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Editorial

5-Fluorouracil as Adjuvant Chemotherapy for Large Bowel Cancer Is it Appropriate for Routine Community Use?

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Adjuvant systemic treatment in large-bowel cancer is designed to increase the cure rates after curative-intent surgical resection. Past experience has clearly indicated that the prognosis for cure after surgery diminishes significantly as tumor penetrates through the entire bowel and involves the regional lymph nodes [1]. Experience has also shown that the relapse pattern in colon lesions is predominantly metastatic. The assumption currently accepted is that microscopic foci of metastatic disease exist in the liver, lungs, bones, etc. at the time of diagnosis. If these foci are to be eradicated a systemic modality is required. The two modalities employed to date to this end have been cytotoxic chemotherapy and immunotherapy.

The Veterans Administration Surgical Adjuvant Group (VASAG) has studied 1,181 patients in adjuvant 5-fluorouracil (5-Fu) trials [5–7]. These patients have been treated according to two protocols, which actually represent five separate therapeutic trials. The first trial involved all patients *not* diagnosed preoperatively by sigmoidoscopic biopsy with resectable adenocarcinoma of the colon. These patients, with a positive sigmoidoscopic biopsy diagnosis, were entered into a preoperative radiation trial. Following surgery, three groups were elucidated: A. Curative resection with no evidence of residual metastases or tumor at the resected margin; B. Histologic proof that residual tumor was left behind, either by biopsy or by the finding of tumor at the cut margins of the resected specimen; C. Clinical evidence of residual tumor not proven histologically. Each group was randomized to receive 5-day courses of 5-FU or not. Groups A and C received two courses, the first within 2 weeks of surgery and the second 7 weeks later. Group B received the same plus repeated courses at 6- to 8-week intervals until either there was evidence of progression or the patient expired. In each of the three groups survival favors 5-FU but in no case are the differences statistically significant (Table 1).

Table 1. Survival in two VASAG 5-FU trials

Trial	Follow-up	% Survival	
		5-FU	Control
I. Curative resection			
5-FU (2 courses)	5 years	58.2	48.0
PIT	5 years	49.1	44.7
II. Proved palliative resection			
5-FU (repeated courses)	18 months	35.7	16.7
PIT	18 months	37.7	26.8

The second study, which is called the prolonged intermittent therapy (PIT) trial, involved all large-bowel cancer patients, including rectal cancer cases not included in the prior protocol. Only those patients were included in whom pathologic study of the removed specimen suggested a high possibility of postoperative recurrence. The unfavorable signs used were: (1) presence of positive lymph nodes, (2) serosal involvement or invasion of perirectal fat, (3) blood vessel or lymphatic invasion, and (4) involvement of an organ other than the colon. This would include B_2 and C lesions in the Astler-Collar modification of the Dukes classification. This study only had two subsets in it, which were the A and B groups of the first trial. All patients randomized to 5-FU received repeated courses at 6- to 8-week intervals, with the identical dose schedule used in the first trial. In this trial again survival favors 5-FU but does not reach the traditional level of statistical significance (Table 1). Nor does the Mantel-Haenzel or log-rank test of differences between two survival curves reveal any statistical benefit in any of the five subgroups of the two trials. If all the subgroups are lumped together then the log-rank test is positive for a 5-FU benefit at a P value < 0.05. The VASAG and others interpret this as demonstrating that adjuvant 5-FU is valuable, albeit not dramatically so. What is not considered is what degree of biologic

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significance can be attached to the statistical manipulations performed when several nonsignificant differences are lumped together. A P value determination is only a statistical or mathematical manipulation. The biologic significance of this calculation assumes comparability of all factors save the treatments under study. Prospective randomization is meant to insure this comparability. The VASAG has taken heterogeneous or noncomparable groups and lumped them so that the numbers become large enough to make the P value come out at < 0.05. This may not imply that a truly meaningful biologic difference has been demonstrated against the risk of toxicity and the psycosocial and economic cost. In my own opinion, the VASAG has not proved that adjuvant 5-FU should now be routinely recommended. For those who might deem these studies as positive, it should be remembered that only two courses of drug in the first study were as positive as multiple courses in the PIT trial for curative resection cases.

In their current study, which began in 1973, the VA group is following the same experimental design, but the chemotherapy is a combination of methyl CCNU + 5-FU. The drugs are administered in 5-day courses, beginning as soon after surgery as the patient's condition permits (about 10—14 days after operation), and repeated at 7-week intervals for 1 year. On the first day, oral methyl CCNU is given in a dose based on 120 mg/m^2 and on the same day and each of the next 4 days, 5-FU is given in a dose of 9 mg/kg IV.

The Central Oncology Group undertook a study that also attempted to determine the effect of long-term adjuvant chemotherapy with 5-FU on the rate of recurrence, time of recurrence, and survival in selected patients treated surgically for carcinoma of the colon and rectum. As in the VA study, there were two treatment groups (i.e., a curative resection group with poor prognosis for cure and a palliative resection group). The COG defined these groups in a similar way to the VA groups. The chemotherapy differed in that 5-FU was given in a single intensive course within 1 month of surgical resection and was followed by weekly maintenance therapy for 1 year.

The results have been reported for 175 patients who had either a curative or a palliative resection and were followed up for 6 months to 3 years [3]. In the curative resection group 77% (49/64) were alive and free of disease after treatment with 5-FU, as against 67% (42/63) in the control group. After palliative resection 39% (9/23) in the treatment group were alive and free of symptoms, against 25% (6/24) in the control group. The median survival after palliative resection was 46 weeks for the treated group vs 61 weeks for the control. None of these differences was significant at the time.

