Adjuvant Chemotherapy of Colorectal Cancer

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ABSTRACT
Advances have been made in the adjuvant therapy of colorectal cancers. Fluorouracil-based chemotherapy has now been demonstrated to improve long-term disease-free survival rates in patients with resected stage III colon cancer. Combined radiation therapy plus fluorouracil-based chemotherapy has been shown to improve both local control and disease-free survival in patients with stage II and III rectal cancer. In this article we will review in detail the current recommendations for treatment of patients with resected colorectal cancers and the data on which these recommendations are based. We will also review some of the more promising investigational approaches which are being pursued in an attempt to further improve the cure rates in patients with local-regionally advanced colorectal cancers. Results from these investigations can be expected to further clarify the role of both currently available and new treatment strategies, and to improve the long-term outlook for patients with resectable colorectal cancers. The Oncologist 1996;1:22-29

INTRODUCTION
Colorectal cancer is a common malignancy in most of the developed countries of the world, with over 155,000 new cases expected annually in the United States alone [1]. While many patients will present with unresectable and, therefore, incurable disease, the majority of patients will be fully resectable at the time of first presentation [2], and hence may be appropriate for consideration of adjuvant therapy. Decisions regarding adjuvant therapy must be based on a number of considerations, including the patient’s risk for recurrence, the effectiveness of available therapies in reducing that risk and the potential complications of therapy. In this review, we will examine the evidence supporting the use of currently available adjuvant treatments, and will review the current indications for these treatments. Recognizing that these treatments are far from satisfactory, we will also examine some of the more promising areas of investigation being pursued in the area of adjuvant therapy for colorectal cancer.

COLON CANCER
The most important prognostic factor in anticipating the risk of recurrence is the stage of the tumor at the time of resection [3, 4]. Tumors which do not penetrate the full thickness of the bowel wall and which have not spread to local regional lymph nodes (T<sub>1</sub>-N<sub>0</sub>M<sub>0</sub>, modified Astler-Coller Dukes stages A and B<sub>1</sub>) typically have in excess of a 90% cure rate with surgery alone [4], and postoperative therapy is not routinely recommended. It is in the higher-risk tumors with either full thickness penetration of the bowel wall (T<sub>3</sub>-N<sub>0</sub>M<sub>0</sub>, modified Astler-Coller Dukes B<sub>2</sub>-<sub>3</sub>, stage II) and/or local regional lymph node involvement (T<sub>any</sub>N<sub>1</sub>-<sub>2</sub>M<sub>0</sub>, modified Astler-Coller Dukes C, stage III) that the risk of recurrent disease increases, and adjuvant therapy is potentially indicated.

Trials of adjuvant therapy following resection of colon carcinomas date back almost 40 years. In the earliest trials, nitrogen mustard or other alkylating agents were administered either during or shortly after surgery [5]. Subsequently, with the demonstration of activity of fluorinated pyrimidines in metastatic disease, efforts were concentrated on exploration of these agents in the adjuvant setting. Results were disappointing; however, inadequate doses and scheduling were usually employed [6-8].

Levamisole is an agent which has been used as an anthelmintic in animals for many years. Preliminary evidence suggested that levamisole had immunostimulatory properties [9, 10], thus its investigation as an anticancer
agent. Based on some encouraging preliminary data [11] the North Central Cancer Treatment Group (NCCTG) conducted a three-arm study which randomly assigned Dukes B and C patients to either surgery alone, surgery followed by levamisole, or surgery followed by fluorouracil (FU) plus levamisole [12]. Encouraging results from this adjuvant trial led to a confirmatory intergroup trial [13, 14], the results of which are summarized in Table 1.

The intergroup confirmatory trial provides the largest sample size and, therefore, the most reliable data on which to base treatment recommendations. A total of 929 eligible patients with node-positive (Dukes C) disease were entered and have now been followed for a minimum of five years (median 6.5 years). Of the patients treated with surgery alone, 44% remained alive and disease-free at five years, as compared to 61% of patients who received FU and levamisole. This difference was highly statistically significant ($p < 0.0001$). There is also substantial clinical significance as well. This 17% difference between disease-free survival rates represents a 39% reduction in mortality. When considering the frequency of stage III (node-positive) colon cancer, with approximately 30,000 cases expected in the United States annually, a potential savings of almost 6,000 lives per year would be realized through the application of this therapy. This treatment schedule, which is outlined in Table 2, is currently recommended as standard therapy for stage III colon cancer [15].

