

# Adjuvant Therapy for Colon Cancer

John S. Macdonald, MD

## Introduction

Colorectal cancer represents a significant health problem in the United States. It is estimated that there will be approximately 131,000 cases of cancer of the colon and rectum in 1997.<sup>1</sup> Of these malignancies, approximately 37,000 will be confined to the rectum and the remainder will be in the colon. Although there is interest currently in the evaluation of molecular markers (ploidy<sup>2-4</sup> and tumor suppressor gene mutation or deletion<sup>5-7</sup>) as prognostic markers, the most important prognostic information available to clinicians managing patients with colorectal cancer is still surgical pathologic staging of the resected primary tumor.<sup>8</sup> Patients with locally advanced (Dukes stages B2, B3, and C; TNM stages II and III) large bowel cancer have a significantly increased risk of relapse after surgical resection alone (Table 1). In stage III patients, the risk of death from cancer is 30% to 60% during the 5 years after surgical resection.

Because of the high risk of relapse after surgery alone, therapies that may be added to surgery to prevent clinical metastatic disease have attracted great interest. Many adjuvant chemotherapy trials have been performed in colon cancer over the last 30 years.<sup>8-10</sup> This article will briefly review the status of adjuvant therapy in colon cancer.

## Historical Background

The predominant single agent used as adjuvant therapy in colon cancer has been fluorouracil (5-FU). In 1988, a meta-analysis of 5-FU as adjuvant therapy in colorectal cancer was published by Buyse and colleagues<sup>10</sup> (Table 2). This meta-analysis evaluated results of phase III clinical trials in which 4,700 patients were randomized between regimens containing 5-FU and surgery only. The results showed that 5-year survival benefits ranged from 2.3% to 5.7%. These survival advantages were not statistically significant compared with those of patients treated with surgery alone. Such meager benefits, which could result from chance, would hardly justify the standard use of 5-FU as adjuvant therapy for colon cancer.

Even though early results were disappointing, 5-FU has continued to serve as the drug upon which many adjuvant therapy programs have been built. A number of studies completed and published within the last decade help define the current state of the art of surgical adjuvant therapy in colon cancer. Three phase III evaluations of 5-FU plus methyl-1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) versus surgery alone were completed in the 1980s.<sup>11-13</sup> One clinical trial conducted by the Veterans Administration Surgical Oncology Group (VASOG)<sup>11</sup> and another carried out by the Gastrointestinal Tumor Study Group (GITSG)<sup>12</sup> encompassed a combined total of more than 1,200 patients. In these studies, 5-FU plus methyl-CCNU with and without nonspecific immunotherapy provided no long-term sur-

Dr. Macdonald is Professor of Medicine, Chief of the Division of Medical Oncology, and Medical Director of the Temple University Cancer Center in Philadelphia, Pennsylvania.

**Table 1**  
**Surgical Stage and Survival in**  
**Colorectal Cancer**

<b>TNM Stage</b>	<b>AJCC Stage</b>	<b>Dukes Stage</b>	<b>5-Year Survival (%)</b>
I	T, T2 N0, M0	A, B1	85–95
II	T3, T4 N0, M0	B2, B3	60–80
III	Any T N1–3, M0	C	30–60
IV	Any T Any N, M1	D	< 5

AJCC = American Joint Committee on Cancer.  
 Adapted from O'Connell.<sup>54</sup>

**Table 2**  
**Meta-Analysis of Phase III 5-FU**  
**Colorectal Cancer Trials (All Stages)**

<b>Treatment Group</b>	<b>No. Entered</b>	<b>No. Dead</b>	<b>Odds Ratio*</b>	<b>Range of 5-Year Survival Advantage</b>
All 5-FU regimens	4,700	2,477	0.9	2.3–5.7% (P = NS)

\*Odds ratio = odds of dying in treatment group/odds of dying in control group.  
 5-FU = fluorouracil; NS = not significant.  
 Data from Buyse et al.<sup>10</sup>

vival benefit compared with surgery alone. Likewise, a Southwest Oncology Group study, which used a control arm with surgical resection alone only through part of its accrual period, showed no benefit for methyl-CCNU plus 5-FU.<sup>13</sup>

The National Surgical Adjuvant Breast and Bowel Project (NSABP) performed a study (CO-1) involving 1,166 patients randomly allocated to bacillus Calmette-Guérin (BCG) or 5-FU and methyl-CCNU and vincristine (MOF)

versus surgery alone.<sup>14</sup> The initial results published in 1988 showed a statistically significant 5-year disease-free survival advantage of 58% versus 51% for the chemotherapy arm versus the control arm. The chemotherapy patients also had an overall survival benefit of marginal statistical significance. There was no benefit in freedom from relapse for the group treated with BCG, but these patients had an overall survival benefit. Such an anomalous result cannot be ex-

plained by an antineoplastic effect of BCG. Further analysis of the CO-1 study has demonstrated a weakening of the disease-free and overall survival benefits originally noted for MOF. Also, the general applicability of an adjuvant program based on chloroethyl nitrosourea is severely limited by the well-demonstrated incidence of treatment-induced acute non-lymphocytic leukemia occurring after methyl-CCNU therapy.<sup>15</sup>

Two studies reported in 1989<sup>16</sup> and 1990<sup>17,18</sup> have had a significant impact not only on clinical investigation of adjuvant treatment of colon cancer but also on the standard of care of patients who have undergone resection of colon cancer. These studies randomized patients after surgical resection of colon cancer to three dif-

ferent treatment arms: 5-FU and levamisole for 1 year versus levamisole alone for 1 year versus no adjuvant therapy. The first study, which involved 401 patients, was performed by the North Central Cancer Treatment Group (NCCTG).<sup>16</sup> The results published in October 1989 showed that 5-FU plus levamisole increased disease-free survival ( $P=0.02$ ) and had a small but significant ( $P=0.03$ ) survival benefit in stage III patients.<sup>16</sup> Levamisole alone did not significantly increase survival in stage III patients. Neither treatment was effective in stage II colon cancer.

