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PROTOCOL GOG #87

SECTION F

A PHASE II TRIAL OF DOXORUBICIN (NSC #123127) AND IFOSFAMIDE (NSC #109724) WITH MESNA (NSC #113891) IN THE TREATMENT OF RECURRENT OR ADVANCED UTERINE LEIOMYOSARCOMAS

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(POINTS - 6)

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SCHEMA

IFOSFAMIDE 5 g/m² by constant infusion/24 hours
MESNA 5.0 g/m² by constant infusion/24 hours
Followed by Mesna 1 g/m² by constant
infusion for an additional 12 hours.
DOXORUBICIN 50 mg/m²/day 1
Repeat every three weeks

OPEN TO PATIENT ENTRY MAY 20, 1991
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1.0 INTRODUCTION AND OBJECTIVES

The treatment of patients with recurrent or advanced metastatic sarcoma remains poor. Although objective resonses may be seen in 10-40% of patients, responses are rarely complete, usually short and have not led to improved survival.

Single agent trials have identified doxorubicin as the most active agent studied to date. Two large trials by the Gynecologic Oncology Group have demonstrated response rates of 16.3% (13 of 80) and 19% (5 of 26) for doxorubicin-treated patients with measurable disease. Complete responses were seen in 5 of 80 and 1 of 26 patients, respectively.(1,2) However, Hannigan and colleagues noted only a 10% response rate with this agent,(3) while Piver noted only a 6% response rate in 12 patients.(4) Other single agents resulting in response have included dactinomycin, fluorouracil(5) and cisplatin.(6)

Several investigators have described more favorable responses to combination chemotherapy regimens in Phase II studies. Azizi and colleagues noted three complete responses and one partial response in six patients treated with dacarbazine, doxorubicin and vincristine.(7) More recently, Piver and colleagues have described a 23% responses rate (12% complete) in 26 patients treated with a combination regimen employing cyclophosphamide, vincristine, doxorubicin and dacarbazine (CYVADIC).(8)

In addition, Hannigan et al noted a 29% response rate (13.3% complete) to a combination of vincristine, dactinomycin, and cyclophosphamide.(9) The GOG, however, in two large randomized trials failed to show superior response for a combination of doxorubicin and dacarbazine or doxorubicin and cyclophosphamide when compared to doxorubicin alone.(1,2) To date, there is no convincing evidence from randomized trials that shows combination chemotherapy for uterine or other soft tissue sarcomas is superior to treatment with doxorubicin alone.

These data indicate the need for identification of new agents and combinations for treating this malignancy. To allow the best possible chance for a new cytotoxic agent to demonstrate activity, this study constitutes a Phase II design in a population of patients who have had no prior drug therapy. The study design will involve treating an average sample size of 30 evaluable patients per drug studied for each of the following cell type categories: mixed mesodermal tumor, leiomyosarcoma, and other sarcomas. This will allow agents found to be ineffective to be rapidly replaced by other agents (see Statistical Section 6.0)

Sections relating to specific agents will be sequentially incorporated into this protocol as each agent is studied.

2.0 PATIENT ELIGIBILITY

2.1 Eligible Patients

2.11 Patients will have histologically confirmed advanced, persistent or recurrent uterine sarcoma with documented disease progression after appropriate local therapy. Histologic types to be included in this study include leiomyosarcoma, malignant mixed mullerian tumor (mixed mesodermal tumor; mixed heterologous mesenchymal sarcoma), mixed malignant mullerian tumor (carcinosarcoma; homologous mesenchymal sarcoma), endometrial stromal sarcoma, and other uterine sarcomas.

2.12 All patients must have measurable disease consisting of abdominal, pelvic, chest or other masses which can be defined in at least two (2) dimensions by palpation, x-ray, computed tomography or ultrasound.

2.13 Patients must have failed local therapeutic measures and must be considered incurable.

2.14 Patients with GOG Performance Grade 0, 1, or 2 (Karnofsky 50 - 100) are eligible.

2.15 Patients will have recovered from effects of recent surgery or radiotherapy and should be free of clinically significant infection.

