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ORIGINAL ARTICLE

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Abstract Colorectal cancer will be diagnosed in approximately 150,000 patients in the USA this year. Chemotherapy has recently been shown to improve survival when given as adjuvant therapy to surgery in patients with stage III colorectal cancer. Demonstration of this benefit required large, randomized controlled trials. Either 5-fluorouracil (5-FU) and leucovorin for 6 months or 5-FU and levamisole for 12 months are currently considered standard adjuvant treatment for stage III colorectal cancer. However, current adjuvant trials are comparing continuous infusion and intravenous bolus 5-FU regimens and oral uracil/Ftorafur with intravenous 5-FU and leucovorin, as well as studying the timing of chemotherapy in the adjuvant setting. Subsequent adjuvant trials will examine newer regimens with activity in advanced colorectal cancer, as well as the efficacy of monoclonal antibodies. Other trials will study which type of surgery is optimal and whether adjuvant therapy is helpful in stage II colon cancer. Trials in metastatic disease will focus on combinations of newer agents which may improve survival in this patient group. Studies in rectal cancer will focus on determining which agents are optimal in combination with radiation therapy in the adjuvant setting. Molecular characteristics of tumor cells are being defined, which may guide therapy in the future. Careful, logically designed clinical trials will hopefully provide more efficacious therapy for this common cancer.

Key words Colon cancer · Chemotherapy · Adjuvant therapy · Clinical trials

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Introduction

Cancer of the colon and rectum represents a major health problem in the USA, with the lifetime risk for development of colorectal cancer being 1 in 17 [10]. Approximately 150,000 new colon cancers are diagnosed annually. While approximately 50% of patients are cured by surgery, 55,000 patients each year succumb to this disease, which is minimally responsive to current chemotherapy. The National Cancer Institute (NCI) has supported large national trials to improve outcome in those patients with operable cancer but high risk of recurrence. These adjuvant trials have led to the establishment of several standard chemotherapy regimens for use after curative surgery. Ongoing efforts aim to develop more effective new agents with activity in colorectal cancer, to conduct controlled clinical trials large enough to detect clinically important improvements in adjuvant therapy, and to preserve organ function with lessened toxicity.

For more than 30 years, 5-fluorouracil (5-FU) has been the most active agent for colorectal cancer, with a response rate of about 20% in advanced disease, depending on dose, schedule, and the characteristics of the patient cohort [4]. The addition of leucovorin, an agent which stabilizes the inhibition of thymidylate synthase (TS) by the 5-FU metabolite fluorodeoxyuridine monophosphate (FdUMP), results in a higher response rate for patients with metastatic disease than does 5-FU alone. This result was obtained whether high or low doses of leucovorin were used. However, the higher response rate did not produce a

Table 1 Completed adjuvant trials of colon cancer using 5-FU modulation (*LEV* levamisole, *HDLV* high-dose leucovorin, *LDLV* low-dose leucovorin, *LV* leucovorin, *IFN* interferon alpha)

Trial	Regimens studied
INT-0089	5-FU + LEV × 12 months
	5-FU + HDLV × 6 months
	5-FU + LDLV × 6 months
	5-FU + LDLV + LEV × 6 months
NSABP C04	5-FU + LEV × 12 months
	5-FU + HDLV × 12 months
	5-FU + HDLV + LEV × 12 months
NCCTG/NCIC	5-FU + LEV × 6 or 12 months
	5-FU + LEV + LV × 6 or 12 months
NSABP C05	5-FU + HDLV × 6 months
	FU + HDLV + IFN × 6 months

significant prolongation of survival [4 and references therein].

Due to its short half-life, bolus 5-FU may only result in temporary and reversible inhibition of TS when used alone. Continuous infusion of 5-FU for prolonged periods should result in prolonged TS inhibition and, theoretically, greater activity than bolus 5-FU. A recent metaanalysis suggests that this may be the case, although continuous infusion 5-FU could not be shown to be superior to bolus 5-FU + leucovorin regimens [13].

Trials of 5-FU as adjuvant therapy in colon cancer

Although the above trials were done in patients with advanced, apparently incurable disease, it was recognized that an adjuvant therapy, which would prevent disease recurrence after surgery, was desirable. While some studies seemed to show a benefit for adjuvant 5-FU, others did not. A metaanalysis of 17 randomized, controlled adjuvant trials published in English before 1987, which compared chemotherapy to observation after definitive surgery, indicated that there was a small benefit to adjuvant 5-FU-based chemotherapy, with a mortality odds-ratio of 0.83 (95% confidence interval 0.7–0.98) [1]. Based on the findings of this metaanalysis, large phase III adjuvant trials of sufficient size to demonstrate small, but clinically significant survival benefits were designed.

