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PROTOCOL GOG #120

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A RANDOMIZED ~~COMPARISON~~ OF HYDROXYUREA VERSUS HYDROXYUREA,
5-FU INFUSION AND BOLUS CISPLATIN VERSUS WEEKLY CISPLATIN AS
ADJUNCT TO RADIATION THERAPY IN PATIENTS WITH STAGES II-B, III,
IV-A CARCINOMA OF THE CERVIX AND NEGATIVE PARA-AORTIC NODES

(PHASE III)

NAV1.954717.002

(POINTS - 6)

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ENCLOSURE (2)

S C H E M A

R E V I S E D
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PRIMARY CARCINOMA OF THE CERVIX
 - SQUAMOUS
 - ADENOSQUAMOUS
 - ADENOCARCINOMA

STANDARD CLINICAL STAGING

CLINICAL STAGES II-B, III-A, III-B & IV-A

EXTRAPERITONEAL SURGICAL SAMPLING OF PA NODES

(+)

(-)

HISTOLOGICALLY CONFIRMED (+) LYMPH NODES

RANDOMIZE

CONSIDER FOR OTHER GOG PROTOCOLS

REGIMEN I	REGIMEN II	REGIMEN III
RT WEEKLY CISPLATIN	RT 5-FU INFUSION CISPLATIN, HYDROXYUREA	RT HYDROXYUREA
CISPLATIN IV 40 MG/M ² DAYS 1,8,15, 22,29,36	CISPLATIN IV 50 MG/M ² DAYS 1, 29 5-FU IV 1000 MG/M ² DAYS 2-5, 30-33 HYDROXYUREA PO 2.0 GM/M ² MON/THURS EVERY WEEK DURING EXTERNAL RT	HYDROXYUREA PO 3 GM/M ² MON/THURS EVERY WEEK DURING EXTERNAL RT

1.0 OBJECTIVE

- 1.1 To determine whether hydroxyurea, hydroxyurea, 5-FU infusion and bolus cisplatin, or weekly cisplatin is superior as a potentiator of radiation therapy in locally advanced cervical carcinoma.
- 1.2 To determine the relative toxicities of hydroxyurea, hydroxyurea, 5-FU infusion and bolus cisplatin, or weekly cisplatin given concurrently with radiation therapy.

2.0 BACKGROUND AND RATIONALE

Cervical cancer remains the second leading cause of death from gynecologic malignancy in the United States[1]. Primary pelvic radiotherapy fails to control 35-90% of patients with locally advanced disease. Approximately two-thirds of these failures occur in the pelvis, presumably within the field of radiation[2].

A variety of agents have been utilized as radiation sensitizers in an effort to increase the effectiveness of radiation and therefore local control. Since 1974, hydroxyurea has been reported to increase survival of patients with advanced cervical cancer[3]. Hydroxyurea is believed to act by inhibiting the repair of radiation-induced damage[4], and it also may induce cell synchrony[5]. These findings have been confirmed by two large cooperative studies performed by the Gynecology Oncology Group. GOG Protocol #4 compared standard radiation therapy to radiation plus hydroxyurea[6]. This study of 104 patients with stage III-B and IV-A squamous cell carcinoma of the cervix showed a significantly increased complete response rate, progression-free interval and survival for those patients receiving radiation and hydroxyurea. GOG Protocol #56 compared hydroxyurea to the hypoxic cell sensitizer misonidazole as an adjunct to radiation[7]. The hydroxyurea patients had a slightly longer progression-free interval and less toxicity. Overall, hydroxyurea appears well tolerated with no apparent increase in normal tissue radiation toxicity. However, hydroxyurea often results in leukopenia which prevents its administration and may lessen its effectiveness. More recently, Protocol #85 compared hydroxyurea to 5-FU infusion and bolus cisplatin[8]. Although final analysis is not yet available at this time, it appears that 5-FU infusion and bolus cisplatin is as effective as hydroxyurea. Based on experience in cancers of the head and neck, Protocol 113, a phase II study of hydroxyurea, 5-FU infusion and bolus cisplatin as concomitant chemotherapy with radiation in patients with locally advanced carcinoma of the cervix was recently conducted. This combination was well tolerated.

A number of other chemotherapeutic agents have been given concomitantly with radiation therapy in cervical cancer patients. Chemotherapeutic regimens used have included cisplatin alone[9-11], 5-fluorouracil and mitomycin-C[12], methotrexate, and bleomycin and cisplatin[13]. Cisplatin is an agent with known activity in cervical cancer[14]. Recent studies

suggest cisplatin is the most effective chemotherapeutic agent in cervical cancer[15]. Cisplatin has limited bone marrow toxicity, which makes it advantageous to use with radiation therapy. Its action as a radiation sensitizer is related to its inhibition of the repair of sublethal radiation damage and hypoxic cell sensitization[5,16].