A cooperative study headed by Dr. L. M. Rousselot, of St. Vincent's Hospital in New York, included several hospitals in the New York City area. Their study compared 5-year survival rates obtained with intraluminal of 5-FU and with 5-FU given IV at the time of surgery and thereafter. This study is based on Rousselot's data showing that 5-FU (30 mg/kg in 50 ml intraluminally) at surgery plus 10 mg/kg IV for 2 days thereafter gave a 74% 5-year survival in 60 patients with stage I and II disease and 65% 5-year survival for 21 patients with stage III disease.

Another study evaluating adjuvant 5-FU after curative resection has been reported by the group at Nassau Hospital in Mineola, New York [9]. This group reported on 88 patients (48 stage II and 40 stage III — staging system not defined). Starting 4—6 weeks after surgery, two courses (500 mg/day × 5 IV in each course) of 5-FU were given with a 3-week interval between, on an ambulatory basis. Eighty-six patients (49 stage II and 37 stage III) operated on between 1960 and 1965 were used as an historical control group. Five-year survival with no evidence of disease (NED) was 69.4% in the chemotherapy group, compared with 45.1% in the control patients. For stage III disease, the 5-year NED rate was 27% for the control and 63.3% for the treated group. While the differences are statistically significant, the use of an historical control makes one cautious about ascribing biologic significance to the data. The drug toxicity was described as minimal and short-lasting, but the effects were not cited in detail.

In total, there are six randomized studies of fluorinated pyrimidines as adjuvant chemotherapy in colorectal cancer, and none has been positive (Table 2).

Mavligit [10] and his co-workers initiated a trial of adjuvant BCG for colon cancer in 1973 and compared the results obtained in one group receiving BCG alone with those recorded in another group receiving a combination of 5-FU and BCG. No difference was noted between these groups in terms of either disease-free interval or survival of patients, but both groups had better survival statistics than a group of historical control patients from the same institution, who were treated by surgical resection alone. Unfortunately, these data are not convincing, despite the fact that the profiles of the patients in the historical control group are quite similar to the more recent experimental groups. Actually, there are no randomized trials of BCG adjuvant therapy that have demonstrated significant benefit in any human cancer thus far. Well-planned clinical trials demonstrating benefit are certainly required before this approach can be recommended for general use.

Adjuvant chemotherapy is conceptually attractive to the practicing physician involved in therapy of large-bowel cancer. Although surgical resection produces long-term control of these tumors in many instances, the overall results for patients with Dukes B and C lesions leave considerable room for improvement in terms of

Table 2. Randomized trials of adjuvant chemotherapy for colorectal cancer

Author	Regimen	No. of patients	Comparative survival
Higgins et al. (1971) [5–7]	5-FU IV 2 weeks and 8–10 weeks postoperatively vs no Rx	308	No significant difference
Higgins et al. (1976) [5–7]	5-FU IV q 6 weeks for 1½ years va Rx	552	No significant difference
Dwight et al. (1973) [2]	FUDR IV and PO vs no Rx	548	No significant difference
Lawrence et al. (1975, 1978) [8]	5-FU intraluminal + q 2 months PO for 1 year vs no Rx	203	No significant difference
Grage et al. (1977) [3]	5-FU IV weekly for 1 year vs no Rx	189	No significant difference
Grossi et al. (1977) [4]	5-FU (intraluminal) vs no Rx	487	No significant difference

end results. As drug treatment of recurrent large-bowel cancer after surgery offers only slight palliation potential, it is tempting for the practicing physician to want to do something immediately after surgery to diminish the possibility of recurrence. While the rationale for doing this in a clinical research setting exists, it cannot be recommended for routine practice use. This can be reflected in the design of most adjuvant trials for this disease. These trials include a 'control' arm of surgery only as the current standard of optimal care. This control arm is not only appropriate, but in my opinion essential, to a well-designed trial. What this means is that it is ethically permissible, within this clinical research setting, to not give adjuvant chemotherapy, since its value is not established. The activitist mode is highly attractive to physicians. Emotionally, most of us would rather give something after surgery, in hopes of improving the results we know we can achieve with surgery only. When taken down to the patient level, however, it must be recognized that two possibilities exist. The first possibility is that the surgery has achieved total tumor eradication. In this situation, the patient will be receiving drug unnecessarily. There is risk with no possible benefit. We design adjuvant trials in such a way that the majority of patients in the sample to be studied will not be cured by surgery only. For any individual patient, it is just either yes or no. The second possibility is that the surgery is not curative and clinical relapse can ultimately be expected if no further therapy is administered. Within this subgroup, two possibilities again exist. The first is that adjuvant chemotherapy will not be effective. Again, therefore, there is risk without benefit. The second possibility is that adjuvant drugs will eradicate residual microscopic disease and that cure will be achieved. In this situation, too, a cost-benefit analysis must be made in terms of acute and chronic toxicity factors.

What this means is that when faced with an individual patient, we must recognize the possibility of harm with adjuvant chemotherapy without benefit. Without a clinical research experience proving that adjuvant chemotherapy improves the survival at an acceptable toxic cost, such a decision for the next patient is based on tenuous logic at best. Even if we had a definitively positive trial, which we do not, we would still have to recognize that we would only be playing the odds with each individual patient we evaluated.

Conclusion

At this time, adjuvant chemotherapy cannot be recommended as routine treatment for curative-resection large-bowel cancer with a high potential for metastatic relapse. 5-FU has been extensively evaluated and has made no significant impact on survival. No properly designed prospectively randomized trial of 5-FU adjuvant treatment has shown statistically significant benefit. The possibility that combination chemotherapy will prove beneficial remains. Several major protocols are on-going and remain to be analyzed. Since these combinations are potentially toxic, they should not be used prematurely by the practicing oncologist.

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