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Phase II study of echinomycin in patients with advanced breast cancer: A report of cancer and leukemia group B protocol 8641

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Summary

Twenty-five women with advanced histologically documented stage IV recurrent or inoperable breast cancer were enrolled on a phase II study of echinomycin administered at a dose of 1.2 mg/m² intravenously over 30 minutes weekly for 4 weeks followed by a two week rest period. Seventy-six percent of patients had visceral dominant disease at study entry and all patients had previously received chemotherapy. One of 21 eligible patients had a partial response lasting 147 days. The median survival for this group of patients was 5.9 months and the median time to treatment failure was 1.7 months. Nausea and vomiting was the primary toxic effect and was severe or life-threatening in 43% of patients. Transient elevation of liver enzymes occurred in 30% of patients. Bone marrow suppression was not significant. Echinomycin as employed in this study did not demonstrate significant antitumor activity in previously treated patients with advanced breast cancer.

Echinomycin (NSC 526417) is one of a family of quinoxaline antibiotics originally isolated from *Streptomyces echinatus* [1,2]. It is thought to act as a bifunctional intercalator in DNA thereby resulting in inhibition of DNA-directed RNA synthesis. The drug's interaction with DNA is due to the polar quinoxaline chromophores located on opposite sides of the cyclic peptide which can intercalate at two sites on the same DNA molecule or on separate DNA molecules resulting in intra- or intermolecular cross-linking [3,4].

In the National Cancer Institute pre-clinical screening systems, echinomycin demonstrated significant antitumor activity against P388 leukemia and B16 melanoma [5]. It was not effective, however, against a number of other tumors including L1210 leukemia, Lewis lung carcinoma, the CD8F1 mammary tumor, the colon 38 tumor or against human colon, lung or mammary xenografts in immune-deficient mice. In the human tumor stem cell assay, the drug demonstrated a 24% response rate for breast cancer, 25% for colorectal cancer and 38% for sarcoma [6].

Pre-clinical toxicology studies in mice and dogs demonstrated gastrointestinal toxicity, mild bone marrow suppression and histologic evidence of liver damage as the primary toxic effects of echinomycin [5]. Several phase I clinical trials using different dose schedules have been conducted [7–9]. The dose limiting toxicity in all studies was severe and often protracted nausea and vomiting. Mild thrombocytopenia, elevation of liver enzymes and hypersensitivity reactions were also noted.

This paper reports the results of a phase II trial of echinomycin conducted by the Cancer and Leukemia Group B (CALGB) in women with advanced breast cancer.

Patients and methods

Patient selection

Women with histologically documented stage IV recurrent or inoperable adenocarcinoma of the breast were eligible for this study provided they had measurable disease, a performance status of 0–2 (CALGB scale), a life expectancy of at least 2 months, treatment with no more than 1 prior chemotherapy program for metastatic disease and recovery from the toxic effects of all prior therapy. All patients had acceptable bone marrow (granulocytes $> 1800/\mu l$, platelets $> 100{,}000/\mu l$), renal (BUN $< 1.5 \times$ normal, creatinine < 1.8 mg/dl), and hepatic (total bilirubin $< 1.5 \times$ normal, SGOT/SGPT $< 1.5 \times$ normal) function prior to entry on protocol. All patients provided written informed consent for participation in this study.

Treatment plan

Echinomycin 1.2 mg/m^2 was administered intravenously once a week for 4 consecutive weeks followed by a 2 week rest period. Cycles were repeated every 6 weeks. Patients received at least 2 cycles of chemotherapy unless severe toxicity or rapid disease progression occurred. The drug was provided as a sterile lyophilized powder and was reconstituted by mixing with Diluent 12 composed of equal parts of polyethoxylated castor oil and ethanol. Once dissolved, the drug was diluted in normal saline and the desired dose was administered as a 30 minute infusion in 150 cc normal saline. Aggressive antiemetic therapy was encouraged although the specific antiemetic regimen employed was left to the discretion of the treating physician. Most patients received combination antiemetic therapy including metaclopropamide, prochlorperazine, lorazepam or diphenhydramine.