The results from the NCCTG study stimulated the initiation of a second clinical trial, Intergroup (INT)-0035, which was planned to enroll 1,300 patients. This study was specifically designed as a confirmatory study for the NCCTG clinical trial. Investigators

from the NCCTG, Southwest Oncology Group (SWOG), and Eastern Cooperative Oncology Group (ECOG) participated in this effort. The results of this study were first published in 1990,<sup>17</sup> updated at an American Society of Clinical Oncology (ASCO) presentation in 1992,<sup>18</sup> and reported in final form in 1995.<sup>19</sup> At the initial publication in 1990 with 3½ years of median follow-up, the study was strikingly positive for stage III patients. 5-FU plus levamisole decreased relapse by 41% ( $P<0.0001$ ) and decreased death from recurrent colorectal cancer by 33% ( $P=0.006$ ). No beneficial effect was noted for therapy with levamisole only in stage III patients. The mature results of this study (6½ years of median follow-up) showed an

improvement in the survival rate (60% versus 46%) persisting for more than 5 years in patients receiving 5-FU plus levamisole compared with those treated with surgery alone. This result is particularly significant, because 99% of expected recurrences in the surgery-only arm have occurred by 5 years after resection in stage III cases. Therefore, 5-FU plus levamisole therapy definitely changed the natural history of resected stage III colon cancer.

In stage II patients there was no significant benefit for 5-FU/levamisole compared with surgery alone.<sup>20</sup> However, relatively small numbers of patients with stage II colon cancer were included in this study (159 in each arm). The 7-year disease-free survival for patients treated with 5-FU plus levamisole was 79% versus 71% for surgery alone ( $P=0.10$ ). Overall survival at 7 years was not

---

***A National Cancer Institute consensus conference in April 1990 recommended 5-FU plus levamisole as the standard of care for patients with resected stage III colon cancer.***

---

increased with adjuvant therapy (72% in both arms,  $P=0.83$ ).

5-FU/levamisole was generally well tolerated, and compliance with therapy was good. Only one drug-related fatality occurred in INT-0035. It was secondary to neutropenic sepsis. Myelosuppression occurring with 5-FU/levamisole is probably secondary to the 5-FU in this regimen, although levamisole may rarely cause agranulocytosis. Other toxicities that may occur include mild elevation of hepatic transaminases, dysgeusia, arthralgia, and depression. These toxic manifestations of therapy tend to be mild and usually do not preclude continued therapy. An unusual syndrome of neurotoxicity may rarely occur. Clinical findings include dysarthria, confusion, and focal neurologic findings. MR imaging

alone in phase III studies of adjuvant therapy in resected colon cancer. As a result, essentially all adjuvant protocols performed in the 1990s used 5-FU plus levamisole as the treatment with which investigational therapies were compared.

### **Current Status of Adjuvant Therapy**

The period from 1990 to 1996 has been one of innovation in conceptual approaches to adjuvant therapy for colon cancer. It also has been a time during which the relative efficacies of various 5-FU-based regimens have been defined in large clinical trials. Several important issues exist in regard to the current status of adjuvant therapy. The first

---

## *Portal vein infusion of chemotherapy is an investigational, not a standard, adjuvant approach.*

---

demonstrates focal demyelination in the brain in a pattern similar to that of multiple sclerosis. This is a rare complication of 5-FU/levamisole and appears to be reversible with cessation of drug therapy in some cases.<sup>21</sup>

The order of magnitude of benefit for 5-FU plus levamisole in both the North Central Group Study and the confirmatory Intergroup study<sup>17,18</sup> resulted in rapid FDA approval of levamisole plus 5-FU as adjuvant therapy for stage III colorectal cancer in 1990. A National Cancer Institute (NCI) consensus conference in April 1990 recommended 5-FU plus levamisole as the standard of care for patients with resected stage III colon cancer.<sup>22</sup> The 5-FU plus levamisole data also mandated that it no longer was acceptable to have a control arm receiving surgery

is the adjuvant role of 5-FU/leucovorin, which for a number of years has been considered the standard of care for patients with advanced colon cancer.<sup>23</sup> The second is the role of regional therapy, particularly portal vein infusion.<sup>24-31</sup> The third area of significant interest is the evolving role of immunotherapy in colorectal cancer.<sup>32,33</sup> Finally, reports in early 1996 of the results of large clinical trials that were aimed at defining the role in clinical research and clinical practice of 5-FU/levamisole and 5-FU/leucovorin have clarified the use of these regimens in patients with resected colon cancer.<sup>34-36</sup> The results of these large phase III studies have given the practicing oncologist and the clinical investigator guidelines for using 5-FU-based regimens in both clinical care and clinical research.

