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PROTOCOL GOG #123

A RANDOMIZED COMPARISON OF RADIATION THERAPY & ADJUVANT HYSTERECTOMY
VERSUS RADIATION THERAPY AND WEEKLY CISPLATIN AND ADJUVANT HYSTERECTOMY
IN PATIENTS WITH BULKY STAGE IB CARCINOMA OF THE CERVIX

(PHASE III)

(POINTS - 6)

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ENCLOSURE (7)

1.0 OBJECTIVES

- 1.1 To determine if weekly cisplatin infusion improves local regional control and survival when added to radiation therapy plus extrafascial hysterectomy.
- 1.2 To determine the relative toxicities of these two treatment arms.

2.0 BACKGROUND AND RATIONALE

Tumor volume is one of the most important prognostic factors in all human malignancies and certainly cervical carcinoma is no exception.[1] The clinical staging system used by the M.D. Anderson Hospital in Houston, Texas for cervical carcinoma, in fact, is based on the combination of extent of tumor spread and size of tumor.[2] Within each of the FIGO Stages of disease larger and more extensive tumors carry a higher failure rate and are more difficult to treat with whatever modality is used. In Stage IB cervical carcinoma larger or bulky tumors, including those described as "barrel shaped", are demonstrably more difficult to cure with primary surgical treatment.[3] The use of radiation therapy for Stage IB carcinoma of the cervix is generally effective but has a poorer track record in providing central disease control within the primary site itself. Thus there has developed considerable literature supporting the concept of adjuvant hysterectomy after radiation therapy in large cervical carcinomas.[4] The role of this adjuvant hysterectomy approach is being tested in current GOG Protocol #71 in a randomized comparison with standard radiation therapy alone.[5]

Preliminary data from Protocol #71 indicates a fairly probable outcome of increased local control in the combined radiation/adjuvant hysterectomy treatment arm with uncertain effect on survival at this point.[5]

There is accumulating experience with the use of radiation in combination with cisplatin alone or cisplatin and other drug combinations. Current GOG Protocol #85 compares radiation plus Hydroxyurea vs. radiation plus cisplatin/5FU infusion therapy for locally advanced cervical carcinoma.[6] This protocol has demonstrated acceptable toxicity for this combination treatment approach and at least a suggestion of more rapid tumor response with uncertain effect on ultimate local tumor control. Another approach that has been used by a number of investigators at Roswell Park,[7] University of Minnesota,[8] and Albany Medical College,[9] includes the use of weekly cisplatin infusion with conventional fractionated radiation therapy in extensive disease. Again both published reports and unpublished experience have indicated good tolerance and response in patients with cervical carcinoma. GOG patients with positive para-aortic nodal metastases have experienced no relapses in either their pelvic disease or in the para-aortic areas.[9]

In this study we to compare the addition of weekly cisplatin infusion with the current apparent better arm of Protocol #71: radiation therapy plus adjuvant hysterectomy in patients with bulky Stage IB carcinoma of the cervix. The rationale for the use of cisplatin is the combination of its effect as the single most effective drug currently available for use in squamous cell carcinoma of the cervix and its demonstrated radiation sensitizing effect. The use of a weekly program during external and intracavitary radiation therapy should accentuate its radiation sensitizing effects and may be responsible for the high rate of local control seen in relatively small numbers of patients treated thus far.

4.3 Radiation Therapy Procedures

Radiation therapy should be started within two weeks of randomization.

4.31 Radiation therapy is identical in both regimens.

4.311 External Radiation

Patients will receive 4500 cGy external beam therapy delivered homogeneously to the pelvis in 4-5 weeks. (See Section 4.33 for dose distribution. Five day/week fractions of 180-200 cGy)

NOTE: If after 4500 cGy it is not possible to deliver adequate intracavitary treatment, external treatment may be continued up to a maximum of 5000 cGy in 5-6 weeks, then intracavitary treatment will be delivered.

4.312 Intracavitary Irradiation

Either one or two intracavitary applications may be used to deliver 3000 cGy to Point A using standard after loading applicators with stem and ovoids.

If the external treatment has been carried to 5000 cGy (see 4.311) the intracavitary application should be modified to deliver 2500 cGy.

NOTE: If the external treatment is carried to 4500 cGy, the intracavitary dose will be 3000 cGy Point A dose, in order to achieve the prescribed 7500 cGy Point A dose total (combined external and intracavitary treatment).

4.313 Completion of Treatment

If necessary to raise the Point B dose to the prescribed 5500 cGy total dose level, additional external radiation with central shielding should be given after the intracavitary applications in order to accomplish this.

NOTE: All radiation therapy must be completed within 10 weeks of its initiation.

4.32 Dose distribution for both regimens: a four field pelvic block technique with opposing anterior and posterior and two opposing lateral fields will be used. Dose distribution across the treatment volume should not vary by more than 5% from the recommended dose. All fields must be treated each day.