The issue of adjuvant treatment for stage II disease (Dukes B) is less well-defined. Data from the randomized levamisole/FU trial [13] failed to show a statistically significant benefit for treatment of this patient population. Certain prognostic factors, however, have been correlated with higher risk for recurrence in these patients. These factors include obstruction of the bowel lumen by tumor and/or perforation of the bowel wall by tumor [16]. Other less well-established risk factors include poorly differentiated histology, high S-phase fraction and elevated preoperative carcinoembryonic antigen. Patients with full thickness tumors and one or more of these risk factors are at higher risk for recurrence; however, the usefulness of adjuvant therapy in these high-risk Dukes B2 patients has not been clearly defined.

The mechanism by which levamisole contributes to the adjuvant treatment of colon cancer is the subject of much debate. While preliminary data suggested that levamisole functions as an immunostimulant, data to suggest that there is an effect on the immune system at the levels which are achieved clinically have not been consistently demonstrated [17, 18]. Some investigators have suggested that levamisole may inhibit intracellular phosphatases which are involved in the degradation of FU, thereby potentiating the effect of FU [19]. However, this effect also is not demonstrable at the concentrations typically achieved clinically [20]. Recent evidence that levamisole stimulates the expression of major histocompatibility complex (MHC) class 1 antigens on the surface of a colon cancer cell line [21], thereby making the cells more vulnerable to immune surveillance, are intriguing. However, this phenomenon has only been reported in vitro and on only one cell line. Furthermore, even if the increase in MHC class 1 antigen expression were to be a widespread in vivo phenomenon, the assumption that this would, in fact, lead to clinically significant improved immune function is purely conjectural at this time [18]. In short, we don’t know just how levamisole works in this regimen. Indeed, many investigators have speculated that perhaps levamisole might not be active at all [22], and that the regimen used represents the results of the first large-scale trials with adequate numbers of patients to detect modest differences and adequate dose-intensity of FU to achieve a clinical benefit. At present these questions remain unanswered.

**INVESTIGATIONAL APPROACHES**

While the issue of how levamisole works remains unsolved, investigators are proceeding with studies which will hopefully move the state of the art forward and thus diminish the importance of levamisole. The National Surgical Adjuvant Breast and Bowel Project (NSABP) C0-3 study, which compared FU and leucovorin to the MOF regimen (methyl-CCNU, vincristine, FU), found superior

<table>
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<tr>
<th>Postoperative Treatment</th>
<th># Patients</th>
<th>Five-year Disease-Free Survival</th>
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<tr>
<td>Observation</td>
<td>315</td>
<td>44%</td>
</tr>
<tr>
<td>Levamisole</td>
<td>310</td>
<td>45%</td>
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<tr>
<td>Levamisole plus FU</td>
<td>304</td>
<td>61%</td>
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Table 2. Currently recommended standard adjuvant therapy for stage III colon cancer [14, 15]

1. Postoperative day 21-35: Begin levamisole 50 mg orally three times daily for three consecutive days, repeated every two weeks for one year.

2. Postoperative day 21-35: FU 450 mg/m²/day by rapid intravenous injection for five consecutive days beginning simultaneously with levamisole.

3. Twenty-eight days after the start of chemotherapy, begin weekly FU 450 mg/m² by rapid intravenous injection for 48 weeks.
long-term disease-free survival for patients treated on the FU plus leucovorin arm [23]. Currently a four-arm trial has completed accrual through the intergroup mechanism. In this study, patients were stratified for stage (Dukes C and high-risk B) and randomized to receive either the standard FU/levamisole regimen, or FU plus high-dose leucovorin, FU plus low-dose leucovorin, or FU plus low-dose leucovorin and levamisole. When these data mature, the standard of care may have to be re-evaluated.