In its initial colorectal cancer adjuvant trial, the National Surgical Adjuvant Breast and Bowel Project (NSABP) randomized 1166 patients with Dukes' stage B and C colorectal cancer to either adjuvant semustine, vincristine + 5-FU, bacillus Calmette-Guérin (BCG), or observation alone [14]. This trial demonstrated a survival advantage for the chemotherapy group. An intergroup trial also confirmed an earlier European report demonstrating that 12 months of adjuvant 5-FU + levamisole was effective in reducing mortality due to stage III (Dukes' C) colorectal cancer by 33%, and in increasing survival from approximately 40% to 60% [6]. In 1990, an NCI consensus panel concluded that 12 months of adjuvant 5-FU + levamisole was the standard of care in Dukes' C colorectal cancer [7].

Due to increased response rates in patients with advanced disease, attention was then turned to modulation of 5-FU activity by leucovorin in the adjuvant setting. Since the 1980s, four trials testing various doses and schedules of 5-FU with leucovorin and levamisole have been completed (Table 1). INT-0089 compared 12 months of 5-FU + levamisole (standard adjuvant treatment) with 6 months of one of three different regimens: weekly 5 FU + high-dose leucovorin; daily×5 treatment with 5-FU + low-dose leucovorin; or the triple drug combination 5-FU, leucovorin, and levamisole. The analysis of this trial is not yet complete. However, based on results at 4 years, 6 months of adjuvant therapy with 5-FU and leucovorin + levamisole appears to be as effective as 12 months of adjuvant therapy with 5-FU + levamisole [3]. In addition, several studies have failed to show any benefit from the addition of levamisole to the 5FU + leucovorin combination, and toxicity may be increased [3,9].

NSABP C-04 demonstrated that in terms of 5-year survival 5-FU + leucovorin weekly×6 weeks, every 8 weeks, for 6 cycles was equivalent to 5-FU + leucovorin + levamisole and to 5-FU + levamisole in for patients with Dukes' B2 and C colon cancer [15]. Similarly, the North Central Cancer Treatment Group (NCCTG) and National Cancer Institute of Canada (NCIC) intergroup trial 89-46-51 has suggested that the survival of patients treated with 6 months of 5-FU + levamisole may be inferior to that of patients treated with 6 months of 5-FU + leucovorin + levamisole. Twelve months of chemotherapy with either 5-FU + leucovorin + levamisole or 5-FU + levamisole did not offer a significant advantage over treatment for 6 months with 5-FU + leucovorin + levamisole [8]. Therefore at present it appears that 6 months of 5-FU + leucovorin or 12 months of 5-FU + levamisole are equally active adjuvant regimens.

NSABP C05, which evaluated the addition of interferon to 5-FU and high-dose leucovorin, has completed accrual, and results are awaited. The dosage of levamisole was also studied in INT-0135, which randomized patients with Dukes B2 or C colorectal cancer to adjuvant treatment with either high-dose or low-dose levamisole in addition to 5-FU + leucovorin. This trial has been closed, and it will be some years before analysis is mature.

Currently, an intergroup trial is studying the relative activity of infusional 5-FU + levamisole vs bolus 5-FU + leucovorin + levamisole as adjuvant therapy in stage III colon cancer. Both of these strategies were designed to inhibit TS for a prolonged time. This study (INT-0153) has accrued approximately 700 patients, and accrual is estimated to continue for about 3 more years (Table 2).

NSABP C-06 currently randomizes patients with stages II and III colon cancer to either 5-FU + leucovorin weekly or oral uracil/Ftorafur (UFT) po + oral leucovorin daily for 28 of every 35 days. Both regimens will be given for a total of 6 months after surgery.

Table 2 Current cooperative group adjuvant trials for colon cancer (*LEV* levamisole, *LV* leucovorin, *UFT* uracil/Ftorafur)

Trial	Regimen
INT-0153	5-FU + LV + LEV daily × 5 q 4 weeks × 6 5-FU, 56-day continuous infusion + LEV q 8 weeks × 3
INT-0136	5-FU, 7-day continuous infusion within 24 h of surgery No perioperative therapy (Dukes' B3 and C receive adjuvant 5-FU + LV for 6 months)
NSABP C06 (6-month treatment)	5-FU + LV weekly × 6 q 8 weeks UFT 100 mg/m²/day po + LV po for 28 of every 35 days
CALGB 9581/ECOG 9581 (stage II)	Stratification Differentiation Vascular/lymphatic invasion Preoperative carcinoembryonic antigen Randomization MoAB 17-1A q month × 5 Observation

Table 3 Cooperative group phase III trials in metastatic colon cancer (*HIA* hepatic arterial infusion, *LV* leucovorin)

