

PART A: MASTER SECTION FOR PHASE II STUDIES IN ADVANCED BREAST CANCER

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1.0 INTRODUCTION

- 1.1 Adenocarcinoma of the breast remains an important medical problem in the United States, with no significant change in the death rate per 100,000 women since 1930 (1). Approximately 27% of all cancers in women (excluding basal cell carcinomas of the skin and carcinoma-in-situ of the cervix) arise in the breast (1).
- 1.2 The results of surgical treatment of localized carcinoma of the breast remain unsatisfactory, with a recurrence rate of up to 90% in patients with >4 positive axillary nodes and a 10 year disease-free survival of only 76% for Stage I disease (2). Of 716 consecutive operable patients followed at the Instituto Nazionale Tumori, Milan, 52.9% had relapsed by 10 years (3).
- 1.3 Estrogen receptor protein (ERP) negative tumors appear to be more aggressive than ERP positive lesions, with clinical relapses occurring after a shorter disease-free interval (4,5,6). Whether the presence of the steroid hormone receptor modifies the response of the tumor to cytotoxic therapy remains unclear (7).
- 1.4 Preliminary results of adjuvant treatment of high-risk patients demonstrate an increase in the disease-free survival in both premenopausal (8-10) and post-menopausal patients (11-14). Unfortunately, disease-free survival after adjuvant treatment does not approach 100% (15). Patients who relapse have already received several of the most active agents against breast carcinoma and ultimately require therapy with new non-cross-reactive drugs.
- 1.5 The treatment of patients with an inoperable primary or metastases remains discouraging (16). Although objective responses to chemotherapy vary from 40-75%, the median duration of response is well under two years. Ultimately all patients relapse, and a smaller fraction of patients respond to each subsequent treatment regimen. More effective non-cross-reactive drugs are required.

2.0 OBJECTIVES

This protocol outlines the procedure for Phase II studies to evaluate single or multiple agents for significant anti-tumor activity in the treatment of inoperable, advanced or recurrent carcinoma of the breast. Activity will be determined by the frequency of complete or partial remission. The duration of response, survival, and the quality of survival will be balanced against toxicity as provided by clinical and laboratory data.

3.0 ELIGIBILITY CRITERIA: Patients must fulfill the following criteria for eligibility: (See also section B 3.0 for eligibility criteria specific to this protocol. Section B 3.0 supercedes A 3.0 if differences exist.)

- 3.1 Histologically confirmed adenocarcinoma of the breast, which is inoperable, recurrent or metastatic.

- 4.62 Cutaneous reactions to Ara-C include rash, erythroderma, or desquamation. Oral steroids during subsequent cycles may ameliorate moderate skin toxicity. Discontinue Ara-C if desquamation or progressive toxicity occurs despite steroid coverage.

5.0 REQUIRED DATA

5.1	Tests and Observations	Prior to Study	Day 1 of Each Cycle
	History	X	
	Physical Examination	X	X
	Pulse, Blood Pressure,	X	X
	Height/Weight/Surface Area	X	X
	Performance Status	X	X
	Tumor Measurements	X	X ^a
	<u>Laboratory</u>		
	CBC, Differential, & Platelet Count	X	X ^b
	BUN, Creatinine	X	X ^b
	SGOT/Alk. Phos./Bili, Electrolytes Mg ⁺⁺	X	X
	Uric Acid, Ca ⁺⁺ , PO ₄ , Glucose	X	PRN
	Total Protein, Albumin	X	X
	Urinalysis	X	PRN
	EKG	X	PRN
	Audiogram	X	PRN
	Creatinine Clearance	X ^c	X
	<u>Staging</u>		
	Chest x-ray	X	X ^e
	Liver Scan	X ^d	X ^e
	Bone Scan	X	X ^e

- X^a If accessible to physical examination, otherwise obtain every 2 cycles.
 X^b Weekly x 4 then d 1 and 14 of each cycle
 X^c Creatinine clearance ≥ 60 ml/min required prior to entry.
 X^d Required if either hepatomegaly or abnormal LFT's are present.
 X^e If abnormal, every two cycles during treatment.
 PRN If clinically indicated.

- 5.2 Modifications of this protocol: It is recognized that this protocol stipulates an ideal clinical design which for a number of reasons may not be approached perfectly. Patient compliance, physician, and test availability, holidays, and other factors may necessitate minor changes in scheduling, dosing, and other aspects of the protocol which do not substantially change the experimental design. The conduct of the study is under the direction of the patient's physician and it is the obligation of the Study Chair and the Committee Chair to ascertain whether cases have been treated in accordance with the intent of this protocol.

6.0 REFERENCES

1. Drewinko, B., Green, C., Loo, T.L.: Combination chemotherapy in vitro with cis-dichlorodiammineplatinum II. Cancer Treat. Rep. 60:1619-1625, 1976.
2. Bergerat, J.P., Drewinko, B., Corry, P., Barlogie, B., Ho, D.H.: Synergistic lethal effect of cis-dichlorodiammineplatinum and 1-B-D-arabinofuranosylcytosine. Cancer Res. 41:25-30, 1981.
3. Schabel, F.M.: Annual progress report of the Southern Research Institute, Section 11, p.9, Birmingham, Alabama 1979.
4. Ho, D.H.W. and Frel, E.: Clinical pharmacology of 1-B-arabinofuranosylcytosine. Clin. Pharm. Ther. 12:944-954, 1971.
5. Ostrow, S., M.J. Egorin, D. Hahn, et al: High dose cis-platin therapy using mannitol versus furosemide diuresis and comparative pharmacokinetics and toxicity. Cancer Treat Rep. 1981: 64:73.