Other investigators are exploring a number of different approaches to adjuvant therapy of colon cancer. Some of the more interesting of these will be reviewed below.

**PORTAL VEIN INFUSION**

The liver is the most common site of metastatic disease in colorectal cancer patients [2-4, 24], with up to half of all fully resected patients who relapse presenting with liver metastases as the first site of failure. It has been recognized for quite some time that tumor cells commonly gain access to the liver via IP lymphatics and venules which empty into the portal vein [25, 26]. Intraportal chemotherapy is thus a logical strategy for attempting to optimize antitumor activity against these micrometastases. Furthermore, animal models have demonstrated that tumors in the 1 to 5 millimeter size range derive a substantial portion of their blood supply from both hepatic and portal circulations, whereas beyond the 5 millimeter size, the vessels become predominantly of hepatic arterial origin [27, 28]. Thus, in the early phase of development, liver metastases would be expected to be exposed to substantial concentrations of chemotherapy delivered by the intraportal route.

Preliminary studies demonstrated the feasibility of intraportal administration of FU, and confirmed that higher doses could be given by infusion intraportally rather than by the intravenous route, owing to the hepatic extraction (“first pass clearance”) of FU [29]. A preliminary report of a small randomized trial in 1979 [30] stimulated extensive interest in this approach, although a later follow up which included a larger number of patients appeared to show a benefit only for Dukes B patients [31].

A large randomized trial of intraportal adjuvant chemotherapy begun in 1981 by the Swiss Group for Clinical Cancer Research (SAKK) has been reported [32, 33]. Five hundred thirty-three patients received either surgery alone or surgery followed by a single intraportal 2 h infusion of mitomycin C (10 mg/m²) and a seven-day intraportal infusion of FU at a dose of 500 mg/m²/day. With a median follow up of eight years, five-year disease-free and overall survival were modestly superior in patients receiving intraportal treatment (57% versus 48% and 66% versus 55%, respectively). However, differences in the incidences of hepatic metastases were not statistically significant.

The NSABP C-02 trial [34] randomly assigned 1158 patients with Dukes A, B or C colon cancers to either no postoperative chemotherapy or a seven-day infusion of 600 milligrams of FU and 5,000 units of heparin per day by portal infusion of seven successive days. Although a modest survival advantage was again demonstrated for the treatment group (74% versus 64% disease-free survival at four years), there was again no difference in the incidence of hepatic metastases.

Although the majority of the studies evaluating adjuvant portal vein chemotherapy have shown a survival advantage over a no-treatment control group, the modest degree of benefit and the consistent failure to show a reduction in the incidence of hepatic metastases have led many to speculate that the clinical benefits derived may stem from the systemic activity of intraportally administered chemotherapy. It is noteworthy, however, that benefits obtained with brief (usually one week) intraportal therapies appear comparable to benefits derived from a year of adjuvant systemic therapy. Important information on this issue can be expected from the results of the second SAKK trial, which completed accrual in 1993. Patients in this three-arm trial were randomized to intraportal chemotherapy, intravenous chemotherapy or surgery alone. The data from this trial are not yet mature enough for analysis.

**INTRAPERITONEAL (IP) CHEMOTHERAPY**

Studies on the failure patterns in resected colorectal cancer patients, done both on the basis of clinical presentation of failure [4] and on the basis of planned second-look laparotomy [35, 36] have demonstrated a high frequency of hepatic and peritoneal metastases. Furthermore, as noted above, hematogenous metastases of colorectal cancer enter the liver via the portal circulation. Since the peritoneal cavity is drained via lymphatics into the portal vein, IP administration of antineoplastic agents would be expected to result in high portal vein drug concentrations. Indeed, direct measurements of drug levels by portal vein sampling during IP drug administration have confirmed this hypothesis [37, 38]. Thus, there is a two-fold rationale for pursuing IP chemotherapy in the postoperative setting. Such an approach delivers high concentrations to the peritoneal surface, thus attacking micrometastases in the peritoneal cavity, while at the same time delivering high intraportal concentrations of drug to potential early hepatic metastases.

