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BRIEF REPORT
Treatment of Colorectal Carcinoma in Adolescents and Young Adults With Surgery, 5-Fluorouracil/Leucovorin/Interferon-α2a and Radiation Therapy

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Colorectal carcinoma in adolescents is rare, with an accrual incidence of approximately 2 in 1,000,000 individuals under the age of 20 years in the United States [1]. Most cases in adolescents are diagnosed late, after development of metastatic disease [2,3]. The index of suspicion for this diagnosis is low, leading to long delays in diagnosis, except in the presence of rupture of the tumor into the peritoneal cavity. The symptoms of this cancer are generally vague, and include abdominal pain, constipation, diarrhea, hematochezia, and weight loss. In adolescents, histology of these tumors is generally that of a mucinous adenocarcinoma, rather than the classic adenocarcinoma [4]. Seventy-five percent of tumors of adolescents are mucinous, compared to 14% for adults [4]. Thus, histology may play an important factor in prognosis, along with extent of disease at the time of diagnosis [5].

DISCUSSION

Chemotherapy for metastatic colorectal carcinoma became possible after the demonstration of the antitumor activity of fluorouracil more than 40 years ago [5]. Since that time, fluorouracil has become the major agent used in the treatment of stage IV metastatic disease, or in the adjuvant setting for stage III disease [5].

Patients with American Joint Commission on Cancer stage III or IV colorectal carcinoma were enrolled in a protocol after diagnosis and attempt at local control. Planned chemotherapy consisted of monthly courses of the following: week 1, leucovorin 400 mg/m^2 IV over 4 hr, days 1–5; fluorouracil 400 mg/m^2, given over 15 min beginning 1 hr into the leucovorin infusion, days 1–5; interferon-α2a 30 MU/m^2 subcutaneously, days 1–3; week 2, repeat interferon-α2a; week 3, repeat interferon-α2a; and week 4, rest.

Chemotherapy was to be given for 8 months or until evidence of disease progression. For patients with primary unresectable tumors of the rectum or recto-sigmoid at diagnosis, we planned to deliver preoperatively 5,040 cGy over 6 weeks (n = 3). A similar dose was delivered if earlier resection had been performed for primary tumors (one patient). Patients with primary tumors at other sites were not eligible for radiation therapy.

Standard gradings of response were used and toxicity was quantitated by the Common Toxicity Criteria of the National Cancer Institute. Survival distributions were estimated using the method of Kaplan and Meier.

Thirteen patients aged 11.8 to 23.1 years (median, 17.0 years) were treated by this protocol. Seven were males; 11 were Caucasian. Primary sites were throughout the large bowel. Two patients, aged 22.9 and 23.1 years, had received prior treatment at our institution for metastatic osteosarcomas 4 and 7 years, respectively, prior to

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their development of ascending colon and rectal carcinoma. Nine patients had the mucious adenocarcinoma histology.

One of three patients with stage III disease completed eight courses of chemotherapy, the other two having developed progressive tumor at 5 and 8 months. Among patients with stage IV disease at diagnosis, one had a partial response, three were nonevaluable, four had stable disease, and two had no responses.

None of these individuals had known adenomatous polyposis. Both individuals with prior osteosarcoma were tested for p53 quantitative abnormalities when they developed colon or rectal carcinoma, and both were found to have abnormalities in exon 5.

Seventy-four courses of this chemotherapy were delivered; median number of courses delivered was six (range, 1–8). Grade 3–4 toxicities following treatment included mucositis, nausea, vomiting, diarrhea, and fever/rigor. In general, second and subsequent courses of chemotherapy were better tolerated in relation to mucositis and hyperpyrexia following interferon-α2a. In eight patients, interferon dosage was reduced; for two patients, it was eventually discontinued.

One of three patients with stage III tumor survives 6.3 years postdiagnosis of rectal carcinoma, but with a third malignant neoplasm, osteosarcoma. The other two stage III patients died, respectively, of metastatic colon carcinoma and recurrent metastatic osteosarcoma at 0.8 and 1.2 years after diagnosis of colorectal carcinoma. Two patients with stage IV tumor survived; one has been free of disease for more than 3 years, and one is living with active tumor. The estimated 2-year survival for the entire group was 26.4% ± 11.3% (Fig. 1). Thus, the requirement is for greater treatment intensity, with chemotherapy ± radiation therapy.

The majority of patients in our cohort, 9 of 13 (67%), had mucinous adenocarcinoma. Three of 13 were initially staged as having stage III disease, and 10 had stage IV disease, indicating that most patients had high-risk features. Overall survival remains poor for adolescents with stage III and IV colorectal carcinoma. Similarly, survival duration following diagnosis is short for these patients. The median time from diagnosis of colorectal carcinoma to death was 11 months (range, 5–33 months).

In the present group of 13 patients, 4 patients received radiation therapy, 3 prior to attempted resection and 1 following successful resection. Only the latter patient survives free of carcinoma and is currently receiving chemotherapy for his second osteosarcoma (of the ilium), which crosses the sacroiliac joint. For the other three patients, resection was possible for two who had no evidence of viable tumor; resection was not possible for the third, who died with active tumor 2.7 years from diagnosis.

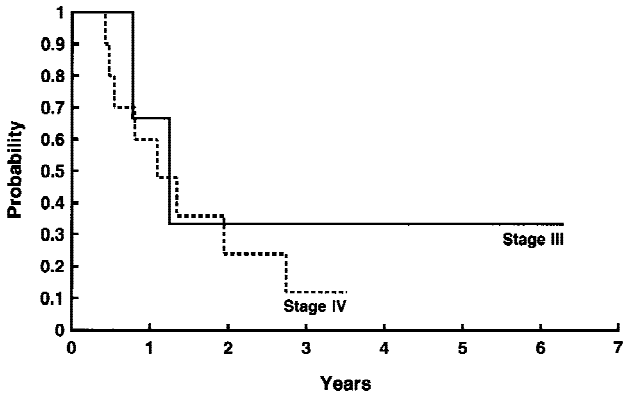

Fig. 1. Survival, by stage, of young patients with colorectal carcinoma

Fluorouracil and leucovorin have become the main agents that are used for the treatment of colorectal carcinoma [6,7]. α-Interferon added significantly to the toxicity experienced by our patients. It is for these reasons that additional chemotherapy trials at our institution are planned for newly diagnosed young patients with stage III and IV colorectal carcinoma with a combination of fluorouracil/leucovorin and irinotecan.

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