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Nine patients with metastatic breast carcinoma refractory to doxorubicin were entered in a Phase II study of liposomal-annamycin, a new anthracycline antibiotic which has shown ability to circumvent multidrug resistance. A total of 14 doses of liposomal-annamycin were given at three different dose levels. Toxicity was mild and limited to granulocytopenia in less than 50% of patients. No antitumor responses were seen.

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INTRODUCTION

Liposomal-Annamycin is a liposome entrapped new anthracycline antibiotic which has shown lack of cross-resistance in vitro and in vivo in different cell lines that express P-glycoprotein and MRP. In a Phase I study conducted in patients with solid tumors, the dose limiting toxicity was myelosuppression. No alopecia, mucositis, cardiac, skin, nor gastrointestinal toxicities were observed. The maximum tolerated dose was 210 mg/m2 administered intravenously every 3 weeks. Because the multidrug resistance phenotype has been associated with some human malignancies, particularly acute leukemia and breast carcinoma, when they become refractory to standard chemotherapy, we proposed and initiated a Phase II study of liposomal-Annamycin in patients with metastatic breast carcinoma refractory to doxorubicin. This report summarizes the status of this study.

REPORT

ELIGIBILITY CRITERIA

1. Metastatic breast carcinoma
2. Anthracycline-resistant
3. Measurable disease
4. Life expectancy >12 weeks
5. Prior anthracycline <350 mg/m2 of doxorubicin equivalent by bolus, <450 mg/m2 by prolonged infusion
6. Adequate bone marrow function
7. Ejection fraction >55%

PATIENT CHARACTERISTICS

A total of nine patients have been entered in the study and a total of 14 doses of liposomal-annamycin have been given. In four courses, the dose given was 190 mg/m2, in eight courses 210 mg/m2 and in the other two courses 250 mg/m2. The following Table summarizes the characteristics of the patients entered.

Number of patients entered	9
Number of patients evaluable	9
Age median (range)	50 (34-73)
Performance status	
1	8
2	1

Sex: female	9
Race:	
Black	4
Hispanic	2
White	2
Histology	
Ductal carcinoma, invasive	9
Prior therapy	
Chemotherapy	9
Hormonal therapy	3
Radiation therapy	6
Surgical therapy	7
Prior chemotherapy: number of regimens	
1	2
2	1
3	4
4	2
number of agents	
3	1
>3	8

TOXICITY

Toxicity has been mild and mostly limited to granulocytopenia as indicated below:

1. Myelosupression

Dose	**No courses**	**Granulocyte nadir (range) (day)**	**Platelet nadir (range) (day)**
190mg/m2	4	1.2 (0.7-1.8) 11	192 (134-251) 14
210	8	1.5 (0.5-3.0) 15	218 (145-288) 10
250	2	0.8 (0.3-1.3) 11	169 (146-192) 8

2. Non-hematological toxicities

Nausea and vomiting was observed after 6 courses (grade 3 in one, grade 2 in two, and grade 1 in three). Diarrhea grade 1 was observed after one course. Stomatitis was observed after 4 courses (grade 2 in two, and grade 1 in two). One grade 1 allergic reaction was observed.

ANTITUMOR ACTIVITY

Eight patients progressed after 1 or 2 cycles of liposomal-annamycin. One patients remained stable after 2 cycles of liposomal-annamycin. No tumor responses have been seen so far.

CORRELATIVE TISSUE STUDIES

Three tissue specimens were obtained pre-therapy for MDR analysis. These samples are kept frozen in Dr. Sahin's laboratory and will be assayed when the study is completed and/or responses are seen.

CONCLUSIONS

Results obtained to date suggest that liposomal-annamycin is very well tolerated with grade 3 granulocytopenia being observed in a minority of patients. Non-hematological toxicity is minimal.

No tumor responses have been observed so far.

The study will continue to complete fourteen fully evaluable patients. Baseline tumor biopsies will be obtained if possible to analize MDR status. If no responses are seen in this cohort of 14 patients, the study will be closed and another Phase II study in patients not anthracycline refractory will be initiated.

REFERENCES

1. Booser D, Zou Y, Priebe W, Perez-Soler R. Phase I clinical and pharmacology study of liposomal-annamycin. In preparation for submission to Clinical Cancer Research.
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