Preliminary animal studies of IP FU yielded encouraging results [38]. In a rat model utilizing injection of colon carcinoma cells both intraportally and intraperitoneally, IP FU prevented macroscopic peritoneal tumor growth in 57% of the animals treated and yielded a 50% decrease in hepatic metastases compared to untreated controls. A third cohort of
rats treated with systemic FU had no reduction in peritoneal metastases, as compared to the untreated controls.

Fluorinated pyrimidines have a high first-pass clearance through the liver, making them favorable candidates for IP administration. Initial pharmacologic investigations of IP FU and fluorouridine demonstrated that IP concentrations 200- to 400-fold higher than were achievable by systemic administration could be obtained [37, 39].

A small randomized study comparing systemic versus IP chemotherapy in patients following resection of colon cancer has been reported [40]. This small study showed a striking decrease in the incidence of peritoneal metastases in the group receiving IP chemotherapy; however, no differences in overall survival or in the incidence of hepatic metastases were noted. A major flaw in the design of this trial was that initiation of therapy was permitted up to two full months after surgery. Earlier initiation of IP therapy might possibly have yielded greater efficacy.

More recently, a phase I trial explored the combination of immediate postoperative IP fluoruridine and leucovorin plus systemic levamisole and FU [41]. Patients received three days of IP therapy every other week for three cycles. Oral levamisole was started with the second IP cycle, and five days of bolus injections of FU were given starting with the beginning of the third IP cycle. On day 29 after the start of FU, weekly standard dose FU and q.o.w. levamisole were started and continued to complete one year of therapy. The regimen was well tolerated, with no resultant increase in perioperative morbidity. At a median follow up of 24 months, 24 of 28 patients were alive and free of disease. Further follow up, and large-scale comparative trials will be required to determine whether this approach is superior to systemic therapy alone; however, the preliminary results are encouraging.

**MONOCLONAL ANTIBODIES**

Monoclonal antibodies (mAb) have been used as anticancer agents in numerous clinical trials, usually with disappointing results. A possible explanation for the lack of success thus far in what would appear to be a promising antitumor approach is that the relatively large molecular size of these agents precludes efficient transport into solid tumor tissue [42]. Targeting of mAb against minimal residual disease could theoretically circumvent this problem. The postresection state is the optimal minimal residual disease scenario. Several investigators have therefore pursued the development of mAb therapies for application in the adjuvant setting in colon cancer patients.

Preliminary studies had demonstrated that mAb could be used to identify micrometastases in bone marrow specimens taken from colorectal cancer patients [43], and that the presence of these bone marrow metastases correlated with a poor prognostic outcome [44]. A murine monoclonal IgG2a antibody directed against the 17-1A antigen had been shown in vitro to induce antibody-dependent cellular cytotoxicity [45-47], and to inhibit growth of human colon carcinoma xenografts in nude mice [48]. Studies of this antibody in patients with clinically advanced metastatic disease demonstrated no major toxicity and a few instances of clinical tumor regression [49].

With tolerable toxicity and evidence of clinical activity demonstrated, a trial was undertaken to evaluate this antibody in the adjuvant setting in patients with stage III resected colon cancer [50]. One hundred sixty-six patients were randomized to receive either mAb or no postoperative therapy. Patients in the treatment group received 500 mg of 17-1A antibody two weeks after surgery by one-hour intravenous infusion, followed by four 100 mg infusions given at four-week intervals.

With a median follow up of five years (range 2.5-7.5 years), 64% of the patients receiving mAb were alive, as compared to 49% of patients receiving surgery only. This 15% difference represents a 30% reduction in mortality, although the relatively small size of the study mandates that these data be interpreted with caution. Nevertheless, these initial results are encouraging, and large-scale phase III testing of this antibody is underway.