Trial	Regimen
SWOG 9420	Continuous 5-FU infusion × 28 days q 5 weeks Weekly 5-FU infusion (2600 mg/m²/24 h) + LV
CALGB 9481 (hepatic metastases)	FUdR + LV HIA days 1–14 q 28 days 5-FU + LV daily × 5 q 28 days
NCCTG/NCIC JCO.10 (asymptomatic patients)	5-FU + LV daily × 5 q 28 days immediately Observation with treatment when symptoms occur

Perioperative chemotherapy in colon cancer

The question of whether perioperative chemotherapy is beneficial is being addressed by intergroup trial INT-0136 (Table 2). In this trial, 2000 patients who probably have Dukes' C disease will be randomized to receive 7 days of perioperative infusional 5-FU, beginning within 24 h of surgery, or no chemotherapy. Those who are subsequently shown to have Dukes' B3 or C disease will continue (on a nonrandomized basis) with standard adjuvant treatment.

Future trials in colon cancer

Subsequent adjuvant trials will compare newer regimens with activity in advanced colon cancer, such as those which include irinotecan + 5-FU + leucovorin, with standard 5-FU + leucovorin regimens, as well as evaluating the efficacy of monoclonal antibodies.

A major concern of all the intergroup trials is to find molecular characteristics of tumors that predict either prognosis or response to adjuvant therapy. Thus, for example, NSABP C-06 will study the prognostic significance of DNA mismatch repair gene mutation, p53 mutation, DCC (deleted-in-colon-cancer) gene deletion, proliferation status, and TS protein expression. These trials are also studying the impact of the various therapies upon quality of life. Other studies are assessing similar molecular markers and/or TS expression as predictors of response or prognosis.

To date, the contribution of adjuvant therapy to survival after resection of stage II disease has been difficult to ascertain. None of the above studies has been able to determine a statistically significant prolongation of survival for this stage of disease with the addition of adjuvant therapy. This may be due in part to lower event rates in patients with this stage of disease, but INT 0035 did not demonstrate any benefit of treatment with 5-FU + levamisole, even after prolonged follow-up [6]. The NSABP has presented a preliminary analysis of the benefit of adjuvant therapy in patients with Dukes' B vs Dukes' C colon cancer by combining results from four adjuvant trials. In this retrospective subgroup analysis, the magnitude of benefit for both groups was similar [5]. The NSABP continues to enrol stage II patients in adjuvant trials to clarify whether adjuvant therapy will benefit this group.

The Cancer and Leukemia Group B (CALGB) is coordinating an intergroup study (Table 2) in patients with stage II colon cancer which will randomize patients to observation alone vs MoAb 17-1A, a murine IgG2a monoclonal antibody directed against a transmembrane glycoprotein preferentially expressed in many adenocarcinomas. This antibody has been reported to be associated with a 30% survival advantage when used as an adjuvant treatment in a small study of 166 patients with Dukes C disease [11]. The accrual goal for this intergroup trial is 2100 patients, and the trial is anticipated to close in 2002. The trial is also designed to allow intensive exploration of potential markers of high vs low risk for recurrence within stage II colorectal cancer.

The optimal type of surgery for colon cancer is being studied in INT-0146, a randomized trial of laparoscopic vs open colectomy. This trial will randomize 600 patients to each of these treatments, followed by standard postoperative therapy, in order to compare recurrence rates, as well as economic, quality of life, and psychosocial effects.

Trials in metastatic and recurrent colon cancer

For metastatic or recurrent colon cancer (Table 3), cooperative group phase III trials are evaluating various schedules of infusion 5-FU (24 h each week vs continuous daily infusion) and, in a study of patients with hepatic metastases, hepatic intraarterial FUdR vs systemic bolus 5-FU + leucovorin. NCCTG/NCIC is evaluating whether there is benefit to giving 5-FU + leucovorin when patients are asymptomatic compared to its administration when symptoms occur. Oral FU prodrugs and combinations of 5-FU with inhibitors of the 5-FU metabolizing enzyme dipyridamole dehydrogenase (DPD) are being studied in patients with advanced disease. Irinotecan, alone and in combination with 5-FU + leucovorin, is being studied for its activity in patients who have not been previously treated, as well as

Table 4 Cooperative group trials for rectal cancer (*LV* leucovorin, *RT* radiation therapy, *PVI* prolonged venous infusion, *LEV* levamisole)