Criteria of response and toxicity

Response to therapy was assessed using standard criteria. Complete response was defined as the disappearance of all measurable disease, signs, symptoms and biochemical changes related to the tumor for at least 4 weeks. Partial response was defined as at least a 50% reduction in the sum of the products of the perpendicular diameters of all measurable lesions lasting at least 4 weeks during which no new lesions could appear. Stable disease was defined as less than a 50% reduction or less than a 25% increase in the sum of the products of two perpendicular diameters of all measured lesions and the appearance of no new lesions for at least 8 weeks. Progressive disease was defined as an increase in the product of two perpendicular diameters of a measured lesion by at least 25% or the appearance of new metastases.

Toxicity was graded according to the CALGB toxicity scale.

Statistical methods

Survival time was defined as the time from registration on study to the date of death from any cause. Time to treatment failure was defined as the time from registration on study to the date of tumor progression or to the date of death without progression or to the date last seen. Survival curves were computed according to the method of Kaplan and Meier [10].

Results

Twenty-five patients were enrolled on this study between April and November, 1986 of whom 4 were deemed ineligible due to absence of measurable disease (2), abnormal liver function (1), or excessive prior chemotherapy (1). Characteristics of the 21 eligible patients are summarized in Table 1. Seventy-six percent of patients had visceral dominant disease at study entry and all had previously received either adjuvant chemotherapy (6), chemotherapy for metastatic disease (11) or both (4).

One patient had a partial response lasting 147 days. Twenty of the 21 patients have died. The median survival was 5.9 months and the median time to treatment failure was 1.7 months.

The toxicity of echinomycin as used in this study is summarized in Table 2. Nausea and vomiting was

Table 1. Characteristics of eligible patients

No. of patients enrolled	25
No. of eligible patients	21
Median age (range) y	56 (27 to 69)
Dominant site of disease at entry	
Visceral dominant	16
Osseous dominant	5
Menopausal status	
Premenopausal	5
Perimenopausal	1
Postmenopausal	14
Unknown	1
Performance status	
0	7
1	10
2	4
Prior therapy	
Any hormonal therapy	11
Any chemotherapy	21
Any radiation therapy	12

the primary toxic effect and was severe or life-threatening in 43% of patients. Four patients were unable to complete the planned four doses per cycle due to severe nausea and vomiting. Transient elevation of liver enzymes occurred in 30% of patients while bone marrow suppression was not significant except for two individuals who developed severe thrombocytopenia.

Discussion

Echinomycin, as employed in this study, did not demonstrate significant antitumor activity in patients previously treated with chemotherapy for advanced breast cancer. This schedule of drug administration was particularly difficult to administer because of severe and sometimes protracted nausea and vomiting despite aggressive anti-emetic therapy. Similar toxicity had been observed by Pazdur and colleagues [8] using this schedule of echinomycin administration in a phase I study. Other toxicities were generally mild and reversible. The relative lack of bone marrow toxicity of echinomycin makes it an attractive agent for combination with other drugs. Further clinical evaluation of echinomycin may be possible with the availability of new effective antiemetics such as ondansetron [11].

Table 2. Toxicity

Toxic effect	No. of patients (%) with grade:				
	1	2	3	4	5
Leukopenia	3(14)	0(0)	0(0)	0(0)	0(0)
Thrombocytopenia	3(14)	0(0)	1(5)	1(5)	0(0)
Anemia	3(14)	2(10)	0(0)	0(0)	0(0)
Hemorrhage	0(0)	1(5)	0(0)	0(0)	0(0)
Infection	3(14)	1(5)	0(0)	1(5)	0(0)
Hepatic	1(5)	2(10)	2(10)	1(5)	0(0)
Nausea/vomiting	1(5)	6(29)	7(33)	2(10)	0(0)
Diarrhea	0(0)	1(5)	1(5)	0(0)	0(0)
Hypersensitivity	0(0)	0(0)	0(0)	0(0)	0(0)

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