**ANTITUMOR VACCINATIONS**

Vaccinations attempt to stimulate the patient’s immune system to do what it has previously failed to do: recognize a tumor cell as foreign and implement effective procedures to destroy it. Such utilization of the immune system to control or prevent cancer is a goal which, although appealing, has thus far proved elusive. Clearly, efforts to control large-volume disease would be premature given the current state of technology. The adjuvant setting, however, is a more conservative and perhaps more practical venue in which to attempt to boost immunologic surveillance and thereby eradicate small-volume micrometastases. The ideal immunologic target would be a tumor-specific antigen which is unique to, and always expressed by, tumor cells and which is never expressed by nonmalignant cells. Thus far, no such perfect tumor-specific antigen has been identified. Efforts have focused either on identifying an antigen with a high degree of expression on tumor cells, or on use of autologous tumor cells with immunoadjuvants.

One group of investigators has targeted the blood group-related epitopes Tn and sialylated Tn (sTn), which are expressed on mucins of many epithelial tumors, including colorectal carcinomas. A vaccine was developed from partially desialylated ovine submaxillary gland mucin (modified OSM), which contains both Tn and sTn determinants.
Cohorts of patients were treated with either modified OSM, modified OSM plus the immunologic adjuvant DETOX, or modified OSM plus BCG [51]. The goal of this study was to determine if antibody titers to Tn and sTn could be raised by these vaccinations. While none of the six patients receiving modified OSM alone developed antibodies, four of eight patients receiving modified OSM plus DETOX and five of six patients receiving modified OSM plus BCG demonstrated marked increases in antibody titers. Attempts to build on these results are being pursued by exploring the use of more potent immune adjuvants, and by augmentation of Tn and sTn by covalent attachment of immunogenic carrier proteins.

Another group has pursued clinical investigations of a technique termed active-specific immunity, or ASI. In this approach, patients receive immunizations with a combination of BCG and a preparation of their own irradiated tumor cells. Irradiation of tumor cells has been shown to destroy tumorigenicity, but not the immunogenicity of the cells. A small randomized trial involving 80 colon and rectal cancer patients showed no benefit of this approach over surgery alone [52]. A retrospective subset analysis did show a statistically significant improved survival rate for the immunized colon cancer patients; however, the small number of patients (47 colon patients randomized) and other serious methodological problems [53] make interpretation of the data difficult. Larger, more carefully constructed trials have been conducted; maturation and analysis of the data are pending.

**Rectal Cancer**

Rectal cancers are those tumors of the large bowel which occur at or below the peritoneal reflection. It is worth noting that this determination, especially in tumors of the proximal rectum, must be made by the surgeon, as such a determination often cannot be made reliably either on a pathology specimen or by preoperative endoscopy. While a lesion a few centimeters from the anal verge is clearly a rectal tumor, a lesion at 10-15 centimeters may be either rectal or colonic, depending on the individual patient’s size and anatomy. The distinction is not a trivial one, since the adjuvant therapy for rectal tumors is substantially different from that of colon tumors.

In addition to the risk of distant metastases, rectal lesions present a particular concern in terms of local recurrence. In contradistinction to the colon, which is intra-abdominal, the rectum is surrounded by pelvic bone. Thus, a local recurrence in the pelvis puts the pelvis at high risk for bony invasion. Furthermore, the risk of bowel obstruction from a local recurrence is high, since the surrounding pelvic bone is inelastic, and since the stool is not as soft in the rectum as compared to higher up in the large intestine. The impingement on pelvic nerves can, in addition to causing considerable pain, lead to sphincter, bladder and sexual dysfunction. Therefore, local recurrence of a rectal cancer can be disastrous for a patient. Accordingly, two separate endpoints are considered in the adjuvant management of rectal cancer patients: overall disease-free survival and local recurrence-free survival.

Evidence from a number of randomized trials strongly suggests that patients with either full thickness tumor involvement of the rectal wall (T2, N1-3, M0, Dukes B2, stage II), and/or node-positive disease (TanyN1-3M0, Dukes C, stage III) have improved local control and survival when treated with combined modality adjuvant chemotherapy plus radiotherapy. A four-arm trial by the Gastrointestinal Tumor Study Group (GITSG) randomized 202 patients with resected rectal cancer to radiation alone, chemotherapy alone, radiation plus chemotherapy, or no postoperative treatment [54, 55]. There was a significant improvement in overall survival in the group which received the combination therapy versus the surgery-only group. Neither chemotherapy alone nor radiation therapy alone produced an improved survival rate over surgery alone. The chemotherapy used in this trial, as in many other earlier trials, was a combination of FU and methyl-CCNU. Subsequent trials have demonstrated that methyl-CCNU does not add a therapeutic benefit [56], but does add toxicity and potentially an increased risk of developing treatment-related leukemia. Thus, methyl-CCNU is not recommended in current management strategies.