**Table 3**  
**Adjuvant Trials Evaluating**  
**5-FU Plus Leucovorin**

Regimen	Total Patients Accrued	≥ 3-Year DFS (%)	≥ 3-Year Survival (%)	Reference
Surgery + 5-FU/LV	239	74	81	Francini <sup>41</sup>
Surgery alone		60	64	
Surgery + 5-FU/LV	309	77	75	NCCTG <sup>38</sup>
Surgery alone		64	71	
Surgery + 5-FU/LV	1,081	73	84	NSABP <sup>39</sup>
Surgery + MOF		64	77	
Surgery + 5-FU/LV	1,526	71	83	IMPACT <sup>40</sup>
Surgery alone		62	78	

5-FU/LV = fluorouracil plus leucovorin; DFS = disease-free survival; IMPACT = International Multicentre Pooled Analysis of Colon Cancer Trials; MOF = methyl-CCNU, vincristine, and 5-FU; NCCTG = North Central Cancer Treatment Group; NSABP = National Surgical Adjuvant Breast and Bowel Project.

#### THE ROLE OF 5-FU PLUS LEUCOVORIN

5-FU plus leucovorin in a variety of doses and schedules has been used as a standard of care for a number of years in patients with advanced colon cancer. A meta-analysis published in the early 1990s showed that in patients with advanced colon cancer overall survival was not increased with 5-FU/leucovorin, but the response rate was significantly increased compared with that seen when 5-FU was given alone.<sup>37</sup> It was therefore logical to test 5-FU/leucovorin as adjuvant therapy in patients with resected high-risk colon cancer. Several major studies evaluating 5-FU/leucovorin schedules versus surgery alone have been reported in the past several years.<sup>38-41</sup>

All of these studies, which encompass more than 2,000 patients, have

shown significant improvements in disease-free and overall survival (Table 3). These studies used different doses and schedules of 5-FU plus leucovorin. The NCCTG study used a regimen common in the United States of 5-FU, 425 mg/m<sup>2</sup>, with leucovorin, 20 mg/m<sup>2</sup>, given daily for 5 days.<sup>38</sup> The International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) study<sup>40</sup> used 5-FU at 400 mg/m<sup>2</sup> and leucovorin at 200 mg/m<sup>2</sup> daily for 5 days, and the NSABP<sup>39</sup> used 5-FU at 500 mg/m<sup>2</sup> and leucovorin at 500 mg/m<sup>2</sup> weekly for 6-week cycles over 1 year. The NSABP study entailed 48 weeks of treatment. The other two studies used chemotherapy for approximately 6 months. As in the case with 5-FU and leucovorin used in advanced colorectal cancer, dosing schedules did not seem to

**Table 4**  
**Portal Vein Infusion Trials**

Case Characteristics	Treatment	No. of Patients	Decrease in Liver Metastases?	Increased Survival?	Investigator
Dukes A, B, and C; colon and rectal	5-FU/heparin Control	127 117	Yes	Yes	Taylor et al <sup>24</sup>
Dukes A, B, and C; colon	5-FU/heparin Control	442 459	No	Yes	NSABP CO-2 <sup>29,30</sup>
Dukes A, B, and C; colon and rectal	5-FU/mitomycin/heparin Control	236 233	Yes	Yes	SAKK <sup>27</sup>
Dukes A, B, and C; colon and rectal	5-FU/heparin Control	103 145	No	No	Fielding et al <sup>31</sup>
Dukes B2 and C; colon and rectal	5-FU/heparin Control	110 109	No	No	NCCTG <sup>28</sup>
Dukes A, B, and C; colon and rectal	5-FU/heparin Urokinase Control	99 103 102	Yes	No	Wereldsma et al <sup>26</sup>

5-FU = fluorouracil; NCCTG = North Central Cancer Treatment Group; SAKK = Swiss Group for Clinical Cancer Research.

produce significant differences in efficacy. In the three studies using surgery-only controls, all 5-FU plus leucovorin regimens of therapy appear active compared with surgery alone. These studies were initiated in the 1980s, when it was appropriate to use a surgery-only control arm for patients with stage III colon cancer. The results of these studies made the comparison of 5-FU plus levamisole versus 5-FU/leucovorin regimens a logical clinical trial strategy. This strategy was pursued in the large clinical trials, the results of which were reported in 1996 and are discussed in the last section of this article.

#### PORTAL VEIN INFUSION

Portal vein infusion of chemotherapy has been explored as an adjuvant therapy for colon cancer for at least the last 20 years. The rationale for this approach is that colon carcinoma micrometastases embolized to the liver via the portal system initially receive their vascular supply from the portal vein. Therefore, effective cytotoxic therapy into the portal system could destroy microscopic metastatic disease in the liver. Obviously, if this rationale is correct, patients treated with effective adjuvant therapy via the portal vein should have a decrease in liver metastases along with an increase in overall survival.

The study that initiated the major interest in portal vein infusion was published by Taylor et al<sup>24</sup> initially in 1977 and updated in 1985. In this study, a decrease in liver metastases was noted in the 127 patients randomized to 5-FU plus heparin by the portal vein versus 117 patients who were treated with surgery alone. There also was a statistically significantly improved 5-year survival ( $P=0.002$ ) in patients receiving intraportal therapy. Of note, the benefit in the study appeared to be limited to patients with stage II colon cancer.

