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PROTOCOL SUMMARY

Title: NSABP R-03, "A Clinical Trial to Determine the Worth of Preoperative Multimodality Therapy (5FU-Leucovorin and Radiation Therapy) in Patients with Operable Carcinoma of the Rectum."

Principal Investigator: [redacted], Major, USAF, MC

Facility: Keesler Medical Center

1. Summary: The proposed multi-group study will evaluate the relative efficacy of two treatment regimens in patients with operable carcinoma of the rectum. Recent data published from cooperative group trials have shown that the use of adjuvant chemotherapy and radiation has altered the natural history of patients with Duke's B and C carcinoma of the rectum. It remains to be determined whether chemotherapy and radiation therapy given prior to surgery may be more optimal than chemotherapy and radiation therapy given after surgery.

The objectives of this study are to determine whether the administration of chemotherapy (5-FU/Leucovorin) with radiotherapy preoperatively is more effective than the administration of chemotherapy and radiotherapy postoperatively in improving disease-free survival and survival in patients with operable carcinoma of the rectum.

Also, the protocol will try to determine if the administration of the above chemotherapy and radiotherapy preoperatively results in improvement in local recurrence rates when compared with the regimen administered postoperatively in this population of patients.

In addition, patients will be followed closely to determine the toxicities which may be associated with each regimen.

2. Technical Approach: Patients age 18 years and older who have biopsy proven carcinoma of the rectum will be considered eligible for entry into this study. The tumor should be either palpable by clinical rectal exam or be accessible via proctoscope or sigmoidoscope, and its distal border should be located no more than 15 cm from the anal verge. The tumor should be movable on clinical examination without evidence of fixation to the pelvis or to surrounding organs, i.e., vagina, prostate, bladder, or beyond the limits of resection via exenteration.

The patients must have no radiologic evidence of metastatic disease as seen on a CT of the abdomen and pelvis prior to entry into the study.

Patients will be randomized to one of two treatment arms. Group I will consist of preoperative and postoperative 5-FU/leucovorin and preoperative radiotherapy. The chemotherapy should begin no

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later than 3 weeks after randomization. In Cycle I, leucovorin, 500 mg/m2, will be administered by i.v. infusion over 2 hours; 5-FU, 500 mg/m2, will be given by i.v. bolus one hour after beginning leucovorin infusion. Treatment will be given weekly for 6 weeks (on days 1, 8, 15, 22, 29 and 36), followed by a rest period. Treatment will be restarted 21 days after the day of administration of the 6th dose of the previous cycle (1 cycle = 8 weeks). Radiotherapy will begin after completion of cycle 1. Since radiotherapy should start on a Monday, the rest period after cycle 1 may vary from 20 to 26 days, based on the day of the week on which the last dose of cycle 1 was administered. 5-FU, 325 mg/m2, per day and leucovorin, 20 mg/m2, per day will be given for 5 days during the first and fifth weeks of radiotherapy (cycles 2 and 3). Surgery will be performed after completion of the radiation therapy, once any toxicity has resolved, but no later than 8 weeks after completion of radiotherapy. After recovery from surgery, but no later than 4 weeks, 4 more cycles of 5-FU with leucovorin will be given as in cycle 1 for a total of 7 cycles.

The radiation will be given at a dose of 4500 cGy for 25 fractions to the pelvis. A small volume excluding the small bowel, will then be treated with an additional 540 cGy for three fractions to give a total dose of 5040 cGy over 28 fractions. The radiation will be administered 5 days a week in a continuous course.

Treatment Arm II will consist of surgery which should be performed no later than 3 weeks after randomization. Chemotherapy will begin after recovery from surgery is complete, but no later than 4 weeks postoperatively. Both the chemotherapy and radiotherapy will be identical as treatment on Arm I, however, since surgery was done prior to treatment, no break will be required after radiotherapy is completed. Cycles 2 and 3 chemotherapy will be given during the first and fifth weeks of radiotherapy. Cycle 4 of 5-FU/leucovorin will be given after completion of the radiotherapy when counts allow, but no later than 5 weeks. Four more cycles of 5-FU/leucovorin will be given as in cycle 1 for a total of seven cycles. The radiotherapy will be identical to that given in treatment arm I.

3. **Equipment and Supplies:** Conventional laboratory and clinical equipment will be furnished by the medical center. 5-FU and leucovorin are commercially available and will be furnished by Keesler Medical Center. Radiation therapy will be given by Keesler Medical Center.

4. **Investigational Schedule:** This study will be available for patient accrual following approval by the IRB and signature of the Commander. The study anticipates enrolling approximately 900 patients nationally over five years.

5. **Experimental Subjects:** All subjects will be treated in compliance with AFR 169-6 and applicable FDA and HHS guidelines.

6. **Investigational Drugs/Devices:** There are no investigational drugs used in this protocol.

7. **Personnel Data:**

a. Medical Center Commander

[redacted], Colonel, USAF, MC

b. Principal Investigator

[redacted], Major, USAF, MC
Staff, Hematology/Oncology

c. Associate Investigators

[redacted], Major, USAF, MC
Chief, Hematology/Oncology

[redacted],,Major, USAF, MC
Staff, Hematology/Oncology

8. Manpower: Total manpower expended will be determined by the number of patients accrued.

No.	Grade	AFSC	Hours/Pt/Month
3	Major	9386H	4
1	Data Manager, GS-8	9825	6
1	Secretary, GS-5	90670	2/Year

9. Bibliography: The bibliography for this study is cited on pages 57 to 60 of the protocol.