In a trial reported from the NCCTG, 204 patients were randomized to receive either postoperative radiation therapy or postoperative radiation therapy plus chemotherapy [57]. Again a combination of FU and methyl-CCNU was used. Patients receiving chemotherapy and radiation had a substantially improved outcome compared to patients receiving only postoperative radiation. With a median follow-up of 7.5 years, the five-year disease-free survival was 59% versus 37%, local failure 25% versus 14%, and distant failure was 46% versus 29% in patients with chemotheraphy/radiation and radiation only, respectively. All of these differences were statistically significant.

A subsequent NCCTG trial [56] compared FU given by continuous infusion versus bolus injection in conjunction with pelvic radiotherapy. The toxicity patterns were different, as would be expected, with diarrhea occurring more commonly with infusional administration and leukopenia being a more common toxicity with bolus administration. The overall survival at four years was improved in patients receiving continuous infusion (70% versus 60%), and the overall relapse rate was lower (37% versus 47%). Again, both of these differences were statistically significant. Thus, this study strongly indicates that when used as a single agent, FU is more effective when given as a continuous
infusion than as a bolus injection. It is not clear, however, how infusional FU compares to biomodulated FU regimens, such as FU plus leucovorin. This issue is being investigated by a large intergroup trial discussed below.

**INVESTIGATIONAL APPROACHES**

Taken together, the above-mentioned studies present a convincing argument that combined FU-based chemotherapy and radiotherapy is appropriate adjuvant treatment following resection of locally advanced (Dukes B; and C) rectal cancer. Current ongoing investigations are attempting to further define the optimal schedule of treatment administration. A four-arm trial run through the intergroup mechanism randomly assigned patients to receive one of four postoperative chemotherapy regimens for six months, with radiotherapy concurrent with the third and fourth treatment cycles. The four chemotherapy arms were FU alone (bolus administration), FU plus low-dose leucovorin, FU plus levamisole, and FU plus low-dose leucovorin and levamisole. Accrual to this trial has been completed, and results are pending. Currently another intergroup trial is accruing patients to a three-arm study to directly compare the role of protracted intravenous infusion of FU to bolus biomodulated FU. The trial design is outlined in Figure 1.

**PREOPERATIVE VERSUS POSTOPERATIVE THERAPY**

With postoperative combined modality therapy having proven effective, many investigators have explored the use of preoperative radiation plus chemotherapy. There are several theoretical advantages to the preoperative approach. Preoperative reduction of the tumor size may downstage the disease and facilitate resection. The possibility of sphincter preservation may be improved, and the institution of preoperative chemotherapy may improve the efficacy against micrometastases by permitting initiation of chemotherapy earlier in the patient’s treatment course.

Most published trials of preoperative treatment have employed less than optimal radiation doses and treatment strategies [58], making interpretation of the available literature difficult. A random assignment trial of pre- versus postoperative therapy is currently in the process of accruing patients.

**CONCLUSION**

Adjuvant chemotherapy of colorectal cancer, although far from satisfactory, has been clearly shown to reduce the incidence of recurrence and to save lives. Clearly there is a need for continued development of improved adjuvant treatment strategies. The maturation of data from trials discussed in this review will add considerably to our understanding of
the current state of the art. New agents, such as tomudex, irinotecan and oxaliplatin, which have shown activity in patients with metastatic disease, will need to be evaluated in the adjuvant setting. Through carefully designed and conducted clinical trials, the adjuvant role of these and other newer technologies will be undergoing intense investigation in the years ahead. Participation of eligible patients in these clinical trials should be actively encouraged. There is every reason to believe that the advances which have been made thus far in the adjuvant therapy of colorectal cancer will be the foundation from which further progress will come.

References

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