The Taylor study stimulated other phase III studies aimed at confirming the

benefit of portal vein infusion of fluorinated pyrimidines. Table 4 lists a number of these studies. As can be seen, with the exception of the NSABP<sup>29,30</sup> and Swiss Group for Clinical Cancer Research (SAKK)<sup>27</sup> studies, most clinical trials enrolled 200 or fewer patients per arm. Also, the results in regard to overall benefit and decrease in liver metastases are mixed. The NSABP study, CO-2, is of interest because it has shown both an increase in disease-free survival and, in the most recent report, an overall increase in survival.<sup>30</sup> However, this study showed no decrease in liver metastases. These data suggest that fluorinated pyrimidine has a systemic adjuvant effect but not a significant impact on hepatic metastases. The clinical benefit seen in CO-2 may be related to the fact that the adjuvant 5-FU is given immediately postoperatively even though it is given for a short period of time (7 days). The results of CO-2 suggest that immediate postoperative fluorinated pyrimidines have a systemic adjuvant effect. This concept is being tested in INT-0136, a phase III study in which 7 days of 5-FU administered by continuous intravenous infusion is initiated within 24 hours of surgery and is compared with a standard 5-FU/levamisole program started within 35 days of colon resection.

A meta-analysis published in 1995 suggests that an increase occurs in overall and disease-free survival with portal vein infusion of fluorinated pyrimidines.<sup>42</sup> However, a careful analysis of published portal vein infusion studies by Crowley<sup>43</sup> pointed out that most phase III studies had significant flaws in design and execution. These include being underpowered to detect realistic levels of treatment effect, frequent use of subset analysis, and high numbers of ineligible cases. Although the meta-analysis encompassing these studies may indeed show statistically significant results, the flawed nature of the component studies requires one to be cautious in applying the results of the meta-analysis to clinical

practice or clinical research. It is appropriate to consider portal vein infusion an investigational approach and not a standard adjuvant approach.

#### IMMUNOTHERAPY

Immunotherapy for any cancer has always been an inviting prospect. The concept of using host immune mechanisms to destroy malignant disease is intrinsically attractive. Levamisole was initially of interest in colon cancer partly because it was thought to be a nonspecific immunomodulator.<sup>44-47</sup> Although animal studies and in vitro analyses suggest that levamisole has an immunomodulatory effect, clinical studies have shown mixed results in regard to immunomodulation.<sup>47,48</sup> The reason for the efficacy of adjuvant levamisole in spite of its demonstrated lack of consistent clinical immunomodulatory activity is still unclear.

There is considerable interest at present in evaluating the 17-1A mono-

clonal antibody as adjuvant therapy for colon cancer. The enthusiasm for this approach is based on a randomized clinical trial reported by Riethmuller et al<sup>32</sup> from Germany. The 17-1A antibody, which recognizes a non-carcinoembryonic antigen (CEA) epitope on malignant and normal cells, was reported to increase disease-free and overall survival in patients with stage III colon cancer in the German study. The degree of increase was approximately the same as that seen with 5-FU plus levamisole in the Intergroup study (INT-0035). International studies are currently evaluating 17-1A in combination with 5-FU-based regimens in patients with stage III colon cancer. There also is a proposal in the United States Intergroup program to test 17-1A as a single agent in patients with stage II colon cancer versus surgery alone. The latter study is a particularly attractive vehicle to evaluate 17-1A because no

**Table 5**  
**Multi-Institutional Trials with Postoperative**  
**Fluorouracil Plus Leucovorin and Levamisole:**  
**Results Reported in 1996**

Study	No. of Patients Accrued	Regimen
NCCTG 894651	915	5-FU + levamisole (6 or 12 months)
		5-FU + leucovorin + levamisole (6 or 12 months)
NSABP C0-4	2,151	5-FU + levamisole
		5-FU + leucovorin weekly
		5-FU + leucovorin + levamisole
Intergroup-0089	3,759	5-FU + levamisole
		5-FU + leucovorin weekly
		5-FU + leucovorin monthly
		5-FU + leucovorin + levamisole

5-FU = fluorouracil; NCCTG = North Central Cancer Treatment Group; NSABP = National Surgical Adjuvant Breast and Bowel Project.

chemotherapy that may alter immune responsiveness would be given. It is probable that the stage II colon cancer study will be initiated within the next year in the United States Intergroup.

Other innovative approaches to immunotherapy are being evaluated in early clinical trials in the United States. The most interesting is an approach pioneered by Foon et al<sup>33,49</sup> in which anti-idiotypic monoclonal antibodies have been developed that are capable of specifically breaking human immune tolerance to CEA in patients with colon cancer. It is not yet known whether this approach of specific sensitization to a tumor-associated antigen in humans will result in an immunotherapeutic effect.

#### STANDARD OF CARE FOR PATIENTS WITH RESECTED COLON CANCER

An essential and clinically important question in regard to adjuvant therapy for colon cancer has been the definition of the relative roles of active therapies. Is 5-FU plus levamisole superior to 5-FU plus leucovorin? Are there differences in toxicity and efficacy that would impel a clinician to choose one regimen over the other? The recent presentation and publication of the results of three large studies performed by the United States cooperative group mechanism have helped answer these relevant clinical questions.

Table 5 shows the schemata of NSABP CO-4,<sup>35</sup> Intergroup-0089,<sup>34</sup> and NCCTG 894651.<sup>36</sup> These studies are all basically similar in concept in that they evaluate 5-FU plus levamisole as a standard therapy versus a series of 5-FU plus leucovorin regimens with and without levamisole arms. These studies were all presented at the 1996 ASCO meeting at a Colon Cancer Symposium. The largest study to be reported was INT-0089.<sup>34</sup> In this study, 3,759 patients were enrolled. Eighty percent of the patients had stage III colon cancer. 5-FU/levamisole was given for 12 months in this study. The 5-FU/low-dose leucovorin/levamisole program was given for 6 months, and the weekly high-dose 5-FU/leucovorin regimen was given for 8 months. INT-0089 was designed as a comparative study and demonstrated that there were no differences in efficacy between (1) 5-FU/high-dose leucovorin and 5-FU/low-dose leucovorin, (2) 5-FU/levamisole and 5-FU/high-dose leucovorin, and (3) 5-FU/low-dose leucovorin and 5-FU/low-dose leucovorin/levamisole. However, the comparisons of 5-FU/levamisole to either 5-FU/low-dose leucovorin or to 5-FU/low-dose leucovorin with levamisole remained blinded because it was still possible that differences among these regimens could evolve in follow-up on this study. The results in the unblind-

