient had prolonged grade 2 thrombocytopenia after one course, and was taken off study when the lung metastases increased 62 days after treatment. L-AN at this dose and on this schedule had no detectable antitumor activity in patients with doxorubicin-resistant metastatic breast cancer.

Keywords Annamycin · Anthracycline · Resistant breast cancer

Introduction

Anthracyclines remain among the most active antitumor agents for breast cancer. Their usefulness is limited because of the development of cumulative dose-dependent cardiac toxicity. In addition, tumors may be resistant to both doxorubicin and epirubicin because of overexpression of p-glycoprotein, known as MDR-1. Annamycin (3′-deamino-4′-epi-3′-hydroxy-2′-iodo-4-demethoxy doxorubicin), a highly lipophilic anthracycline, was developed with a potential ''double advantage''. Its molecular design would avoid the MDR-1 mechanism of cellular drug resistance, and its increased affinity for liposomes was expected to improve drug targeting to tumors and reduce cardiac drug levels [1].

The phase I study of liposomal annamycin (L-AN) established 210 mg/m^2 as the maximum tolerated dose (MTD). No tumor regression was seen in the 20 patients treated with potentially myelosuppressive doses (180–240 mg/m^2). Following a change in the formulation of the drug, the MTD was changed to 190 mg/m^2 [2]. This phase II study was undertaken to determine the activity of L-AN given at the MTD to patients with metastatic breast cancer resistant to doxorubicin.

D.J.B. was supported by a grant from Aronex Pharmaceuticals, Inc., The Woodlands, Texas.

D.J. Booser (✉) · F.J. Esteva · E. Rivera · V. Valero
L. Esparza-Guerra · G.N. Hortobagyi
Department of Breast Medical Oncology,
The University of Texas M. D. Anderson Cancer Center,
1515 Holcombe Boulevard, Box 424, Houston,
Texas 77030-4095, USA
E-mail: dbooser@mdanderson.org
Tel.: +1-713-7922817
Fax: +1-713-7944385

W. Priebe
Department of Immunobiology & Drug Carriers,
The University of Texas M. D. Anderson Cancer Center,
Houston, Texas, USA

Materials and methods

Patient selection

All patients were ambulatory with a Zubrod performance status of 2 or better, and had an estimated life expectancy of at least 12 weeks (Table 1). Resistance to doxorubicin was defined as no response (stable or increasing disease) on treatment, or relapse within six months of discontinuing treatment as adjuvant therapy or for metastatic disease. Other eligibility criteria included the presence of a tumor measurable in two dimensions, and adequate bone marrow, hepatic and renal function as evidenced by an absolute granulocyte count of ≥1500/mm^3, platelet count of ≥100,000/mm^3, bilirubin level of ≤ 1.5 mmol/l, and creatinine level of ≤ 1.5 mmol/l. No chemotherapy or radiation therapy was given within 3 weeks of study entry. The prior doxorubicin dose was limited to 350 mg/m^2 by bolus or 450 mg/m^2 by prolonged infusion (at least 48 h). An ejection fraction of ≥55%, as shown by two-dimensional echocardiography, was required, and patients with a history of heart failure were excluded. None of the patients had brain metastases, and none had prior treatment with mitomycin.

All patients had a baseline history and physical examination; full blood count with differential; a biochemical profile including CEA or CA27-29 measurement, if appropriate; chest radiography;

Table 1. Patient characteristics

	No. of patients	Years
Patients entered	13	
Age		
Median		50
Range		34–73
Prior chemotherapy		
Adjuvant only (pre- or postoperative)	4	
For metastatic disease		
One regimen	2	
Two regimens	1	
Three regimens	6	

computerized tomography of the abdomen; bone scan and radiographic views of bones showing abnormal uptake; and electro- and echocardiography. Hematological parameters were checked weekly, and biochemical parameters were checked before each course. Radiological studies that showed abnormal findings were to be repeated after three courses of therapy unless there was an earlier suspicion of increasing disease, in which case they were performed sooner. Echocardiography was to be repeated every three courses. All concomitant medication was documented, and no other investigational drugs were administered.

During the study, all patients were seen every 3 weeks in the outpatient clinic by the physician and the research nurse to record all toxicities and to evaluate abnormalities detected on physical examination. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria, and standard response criteria were used for assessment. A minimum of two courses was required for a patient to be considered as having received an adequate trial to be evaluable for efficacy. Treatment was discontinued after one course if there was clear worsening of the tumor or the development of new lesions.