2.16 Patients must have adequate:

Bone marrow function: WBC greater than or equal to 3,000/mcl, platelet count greater than or equal to 100,000, granulocyte count greater than or equal to 1,500.

Renal function must be adequate: creatinine less than or equal to 2.0.

Hepatic function must be adequate (bilirubin, SGOT and alkaline phosphatase less than or equal to 2 x normal) unless abnormal hepatic function is secondary to documented metastatic tumor of liver.

2.17 Specific alterations of eligibility criteria may be made and will be detailed in the section of the protocol dealing with a specific agent being studied.

2.18 Patients or guardians must sign an informed consent in accordance with institutional, FDA and NCI policy.

2.2 Ineligible Patients

2.21 Patients without measurable disease.

2.22 Patients who have had prior therapy with cytotoxic drugs.

2.23 Patients with another malignancy (prior or concomitant) other than skin (excluding melanoma).

2.24 Specific alterations of ineligibility criteria may be made and will be detailed in the section of the protocol dealing with a specific agent being studied.

3.0 PATIENT ENTRY

3.1 Although this study requires one form of treatment at any given time, patients are to be entered by telephone through the GOG Operations Office as non-randomized cases.

3.2 Before informed consent is obtained from a prospective patient for any section of this protocol, investigators are required to telephone the Statistical Office via the WATS line: 1-800-523-2917; Monday through Friday 9:00 a.m. to 5:00 p.m. EST/EDT to verify which drug the patient will receive.

3.3 When the appropriate drug assignment has been made by the Statistical Office and a potential patient has fulfilled all eligibility requirements according to Section 2.0, Fast Fact Sheet data should be gathered. With this data in hand, the Statistical Office should again be called at the above numbers during the indicated hours. Patients will be entered over the telephone after consideration of Fast Fact Sheet data.

3.4 Control Book Log pages will be provided to each participating institution. As patients are entered onto protocol, their name and relevant information should be entered on the log pages to serve as a record of the patient's entry and assigned treatment.

4.0 CRITERIA FOR EVALUATION AND RESPONSE

4.1 Evaluability

4.11 Patients evaluable for response are those who receive one or more courses of drug. Patients who survive less than 3 weeks from study entry will be considered nonresponders.

4.12 Patients evaluable for adverse effects are those who receive one or more courses of drug regardless of subsequent survival.

4.2 Parameters of Response

Where possible, measurement of lesion size in 2 perpendicular diameters should be required for follow-up. Change in the product of these 2 diameters affords some estimate of change in tumor size and hence therapeutic efficacy. Reporting of these changes in an individual case should be in terms of the best response achieved by that case.

4.21 Complete response: Disappearance of all gross evidence of disease for at least one month.

4.22 Partial response: 50% or greater reduction in the product of the largest diameter and its perpendicular of each measurable lesion for a period of at least one month.

4.23 Increasing disease is a 50% or greater increase in the product from any lesion documented within two months of study entry or the appearance of any new lesion within eight weeks of entry into study.

4.24 Stable disease: Any condition not meeting the above criteria.

4.25 Survival: Observed length of life from initiation of treatment to death or the date of last contact.

4.26 Progression-free interval: The period from study entry to disease progression or last date of contact.

4.27 Subjective parameters: Performance status and specific symptoms graded as follows: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = life threatening/most severe.

5.0 DURATION OF STUDY

5.1 Specific details of treatment duration will be given in the section dealing with the particular agent to be studied.

5.2 A minimum treatment period will be one cycle with survival measured to the beginning of the next cycle.

5.3 Patients with progressive disease will be removed from study.

5.4 Patients with progressive disease and Grade 1 adverse effects may receive a second course at an escalated dose if so provided in the description of the specific agent to be studied.

5.5 Patients who respond or who have stable disease will continue to receive the agent until progression or unacceptable toxicity occurs.