**Table 6**  
**Intergroup-0089: Toxicity of Grade 3 or Worse (%)**

	5-FU/Low-Dose LV	5-FU/High-Dose LV	5-FU/LEV	5-FU/LV/LEV
Leukopenia	11.9	2.8	9.0	14.9
Neutropenia	24.1	3.9	18.8	35.1
Stomatitis	18.2	1.4	3.6	22.6
Diarrhea	21.1	30.0	11.4	17.9

5-FU = fluorouracil; LEV = levamisole; LV = leucovorin.

**Table 7**  
**Current Colon Cancer Adjuvant Trials**

Study	Accrual Goals	Regimen
Intergroup-0130 (TNM T4 or N1, 2)	700	5-FU + levamisole versus 5-FU + levamisole and tumor bed irradiation
Intergroup-0136	800	Perioperative 5-FU intravenous infusion followed by 5-FU + levamisole beginning 4 weeks postoperatively versus 5-FU + levamisole beginning 4 weeks postoperatively
Intergroup-0153	1,800	Prolonged continuous infusion 5-FU + levamisole versus Bolus 5-FU, leucovorin + levamisole
NSABP CO-5*	2,100	5-FU + leucovorin versus 5-FU + leucovorin and interferon alpha

\* Closed to accrual; analysis not completed.  
5-FU = fluorouracil; NSABP = National Surgical Adjuvant Breast and Bowel Project.

ed comparisons show that the disease-free and overall survival curves of patients with stage III colon cancer treated on INT-0089 are comparable with the 5-FU/levamisole results from INT-0035.

The analysis of toxicity in this study, which is summarized in Table 6, is important. As may be seen, interesting differences are present in toxicity profiles. When grade 3 or worse toxicities are analyzed, the 5-FU/low-dose leucovorin with and without levamisole regimens have significantly higher incidences of stomatitis than are seen with 5-FU/levamisole or 5-FU/high-dose leucovorin regimens. Conversely, grade 3 diarrhea was almost three times more common with 5-FU/high-dose leucovorin than with 5-FU/levamisole. The toxicity analysis of INT-0089 also showed interesting and clinically important differences in qualitative toxicity according to age and gender. Patients older than 70 years<sup>50</sup> and females<sup>51</sup> have significantly higher inci-

dences of stomatitis and leukopenia. Therefore, since leukopenia and stomatitis are most commonly associated with low-dose 5-FU/leucovorin regimens, clinicians may wish to carefully consider the use of these programs in women and the elderly.

The mature findings of INT-0089, a very large phase III clinical trial, provide several important pieces of information. First, the efficacy comparison suggests that 5-FU/leucovorin and 5-FU/levamisole regimens are similar in efficacy. Second, the toxicity analyses are important because they provide clinicians a rationale for choosing among equally efficacious regimens according to the qualitative toxicity patterns that a given patient may best tolerate.

A second significant study was that reported by O'Connell et al.<sup>36</sup> This study, NCCTG 894651, addressed the important issue of whether 12 or 6 months of adjuvant therapy was required for pa-

**Table 8**  
**Commonly Used Adjuvant Therapy Programs**

5-FU, 450 mg/m <sup>2</sup> IV bolus daily x 5 days → 28 days rest → weekly IV bolus x 1 year Levamisole, 50 mg po tid x 3 days every 2 weeks x 1 year	
5-FU, 425 mg/m <sup>2</sup> IV bolus daily x 5 days Leucovorin, 20 mg/m <sup>2</sup> IV bolus daily x 5 days +/- levamisole, 50 mg po tid x 3 days every 2 weeks	} Repeat every 4–5 weeks for 6 cycles
Leucovorin, 500 mg/m <sup>2</sup> over 2 hours followed by 5-FU, 500 mg/m <sup>2</sup> IV bolus	
	} Weekly x 6 weeks followed by 3 weeks' rest Repeat for 6 cycles

5-FU = fluorouracil; IV = intravenous; po = orally; tid = three times a day.

tients with resected colon cancer. It compared 5-FU/low-dose leucovorin plus levamisole for both 12 months and 6 months to 5-FU/levamisole for both 12 months and 6 months. The analysis included 890 eligible patients. This study demonstrated that the three-drug regimen of 5-FU/levamisole plus leucovorin for 6 months resulted in superior overall survival compared with 5-FU/levamisole for 6 months (75% versus 63%;  $P < 0.03$ ). However, 5-FU/levamisole for 12 months produced survival benefits equal to those of 5-FU/levamisole/leucovorin for 6 months. This study suggests that 6 months of 5-FU/leucovorin/levamisole and 12 months of 5-FU/levamisole are equally efficacious.