Trial	Regimen
INT-0147 (completed) (clinically T3, resectable)	Randomize Treatment A: Bolus 5-FU + LV + RT Surgery Bolus 5-FU + LV Treatment B Surgery Bolus 5-FU + LV Bolus 5-FU + LV + RT Bolus 5-FU + LV
INT-0144 (completed) (stage B2, B3, and C)	Randomize Bolus 5 – FU-RT + PVI 5-FU – bolus 5-FU PVI 5-FU – RT + PVI 5-FU – PVI 5-FU 5-FU + LV + LEV – RT + 5-FU/LV – 5-FU + LV + LEV
NSABP R03 (T3 resectable)	Randomize Preoperative 5-FU + LV q week × 6 – RT + 5-FU/LV daily × 5 – Surgery – 5+FU/LV weekly × 6 (× 3) Surgery – 5-FU/LV weekly × 6 – RT + 5-FU/LV daily × 5 – 5-FU/LV weekly × 6 (×3)
INT-0114 (adjuvant to surgery)	5-FU/LV daily × 5 q 28 days × 2 – RT + bolus 5-FU weeks 1 and 5 – 5-FU daily × 5 q 28 days × 2 5-FU/LV daily × 5 q 28 days × 2 – RT + bolus 5-FU weeks 1 and 5 – 5-FU/LV daily × 5 q 28 days × 2 5-FU/LEV × 2 – RT + bolus 5-FU weeks 1 and 5 – 5-FU/LEV × 2 5-FU/LV/LEV × 2 – RT + bolus 5-FU/LV weeks 1 and 5 – 5-FU/LV/LEV × 2

in those who are resistant to 5-FU. Various doses and schedules of this combination are being studied to ascertain whether there is an optimal regimen, or one which demonstrates sequence effects, as has been reported in vitro [2]. Other clinical trials to assess the activity of oxaliplatin, alone or in combination with other active drugs, are also underway. Other novel agents, such as those with antiangiogenesis effects, monoclonal antibodies or vaccines, farnesyl transferase inhibitors, and cell cycle progression inhibitors, will be evaluated in the near future.

Trials in rectal cancer

For rectal cancer, cooperative group trials have concentrated on improved local control, increased resectability, and/or organ/sphincter preservation goals (Table 4). INT-0114 randomized nearly 1700 patients to four different chemoradiation regimens as postoperative adjuvant therapy. These regimens compared 5-FU + leucovorin, 5-FU + levamisole, and 5-FU + leucovorin + levamisole prior to and following radiation combined with chemotherapy. With a median follow-up duration of 48 months there was no statistically significant advantage to any of the treatment regimens compared to bolus 5FU alone, but there was increased toxicity with the three-drug combination [12]. INT-0147, an adjuvant trial for stage II and III resectable rectal carcinoma, compared preoperative vs postoperative combined modality therapy with concomitant bolus 5-FU + leucovorin. Patients randomized to preoperative combined modality therapy were treated with 5-FU + leucovorin daily×5 every 28 days concomitantly with radiation therapy (50.4 Gy), followed by surgery, followed by four courses of the same chemotherapy. Patients randomized to postoperative combined modality therapy received two courses of 5-FU + leucovorin daily×5 after surgery, followed by concomitant bolus 5-FU + leucovorin + radiation as in the preoperative arm, followed by two further courses of chemotherapy. Final results are still pending.

A recently completed study, INT 0144, randomized patients with stage II or III rectal cancer to bolus vs prolonged venous infusion (PVI) 5-FU vs 5-FU + leucovorin + levamisole before and after combination chemoradiation therapy. The control arm was the standard single-agent bolus 5-FU daily×5 every 28 days before and following radiation therapy with PVI 5-FU. In all arms, two cycles of chemotherapy were administered prior to radiation therapy, following which radiation therapy was given along with either PVI 5-FU or 5-FU + leucovorin, followed by 2 additional cycles of chemotherapy. Whether or not PVI 5-FU or the triplet therapy will prove superior to bolus 5-FU awaits further follow-up.

NSABP-R-03 is attempting to define and refine the timing of the use of various modalities for T3 resectable cancer of the rectum. Patients are randomized to one of two treatments: treatment A, 5-FU + leucovorin + radiation therapy, followed by surgery, followed by 5-FU + leucovorin; or treatment B, surgery, followed by 5-FU + leucovorin, followed by combined 5-FU + leucovorin + radiation therapy, followed by 5-FU + leucovorin. At present, clinicians have strong biases regarding the timing of these various modalities in the treatment of rectal cancer, creating some challenges for accrual to a truly randomized trial. Due to the success of radiation + chemotherapy, further studies may focus on improvement of organ preservation and amelioration of toxicity.

Conclusions

Clearly, large, adequately sized, randomized phase III trials in colorectal cancer have demonstrated the role of adjuvant 5-FU-based chemotherapy regimens in locally advanced colon cancer, and have established chemotherapy + radiation therapy as useful in patients with locally advanced rectal cancer. As new, promising agents are developed, these will be tested for activity in patients with metastatic disease, and as adjuvant therapy to radiation therapy and/or surgery. The careful, logical investigations of the value of various treatments in colorectal cancer to date will serve as templates for future trials, and will hopefully lead to improved survival for the majority of patients with colorectal cancer.

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