Administration

L-AN was prepared as a preliposomal lyophilized powder in vials containing 10 mg annamycin, 500 mg phospholipids, and 17 mg Tween 20, or it was prepared in a 15-mg vial with 2500 mg phospholipids and 85 mg Tween 20. On the day of use, the vials were reconstituted with 10 ml or 50 ml saline at 37°C and hand-shaken for 1 min. This resulted in a red milky suspension formed of liposomes measuring around 150 nm in diameter. The drug was given as an intravenous infusion over 1–2 h, usually through a peripheral vein, at 3-week intervals.

Dosage

The first six patients received 210 mg/m^2 L-AN intravenously. If no significant toxicity was observed, the dose was increased by 20% to 250 mg/m^2. Following a change in the formulation of the drug, the subsequent seven patients received 190 mg/m^2 L-AN intravenously.

Statistics

This phase II study was designed according to Simon's optimal design. If at least one response was observed in the first 14 patients, an additional 16 patients were to be entered. Because no responses were seen in the first 13 patients (95% CI 0–25), the study was closed at the request of the sponsor.

Results

A total of 13 patients received 20 doses of L-AN. All were eligible for the trial and evaluable for toxicity.

Hematological effects

Two patients had grade 3 granulocytopenia, and three patients had four courses with asymptomatic grade 4 granulocytopenia. One had neutropenic fever without an identified source of infection. One patient had grade 3 and one patient grade 4 thrombocytopenia, without bleeding. The grade 3 thrombocytopenia persisted until day 35 after the second course of treatment. Another patient who developed grade 2 thrombocytopenia had a platelet count of 89,000/mm^3 on day 55 after the first course of L-AN and was then taken off study on day 62 when the pulmonary metastases were found to have worsened. Subsequently she had satisfactory hematological tolerance to paclitaxel, and then to vinorelbine.

Two patients without myelosuppression on the first course were given a 20% dose increase with the second course. One of these then had grade 4 asymptomatic granulocytopenia.

Other side effects

In general, the drug was well tolerated. Gastrointestinal side effects were minimal. Three patients had mild vomiting, and only one had grade 2 stomatitis. One patient had fever during the infusion, but there were no hypersensitivity reactions. No patient received more than two courses, and so none required routine re-evaluation of cardiac function. No patient developed heart failure.

Responses

Six patients were given two courses of L-AN, and seven patients received only one course. No tumor regression was noted. All six patients who received two courses had clear worsening of tumor and were taken off study, including one who had no significant drug toxicity. Treatment was discontinued when tumor clearly worsened after one course in four patients, two of whom had no significant drug toxicity. Two others with liver metastases had rapidly worsening liver function tests and declining performance status after one course and were taken off study. One patient could not receive a second course because of grade 2 thrombocytopenia (despite normal megakaryocytes in the bone marrow) for 55 days after the first course, and her lung metastases were found to have increased on chest radiography 1 week later.

Nine patients received a total of 17 chemotherapy regimens after L-AN. One with a HER-2/neu-positive tumor had clinical benefit from three subsequent chemotherapy regimens (two given with trastuzumab), and the disease remained chemoresistant for the other eight.

Discussion

L-AN at the doses and in the schedule used in this study showed no activity against doxorubicin-resistant breast cancer. While the drug was well tolerated, the side effects observed were in keeping with the phase I trial suggesting appropriate bioavailability. There are many laboratory models of cellular resistance to multiple drugs including anthracyclines, but the precise cause of clinical anthracycline resistance is poorly understood. It may be multifactorial. Although L-AN is able to bypass the permeability glycoprotein (the protein responsible for MDR-1) in vitro, this was not sufficient to reverse clinical doxorubicin resistance.

Annamycin was generally well tolerated clinically, and it appears to be less cardiotoxic than doxorubicin [2, 3]. However, because no objective responses or prolonged stability were observed, no patient received sufficient L-AN to test the drug's cardiotoxic potential. While additional evaluation in anthracycline-naive or -sensitive patients is appropriate, no additional assessment in anthracycline-resistant populations is recommended. The occasional prolonged thrombocytopenia observed in this study and in the phase I study suggests an interesting potential for L-AN in the treatment of acute leukemias.

References

1. Priebe W, Perez-Soler R (1993) Design and tumor targeting of anthracyclines able to overcome multidrug resistance: a double-advantage approach. Pharmacol Ther 60:215
2. Booser DJ, Perez-Soler R, Cossum P, Esparza-Guerra L, Wu QP, Zou Y, Priebe W, Hortobagyi GN (2000) Phase I study of liposomal annamycin. Cancer Chemother Pharmacol 46:427
3. Zou Y, Priebe W, Stephens LC, Perez-Soler R (1995) Preclinical toxicity of liposome-incorporated annamycin: selective bone marrow toxicity with lack of cardiotoxicity. Clin Cancer Res 1:1369