The third important study reported was the NSABP CO-4 clinical trial.<sup>35</sup> In this study, six cycles of 5-FU/high-dose leucovorin (each consisting of 5-FU, 500 mg/m<sup>2</sup>, and leucovorin, 500 mg/m<sup>2</sup>/week for 6 weeks) was compared with either the standard 5-FU/levamisole regimen or a combination of 5-FU/high-dose leucovorin plus levamisole. A total of 2,151 patients with stage II and III colon cancers were randomized onto this clinical trial. Results showed that 5-FU/leucovorin was superior in disease-free (64% versus 60%;  $P < .05$ ) and overall 5-year survival (74% versus 69%;  $P < .05$ ) to 5-

FU/levamisole. 5-FU/leucovorin/levamisole was intermediate in efficacy and not significantly different from either of the other two regimens. This study suggests that 5-FU/high-dose leucovorin for six cycles is superior to standard 5-FU plus levamisole. INT-0089 showed that 5-FU/high-dose leucovorin was not superior but rather equal to 5-FU/levamisole.


Another important study reported at the 1996 ASCO meeting addressed the efficacy of adjuvant therapy in stage II colon cancer patients. This question has been an important concern of clinicians. As described previously, the original NCCTG 5-FU/levamisole study and INT-0035 both demonstrated no significant overall or disease-free survival benefit of adjuvant therapy in patients with stage II colon cancer. In contrast, NSABP studies have shown benefit for 5-FU-based regimens in node-negative patients. The NSABP reviewed the mature results of adjuvant therapy with stage II patients in CO-1, CO-2, CO-3, and CO-4.<sup>52</sup> In the four colon cancer adjuvant trials reviewed, 1,567 stage II and 2,254 stage III colon cancer patients were treated. The authors point out that the non-NSABP intergroup studies treated relatively small numbers of stage II patients, and the lack of statistically signifi-

cant efficacy in these studies may be related to the low number of patients and the small number of relapses expected in the stage II patients, who have an inherently good prognosis. The compilation of NSABP data showed that untreated stage II patients had a 5-year survival of approximately 75%. The relative treatment-induced reductions in mortality in patients with stage II and III colon cancer were similar. The combined results from the four NSABP studies indicate that stage II as well as stage III patients benefit from adjuvant chemotherapy.

### Summary

Adjuvant therapy for colon cancer is now a mature and widely accepted standard of care for patients with resected large bowel tumors; adjuvant therapy for stage III colon cancer has also been shown to be highly cost-effective.<sup>53</sup> The cost of 5-FU/levamisole therapy for stage III colon cancer per year of life saved is less than \$5,000, which represents a favorable cost-benefit relationship for a medical intervention. The clinician managing a patient with colon cancer at the present time has several options for therapy. In patients with stage III colon cancer, therapy with 5-FU-based regimens clearly increases overall and disease-free survival. It is also clear that the results that have been obtained are not perfect; therefore, the first option of therapy should always be an ongoing clinical trial. Many such trials

are available, and Table 7 lists currently active studies in the United States. The clinician managing a patient with stage III colon cancer who is not in a clinical trial may choose a variety of regimens administered for durations of 6 to 12 months (Table 8). The preponderance of evidence suggests that 5-FU plus levamisole for 12 months is equal in efficacy to 5-FU plus leucovorin-based regimens given for a shorter period of time. A clinician may still choose the 5-FU plus levamisole regimen because of the decreased oral, myelosuppressive, and diarrheal toxicities associated with that regimen as opposed to the 5-FU/leucovorin regimens. Portal vein infusion of fluorinated pyrimidines still must be considered investigational.

Finally, although we cannot be absolutely sure about the benefit of adjuvant therapy in patients with resected node-negative colon cancer, the NSABP data suggest that some benefit may be seen in these patients. It is known that patients with stage II cancers demonstrating high-grade bowel obstruction or bowel perforation have poor prognoses with surgery alone. Such patients may be good candidates for adjuvant therapy. Also, a major effort to define high risk and low risk for recurrence in patients with stage II colon cancer by analyzing molecular genetic factors (tumor ploidy<sup>2-4</sup> and alternations in tumor suppressor genes<sup>7</sup>) may lead to a selection of Dukes B patients definitely requiring adjuvant therapy. 

### References

1. Parker SL, Tong T, Bolden S, et al: Cancer statistics, 1997. *CA Cancer J Clin* 1997;47:5-27.
2. Kokal W, Sheibani K, Terz J, et al: Tumor DNA content in the prognosis of colorectal carcinoma. *JAMA* 1986;255:3123-3127.
3. Bauer KD, Bagwell CB, Giaretti W, et al: Consensus review of the clinical utility of DNA flow cytometry in colorectal cancer. *Cytometry* 1993;14:486-491.
4. Tomoda H, Kakeji Y, Furusawa M: Prognostic significance of flow cytometric analysis of DNA

content in colorectal cancer: A prospective study. *J Surg Oncol* 1993;53:144-148.

5. O'Connell MJ, Schaid DJ, Ganju V, et al: Current status of adjuvant chemotherapy for colorectal cancer: Can molecular markers play a role in predicting prognosis? *Cancer* 1992;70 (Suppl 6): 1732-1739.
6. Zeng ZS, Sarkis AS, Zhang ZF, et al: p53 nuclear overexpression: An independent predictor of survival in lymph node-positive colorectal cancer patients. *J Clin Oncol* 1994;12:2043-2050.
7. Jen J, Kim H, Piantadosi S, et al: Allelic loss of