The regimen of weekly cisplatin for six weeks is, on the basis of its schedule, a dose-intensive therapy. This regimen was first reported for patients with metastatic disease[17], and has been used for patients with disease limited to the pelvis[9,10,18,19]. In a pilot study at the University of Massachusetts, the regimen has been well tolerated and to date no drug-related toxicity has been observed.

The intention of this current phase III three-arm study is to compare weekly cisplatin against hydroxyurea, 5-FU infusion and bolus cisplatin against the control regimen of hydroxyurea alone in locally advanced cervical cancer. Because the major objective of this study is to evaluate local control and survival, this study will be open only to those patients with documented negative para-aortic nodes.

3.0 PATIENT ELIGIBILITY

3.1 Eligible

- 3.11 Patients with primary, previously untreated, histologically confirmed invasive squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma of the uterine cervix, Stages II-B, III-A, III-B, and IV-A, with negative para-aortic disease.
- 3.12 Patients who have had para-aortic lymph node samplings as outlined in Section 4.2 and Appendices IV & V.
- 3.13 Patients with adequate bone marrow function: WBC equal to or greater than 3,000/mcl; platelets equal to or greater than 100,000/mcl.
- 3.14 Patients with adequate renal function: creatinine equal to or less than 2.0 mg%.
- 3.15 Patients with adequate hepatic function: bilirubin and SGOT equal to or less than 2 x normal.
- 3.16 Patients who have met the pre-entry requirements specified in Section 7.0.
- 3.17 Patients who have signed an approved informed consent.
- 3.18 Patients with GOG Performance Grade of 0, 1, 2, or 3.

3.2 Ineligible

- 3.21 Patients with recurrent, invasive carcinoma of the uterine cervix regardless of previous treatment, or cancers other than squamous cell, adenosquamous, or adenocarcinoma.
- 3.22 Patients who cannot be or have not been adequately clinically staged.
- 3.23 Patients who for any reason have previously been treated with pelvic irradiation or have received cytotoxic chemotherapy.
- 3.24 Patients with septicemia or severe infection.
- 3.25 Patients with circumstances that will not permit completion of the study or required follow-up.
- 3.26 Patients with GOG Performance Grade of 4.
- 3.27 Patients with past or concomitant malignancy other than skin (excluding melanoma).
- 3.28 Patients who have not had surgical exploration as outlined in Section 4.2.
- 3.29 Patients who are pregnant.

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4.0 STUDY MODALITIES

All eligible patients with invasive squamous cell, adenocarcinoma, or adenosquamous carcinoma of the cervix, Stages II-B, III-A, III-B, and IV-A will undergo clinical staging as permitted by the FIGO rules (Appendix III). All patients will undergo surgical staging to include extraperitoneal sampling of the para-aortic lymph nodes. (Appendices IV & V)

All patients with cancer confined to the pelvis will receive pelvic irradiation and will be randomly assigned to receive either hydroxyurea or hydroxyurea, 5-FU infusion and bolus cisplatin, or weekly cisplatin. Patients with disease outside the pelvis are not eligible for this protocol. They may be eligible for other GOG protocols.

4.1 Preoperative Clinical Staging - Standard Clinical Staging

Patients will have a chest x-ray and an intravenous pyelogram prior to therapy. Pelvic examination will be performed under anesthesia as permitted under FIGO rules to determine the clinical stage of their cancer (Appendix III). An abdominal pelvic CAT scan with intravenous contrast may be used in place of the intravenous pyelogram.

4.2 Surgical Procedures - Para-Aortic Lymphadenectomy

Must be accomplished by an extraperitoneal approach. See Appendices IV & V for content of procedure. (Pelvic lymphadenectomy is not a requirement of this protocol.)

4.3 Radiotherapy Procedures

Radiation therapy must be started within 6 weeks post surgery. The radiation therapy is the same for all regimens.

4.31 Radiotherapy for Stage II-B

4.311 External Irradiation

Patients with Stage II-B lesions will receive 4080 cGy external beam therapy delivered homogeneously to the pelvis in 24 fractions 170 cGy/x. This may not complete external beam radiation. See Section 4.312, parametrial boost.

4.312 Intracavitary Therapy

Following the completion of external beam therapy, the patient will receive 4000 cGy to Point "A" by intracavitary implant with radium or its equivalent. The patient may receive this in one or two applications at the discretion of the radiation therapist.

The first insertion shall not be sooner than one week following external beam therapy and no later than three weeks. If two implants are contemplated, the second implant should commence not later than two weeks after completion of the first.

