Adjuvant Therapy of Colon Cancer

John S. Macdonald, MD

Abstract
Adjuvant therapy, believed by some to be of no benefit for colorectal cancer as recently as 10 years ago, now offers thousands of patients considerable hope after surgical resection. The first effective adjuvant regimen—combined fluorouracil (5-FU) and levamisole—described in 1989, was soon supplanted by a variety of 5-FU-based regimens, usually combined with leucovorin.

Although most recent research in the adjuvant setting has focused on refining chemotherapy doses, schedules, and combinations, with the aim of improving efficacy and decreasing toxicity, investigators have also explored other approaches, such as portal vein infusion, monoclonal antibodies, interferon-alpha, and vaccines.

Future directions being evaluated for adjuvant therapy of colon cancer include the use of oral fluorinated pyrimidines, which may replace current intravenous treatments, as well as the incorporation of new agents, such as oxaliplatin and CPT-11, into adjuvant chemotherapy programs.

Introduction
Colorectal cancer is a very significant health problem in the United States, with approximately 129,400 cases expected to occur in 1999.1 Of all large bowel malignancies expected to be diagnosed in 1999, approximately 34,700 (27%) will be confined to the rectum, with the remainder occurring in the colon.

Although researchers are studying the use of molecular markers (i.e., ploidy2-4 and tumor suppressor gene mutation/deletion5-7) as prognostic tools, the most important prognostic information available to clinicians managing patients with colorectal cancer is still derived from surgical pathologic staging of the resected primary tumor.8

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), and in patients with stage III disease (node positive), the risk of death from cancer is as high as 70% during the five years after surgical resection.8

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. This approach to post-resection treatment, called adjuvant therapy, is aimed at destroying microscopic metastatic disease and, ideally, at preventing death from metastatic cancer.

Adjuvant therapies for colon cancers are quite distinct from those developed to treat rectal cancers. Radiation therapy, for example, is almost always a major part of adjuvant programs for rectal cancer (tumors below the peritoneal
reflection). In contrast, radiation is not utilized to treat colon cancer (tumors above the peritoneal reflection). This review will cover only the adjuvant therapy of colon cancer.

Thirty Years of Adjuvant Therapy

Many adjuvant chemotherapy and/or immunotherapy trials have been conducted to evaluate various protocols for colon cancer over the past 30 years. The most commonly used single agent for adjuvant therapy in colon cancer has been fluorouracil (5-FU).

In 1988, a meta-analysis of studies using 5-FU as adjuvant therapy in large bowel cancer, published by Buyse and colleagues (Table 2), evaluated results of phase III clinical trials in which 4,700 patients were randomized to receive adjuvant 5-FU or surgery alone. Five-year survival benefits associated with 5-FU ranged from 2.3% to 5.7%, which was not a statistically significant difference when compared with survival of patients treated with surgery alone. Such unimpressive survival benefits, which could result from chance, would hardly justify the standard use of 5-FU as adjuvant therapy for colon cancer.

Until 1989, there was considerable doubt in the medical community that adjuvant therapy of colon cancer was of any value. Two studies reported in 1989 and 1990 significantly influenced not only clinical investigation of adjuvant treatment in colon cancer but also the standard of care of patients with resected colon cancer. These studies randomized patients after surgical resection of colon cancer to three different treatment arms: 5-FU plus levamisole for one year; lev-

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

AJCC=American Joint Committee on Cancer
Adapted from O’Connell
Levamisole alone for one year; and no adjuvant therapy.

Levamisole is an antihelminthic agent that was tested as adjuvant therapy for cancer because it appeared to positively modulate the human cellular immune system. The first 5-FU-plus-levamisole study conducted in the United States included 401 patients and was carried out by the North Central Cancer Therapy Group (NCCTG). The results, published in October 1989, demonstrated that the combination of 5-FU plus levamisole increased disease-free survival (p=0.02) and was associated with a small but significant (p=0.03) survival benefit in stage III patients. In contrast, levamisole alone did not significantly increase survival in stage III patients, and neither treatment was effective in patients with stage II colon cancer.

Results from this NCCTG study stimulated the initiation of a second clinical trial, Intergroup (INT)-0035, which was specifically designed as a statistically well-powered (1,300 patients) study to confirm results of the smaller (401 patients) NCCTG trial. Investigators with the NCCTG, the Southwest Oncology Group (SWOG), and the Eastern Cooperative Oncology Group (ECOG) participated in this collaborative effort.