- chromosome 18q and prognosis in colorectal cancer. *N Engl J Med* 1994;331:213-221.
8. Cohen AM, Shank B, Friedman MA: Colorectal cancer, in DeVita VT, Hellman S, Rosenber SA (eds): *Cancer: Principles and Practice of Oncology*, ed 3. Philadelphia, JB Lippincott, 1989, pp 895-964.
  9. Potter JD, Slattery ML, Bostick RM, et al: Colon cancer: A review of the epidemiology. *Epidemiol Rev* 1993;15:499-545.
  10. Buyse M, Zeleniuch-Jacquotte A, Chalmers TC: Adjuvant therapy of colorectal cancer: Why we still don't know. *JAMA* 1988;259:3571-3578.
  11. Higgins GA Jr, Amadeo JH, McElhinney J, et al: Efficacy of prolonged intermittent therapy with combined 5-fluorouracil and methyl-CCNU following resection for carcinoma of the large bowel: A Veterans Administration Surgical Oncology Group report. *Cancer* 1984;53:1-8.
  12. Gastrointestinal Tumor Study Group: Adjuvant therapy of colon cancer: Results of a prospectively randomized trial. *N Engl J Med* 1984;310:737-743.
  13. Panettiere FJ, Goodman PJ, Costanzi JJ, et al: Adjuvant therapy in large bowel adenocarcinoma: Long-term results of a Southwest Oncology Group study. *J Clin Oncol* 1988;6:947-954.
  14. Wolmark N, Fisher B, Rockette H, et al: Postoperative adjuvant chemotherapy or BCG for colon cancer: Results from NSABP Protocol C-01. *J Natl Cancer Inst* 1988;80:30-36.
  15. Boice JD Jr, Greene MN, Killen JY, et al: Leukemia and preleukemia after adjuvant treatment of gastrointestinal cancer with semustine (methyl-CCNU). *N Engl J Med* 1983;309:1079-1084.
  16. Laurie JA, Moertel CG, Fleming TR, et al: Surgical adjuvant therapy of large-bowel carcinoma: An evaluation of levamisole and the combination of levamisole and fluorouracil: The North Central Cancer Treatment Group and the Mayo Clinic. *J Clin Oncol* 1989;7:1447-1456.
  17. Moertel CG, Fleming TR, Macdonald JS, et al: Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 1990;322:352-358.
  18. Moertel C, Fleming T, Macdonald J, et al: The intergroup study of 5-fluorouracil (5-FU) plus levamisole (LEV) and levamisole alone as adjuvant therapy for stage C colon cancer. A final report. *Proc Am Soc Clin Oncol* 1992;11:161. Abstract.
  19. Moertel CG, Fleming TR, Macdonald JS, et al: Fluorouracil plus levamisole as effective adjuvant therapy after resection of stage III colon carcinoma: A final report. *Ann Intern Med* 1995; 122: 321-326.
  20. Moertel CG, Fleming TR, Macdonald JS, et al: Intergroup study of fluorouracil plus levamisole as adjuvant therapy for stage II/Dukes' B2 colon cancer. *J Clin Oncol* 1995;13:2936-2943.
  21. Shulman K, Schilsky RL: Adjuvant therapy of colon cancer. *Semin Oncol* 1995;22:600-610.
  22. NIH Consensus Conference: Adjuvant therapy for patients with colon and rectal cancer. *JAMA* 1990;264:1444-1450.
  23. Leichman CG, Fleming TR, Muggia FM, et al: Phase II study of fluorouracil and its modulation in advanced colorectal cancer: A Southwest Oncology Group study. *J Clin Oncol* 1995;13:1303-1311.
  24. Taylor I, Machin D, Mullee M, et al: A randomized controlled trial of adjuvant portal vein cytotoxic perfusion in colorectal cancer. *Br J Surg* 1985;72:359-363.
  25. Gray BN, Dezwart J, Fisher R, et al: The Australian and New Zealand trial of adjuvant chemotherapy in colon cancer, in Salmon SEW (ed): *Adjuvant Therapy of Cancer V*. Orlando, Grune & Stratton, 1987, pp 537-554.
  26. Wereldsma J, Bruggink ED, Meijer WS, et al: Adjuvant portal liver infusion in colorectal cancer with 5-fluorouracil/heparin versus urokinase versus control: Results of a prospective randomized clinical trial (colorectal adenocarcinoma trial I). *Cancer* 1990;65:425-432.
  27. Swiss Group for Clinical Cancer Research (SAKK): Long-term results of single course of adjuvant intraportal chemotherapy for colorectal cancer. *Lancet* 1995;345:349-353.
  28. Beart RW Jr, Moertel CG, Wieand HS, et al: Adjuvant therapy for resectable colorectal carcinoma with fluorouracil administered by portal vein infusion: A study of the Mayo Clinic and the North Central Cancer Treatment Group. *Arch Surg* 1990;125:897-901.
  29. Wolmark N, Rockette H, Wickerham DL, et al: Adjuvant therapy of Dukes' A, B and C adenocarcinoma of the colon with portal-vein fluorouracil hepatic infusion: Preliminary results of National Surgical Adjuvant Breast and Bowel Project Protocol C-02. *J Clin Oncol* 1990;8:1466-1475.
  30. Wolmark N, Rockette H, Petrelli N, et al: Long-term results of the efficacy of perioperative portal vein infusion of 5-FU for treatment of colon cancer: NSABP C-02. *Proc Am Soc Clin Oncol* 1994;13:194. Abstract.
  31. Fielding LP, Hittinger R, Grace RH, et al: Randomised controlled trial of adjuvant chemotherapy by portal-vein perfusion after curative resection for colorectal adenocarcinoma. *Lancet* 1992;340:502-506.
  32. Riethmuller G, Schneider-Gadicke E, Schlimok G, et al: Randomised trial of monoclonal antibody for adjuvant therapy of resected Dukes' C colorectal carcinoma: German Cancer Aid 17-1A Study Group. *Lancet* 1994;343:1177-1183.
  33. Foon KA, Bhattacharya-Chatterjee M, Chakraborty WJ, et al: Murine anti-idiotypic monoclonal antibody induces specific humoral responses to carcinoembryonic antigen (CEA) in colorectal cancer patients. *Proc Am Soc Clin Oncol* 1994;13:294. Abstract.
  34. Haller DG, Catalano PJ, Macdonald JS, et al: Fluorouracil (FU), leucovorin (LV) and levamisole (LEV) adjuvant therapy for colon cancer: Preliminary results of INT-0089. *Proc Am Soc Clin Oncol* 1996;15:211. Abstract.