Patients will receive a minimum dosage of 5500 cGy total at point B by both modalities. A parametrial boost may be utilized to accomplish this.

The total elapsed time for completion of external and intracavitary therapy shall not exceed ten weeks.

4.32 Radiotherapy for Stages III-A, III-B, IV-A

4.321 External Irradiation

Patients staged as having Stage III-A, III-B and IV-A disease will receive 5100 cGy delivered homogeneously to the pelvis in 30 fractions (170 cGy/fx). The whole pelvis should receive no more than 5100 cGy.

If no intracavitary brachytherapy is planned, the patient must receive 6120 cGy of external teletherapy delivered to the described tumor with adequate margins.

4.322 Intracavitary Therapy

Following the completion of external beam therapy, the patient should receive intracavitary therapy.

If the patient received, or is to receive, 5100 cGy external pelvic teletherapy and an intracavitary implant is contemplated, the dosage will be 3000 cGy to Point "A" from the intracavitary source.

The first insertion shall not be sooner than one week following external beam therapy and no later than three weeks. If two implants are contemplated, the second implant should commence not later than two weeks after completion of the first.

Point "B" shall receive a minimum dosage of 6000 cGy total by both modalities. A parametrial boost may be utilized to accomplish this.

The total elapsed time for completion of external and intracavitary therapy shall not exceed ten weeks.

4.33 Dose Distribution

The patient should be treated with a four field box technique. AP-PA parallel opposed fields may be used. Dose distribution across treatment volume should not vary more than 5% from recommended dose.

4.34 Radiation Sources

Radiation sources employed in these clinical trials will be x-ray generators which produce x-ray beams with a photon energy of 4 MeV or more. Radiation output of the unit must be adequate to permit employment of a TSD, SAD or SSD of 100 cm or more.

Simulator localization films and verification films taken on the treatment machine will be necessary in all cases. Standard 3 1/2"x 4" polaroid pictures of all treatment portals with the patient in the treatment position are recommended.

Intracavitary radiation may be delivered by radium, cesium, or cobalt sources in standard or commonly used applicators provided that acceptable dosimetry can be determined. Interstitial therapy is not acceptable for this protocol.

4.35 The volume irradiated will include the totality of the obvious disease, the whole uterus, paracervical, parametrial, and uterosacral regions as well as the areas of the external iliac. The volume would have the following boundaries for the AP-PA fields:

Superior -- the upper margin of L5

Inferior -- the mid portion of the obturator foramen or the lowest extension of the disease with adequate margin (3 cm).

Lateral -- 1½-2 cm beyond the lateral margins of the bony pelvic wall at the widest plane of the pelvis (must be at least 7 cm from the midline in this plane).

Lateral Fields:

Superior -- same as AP-PA

Interior -- same as AP-PA

Anterior -- Anterior edge of symphysis pubis or 3 cm in front of sacral promontory.

Posterior -- S2-3 interspace (unless posterior extension of tumor requires more margin).

Blocks: customized cerrobend blocks may be used to protect the acetabulum, spare bone marrow, soft tissue, and bowel as long as tumor volume with adequate margin is treated.

- 4.36 Beam verification films will be obtained and submitted with the patient's records.

Orthogonal dosimetry films will be taken following the intracavitary insertion, and the films and calculations will be submitted to the GOG Statistical Office with the patient's records.

- 4.37 Radiation Therapy Quality Control and Documentation

The Radiologic Physics Center, under the sponsorship of the American Association of Physicists in Medicine, will supervise the dosimetry control for this clinical trial. To participate in the trial, the institution must demonstrate the ability to achieve an accuracy of +3% in measuring the output of their sources and +5% in delivering the prescribed dose.

- 4.4 Required Pathology Material and Data

Representative stained slides showing documentation of invasive cancer, as well as a slide for each additional positive site and a dictated pathology report from the participating institution. The pathologists must specify type and pattern of invasion, location of lesion, greatest depth of invasion (if available), and histologic grade and type.

The surgeon must dictate, preferably in the introductory paragraph of the operative note, the measurements of the size of the lesion in two dimensions, location of the lesion, extension of the lesion into the parametrial areas, bladder, or rectum, clinical status of supraclavicular nodes.

Within the body of the operative note, the limits of the lymph node dissection should be carefully described as to their location.

- 4.5 Chemotherapy

- 4.51 Fluorouracil (5-Fluorouracil, 5-FU) NSC #19893

4.511 Formulation: 5-FU is available as a white crystalline powder and is supplied in 10 ml vials containing 500 mg of the drug.

4.512 Preparation: The drug is available in single use vials containing 500 mg of the drug.