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Award Number: DAMD17-96-C-6105

TITLE: Treatment of Metastatic Breast Carcinoma Refractory to Doxorubicin with Liposomal-Annamycin

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REPORT DATE: October 2000

TYPE OF REPORT: **Annual**

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	October 2000	Annual (23 Sep 99 - 22 Sep 00)

4. TITLE AND SUBTITLE
Treatment of Metastatic Breast Carcinoma Refractory to Doxorubicin with Liposomal-Annamycin

5. FUNDING NUMBERS
DAMD17-96-C-6105

6. AUTHOR(S)
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 Words)*

We studied the toxicity and antitumor activity of Liposomal-Annamycin in patients with metastatic breast carcinoma. Sixteen patients have been treated. Toxicity was mild and consisted mostly of bone marrow suppression, particularly granulocytopenia. Non-hematological toxicity was less than what is usually seen with other anthracyclines. No responses have been seen. The study is continuing accruing a total of 12 additional less heavily pretreated patients

14. SUBJECT TERMS
Breast Cancer

15. NUMBER OF PAGES
6

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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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/m^2 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

The study has accrued a total of 16 patients so far. Although no clinical responses have been observed, the research team is committed to continue the study accruing less heavily pretreated patients. Twelve additional patients will be needed. If no responses are seen in these twelve patients, Liposomal-Annamycin will be declared an inactive agent in this less heavily pretreated patient population. A final extension of one year is being requested. Drs. Volm and Muggia are committed to the study and will make an extra effort to complete accrual in this period of time.

OBJECTIVES OF THE STUDY

1. To evaluate the antitumor activity of Liposomal-Annamycin in patients with metastatic breast carcinoma resistant to anthracyclines.
2. To correlate responses with MDR-1 expression in tumor tissue.

ELIGIBILITY CRITERIA

1. Metastatic breast carcinoma
2. Anthracycline-resistant. Amended during the last year to allow accrual of patients who have received prior anthracyclines in the adjuvant setting, but in whom there is no demonstration of clinical resistance to anthracyclines. This modification was introduced to test Liposomal-Annamycin in a less heavily pretreated population since no responses were seen in the first 14 patients.
3. Measurable disease
4. Life expectancy >12 weeks
5. Prior anthracycline <350 mg/m^2 of doxorubicin equivalent by bolus, <450 mg/m^2 by prolonged infusion
6. Adequate bone marrow function
7. Ejection fraction >55%

PATIENT CHARACTERISTICS

A total of sixteen patients have been entered in the study. The recommended dose was 190mg/m^2. It was escalated to 210 mg/m^2 in 8 courses and to 250 mg/m^2 in 2 courses. The following Table summarizes the characteristics of the patients entered.

Number of patients entered	16
Number of patients evaluable	16
Age median (range)	47 (34-73)
Performance status	
1	14
2	2
Sex: female	16
Race:	
Black	7
Hispanic	4
White	5
Histology	
Ductal carcinoma, invasive	16
Prior therapy	
Chemotherapy	16
Hormonal therapy	3
Radiation therapy	6
Surgical therapy	7
Prior chemotherapy: number of regimens	
1	4
2	2
3	8
4	2
Number of agents	
≤3	3
>3	13

TOXICITY

Liposomal-Annamycin is well tolerated, the dose limiting toxicity being myelosuppression particularly granulocytopenia. The nadir occurs on days 11-14 and in no cases the second dose was delayed. No significant thrombocytopenia was seen. Mild gastrointestinal toxicity such as nausea and vomiting was observed in about 30% of patients and mild mucositis was rare. No alopecia was observed. Fatigue was observed in only a few patients. No events of potential cardiotoxicity were recorded. These results lead to the conclusion that Liposomal-Annamycin is less toxic than the other anthracyclines doxorubicin (Adriamycin) and Daunorubicin.

ANTITUMOR ACTIVITY

No partial responses have been observed in this group of 16 patients. However, only four of these patients received Liposomal-Annamycin as a second line therapy. It is well known that pan-resistance to most agents occurs after 2 and 3 different regimens are given to patients with metastatic solid tumors. As a result, we are now only accruing patients with one prior regimen as adjuvant therapy or for metastatic disease. Unfortunately, this has also resulted in a lower accrual because these patients have a number of alternative options. However, we do not believe patients with ≥ 2 prior regimens should be entered in the future since we have already demonstrated that there were no responses in 14 such patients.

CORRELATIVE TISSUE STUDIES

Five 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. However, the grand majority of patients had received two or more prior chemo regimens.

The study will continue to complete fourteen fully evaluable patients who have received no more than one prior chemotherapy regimen. Baseline tumor biopsies will be obtained to analyze MDR status.

REFERENCES

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