35. Wolmark N, Rockette H, Mamounas EP, et al: The relative efficacy of 5-FU + leucovorin (FU-LV), 5-FU + levamisole (FU-LEV), and 5-FU + leucovorin + levamisole (FU-LV-LEV) in patients with Dukes' B and C carcinoma of the colon: First report of NSABP C-04. *Proc Am Soc Clin Oncol* 1996;15:205. Abstract.
36. O'Connell MJ, Laurie JA, Shepherd L, et al: A prospective evaluation of chemotherapy duration and regimen as surgical adjuvant treatment for high-risk colon cancer: A collaborative trial of the North Central Cancer Treatment Group and The National Cancer Institute of Canada Clinical Trials Group. *Proc Am Soc Clin Oncol* 1996;15:209. Abstract.
37. Advanced Colorectal Cancer Meta-Analysis Project: Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: Evidence in terms of response rate. *J Clin Oncol* 1992;10:896-903.
38. O'Connell MJ, Mailliard JA, Kahn MJ, et al: Controlled trial of fluorouracil and low-dose leucovorin given for 6 months as postoperative adjuvant therapy for colon cancer. *J Clin Oncol* 1997;15:246-250.
39. Wolmark N, Rockette H, Fisher B, et al: The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: Results from National Surgical Adjuvant Breast and Bowel Project protocol C-03. *J Clin Oncol* 1993;11:1879-1887.
40. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT): Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. *Lancet* 1995;345:939-944.
41. Francini G, Petrioli R, Lorenzini L, et al: Folinic acid and 5-fluorouracil as adjuvant chemotherapy in colon cancer. *Gastroenterology* 1994;106:899-906.
42. Piedbois P, Buyse M, Gray R, et al: Portal vein infusion is an effective adjuvant treatment for patients with colorectal cancer. *Proc Am Soc Clin Oncol* 1995;14:192. Abstract.
43. Crowley JJ: Perioperative portal vein chemotherapy, in *ASCO Educational Book* 1994. Chicago, American Society of Clinical Oncology, 1994, p 171.
44. Davies N, Kynaston H, Yates J, et al: Reticuloendothelial stimulation: Levamisole compared. *Dis Colon Rectum* 36:1993;1054-1058.
45. Taylor DD, Gerceel-Taylor C, Fowler WC, et al: Enhancement of antitumor effects of combined chemoimmunotherapy. *J Immunother* 1993;13:91-97.
46. Holcombe RF, Stewart RM, Betzing K, et al: Alteration of lymphocyte phenotype in patients receiving adjuvant 5FU-levamisole. *Proc Am Soc Clin Oncol* 1993;12:295. Abstract.
47. Holcombe RF, Stewart RM, Betzing K, et al: Clinical outcome in patients with Dukes' stage C colon cancer correlates with changes in natural killer (NK) cells and CD8+ T-cells during adjuvant therapy with 5-FU and levamisole. *Proc Am Soc Clin Oncol* 1994;13:228. Abstract.
48. Schiller JH, Lindstrom M, Witt PL, et al: Immunological effects of levamisole in vitro. *J Immunother* 1991;10:297-306.
49. Clinical Immunology Society: New progress in immunotherapy for colorectal cancer patients. *Clin Immunol Spectrum* 1994;6:1.
50. Hodi FS, Catalano P, Macdonald JS, et al: Age as a factor influencing the toxicity of adjuvant chemotherapy for colorectal cancer. Pending submission, 1996.
51. Haller DG, Catalano P, Macdonald JS, et al: Gender as a factor influencing the toxicity of adjuvant chemotherapy for colorectal cancer. Second International Conference on Biology, Prevention, and Treatment of Gastrointestinal Malignancies, Koln, Germany, January 1995. Abstract.
52. Mamounas EP, Rockette H, Jones J, et al: Comparative efficacy of adjuvant chemotherapy in patients with Dukes' B vs C colon cancer: Results from four NSABP adjuvant studies (EO1, EO2, EO3, EO4). *Proc Am Soc Clin Oncol* 1996;15:205. Abstract.
53. Brown ML, Nayfield SG, Shibley LM: Adjuvant therapy for stage III colon cancer: Economics returns to research and cost-effectiveness of treatment. *J Natl Cancer Inst* 1994;86:424-430.
54. O'Connell MJ: Surgical adjuvant therapy of colorectal cancer, in *ASCO Educational Book* 1994. Chicago, American Society of Clinical Oncology, 1994.

**American Cancer Society National Conference on  
Informing Purchasing Decisions for Oncologic Services:  
Current Methods and Models in the Marketplace  
Chicago, Illinois • September 11-12, 1997**

The purpose of this conference is to develop recommendations to assist purchasers of health care in making better informed decisions when procuring benefits packages for oncology services.

For further information please contact Terri Ades, RN, CS, MS, OCN, Director, Health Care Initiatives, American Cancer Society, 1599 Clifton Road, NE, Atlanta, GA 30329-4251; telephone: 404-329-7617; fax: 404-325-2548.