The results of this study were published in 1990, updated at an American Society of Clinical Oncology meeting in 1992, and reported in final form in 1995. At the time of the initial report in 1990, with three and a half years of median follow-up, the combination of 5-FU plus levamisole was strikingly positive for stage III patients. This adjuvant regimen decreased relapse by 41% (p<0.0001) and decreased death from recurrent colorectal cancer by 33% (p=0.006). Again, levamisole alone had no beneficial effect in stage III patients.

The mature results of this study (seven years of median follow-up) demonstrated an increase in the survival rate (60% versus 46%) 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 will have occurred by five years after resection in patients with stage III colon cancer. Clearly, combination adjuvant therapy with 5-FU plus levamisole changed the natural history of resected stage III colon cancer.

STAGE III DISEASE VERSUS STAGE II DISEASE

Although investigators primarily sought to assess the benefits for 5-FU plus levamisole in stage III colon cancer, it became clear that the combination was not associated with similar benefit in pa-

### Table 2

| Treatment Group | Number Entered | Number Dead | Odds Ratio* | Range of Five-Year Survival Advantage |
|-----------------|----------------|-------------|-------------|---------------------------------------|
| 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 

![Table 2](https://example.com/table2.png)
tients with stage II disease compared with surgery alone. While relatively small numbers of patients with stage II colon cancer were included in this study (159 in each arm), the seven-year disease-free survival for stage II patients treated with 5-FU plus levamisole was 79% versus 71% with surgery alone. A levamisole-alone arm was not included in the stage II study. The apparent 8% benefit in disease-free survival was not statistically significant (p=0.10). Overall survival of patients with stage II colon cancer was not increased with adjuvant therapy at seven years (72% in both treatment arms, p=0.83).

SAFETY OF 5-FU PLUS LEVAMISOLE
The combination of 5-FU plus levamisole was generally well tolerated, and compliance with therapy was good. Only one drug-related fatality resulting from neutropenic sepsis occurred in the INT-0035 trial.

Myelosuppression seen with the combination regimen is probably attributable to the 5-FU, although levamisole has been associated with agranulocytosis in rare instances. Other toxicities that have been reported with the combination of 5-FU and levamisole include mild elevation of hepatic transaminases, dysgeusia, arthralgia, neurotoxicity, and depression. These adverse events tend to be mild and usually do not preclude continued therapy.

The magnitude of the benefit associated with combination adjuvant therapy using 5-FU plus levamisole demonstrated in both the NCCTG and the confirmatory INT studies resulted in rapid FDA approval of the regimen for stage III colorectal cancer in 1990. 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. The 5-FU-plus-levamisole data also made clear that it was no longer acceptable for phase III trials in adjuvant therapy of resected colon cancer to include surgery-only control arms. As a result, studies conducted in the 1990s have used the combination of 5-FU plus levamisole as the standard against which investigational therapies are compared.

Current Status of Adjuvant Therapy
The period between 1990 and 1999 has been one of innovation in conceptual approaches to adjuvant therapy for colon cancer. It also has been a time during which results of large clinical trials have defined the relative efficacies of various 5-FU-based regimens, including those that used leucovorin. These trials have resulted in definitions of standards of care for adjuvant therapy and have established and confirmed the role of 5-FU plus leucovorin as the standard in advanced colon cancer. Other therapeutic strategies that have been actively studied in colorectal cancer include regional therapy, particularly portal vein infusion, and immunotherapy.

THE ROLE OF 5-FU PLUS LEUCOVORIN
The combination of 5-FU plus leucovorin in a variety of doses and schedules...
has been used as a standard of care in patients with advanced colon cancer for a number of years. A meta-analysis published in 1992 demonstrated that while overall survival was not increased with 5-FU plus leucovorin in patients with advanced colon cancer, the response rate was significantly increased compared with that achieved with 5-FU alone. The next logical step, therefore, seemed to be to test the combination of 5-FU plus leucovorin as adjuvant therapy in patients with resected high-risk colon cancer.

Many Doses and Schedules—Same Results

Several large phase III clinical trials reported within the last three years have defined the role of 5-FU and various permutations of leucovorin, with and without levamisole, as adjuvant therapy. Some of these major studies evaluated 5-FU-plus-leucovorin regimens compared with surgery alone or compared with a “control” chemotherapy arm.

These early studies, involving more than 2,000 patients and a variety of different 5-FU-plus-leucovorin doses and schedules, evaluated the role of the combination and showed significant improvements in disease-free and overall survival (Table 3).

The NCCTG study used a common monthly regimen consisting of 5-FU at 425 mg/m² with leucovorin at 20 mg/m², given daily for five days. The International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) study used 5-FU at 400 mg/m² and leucovorin at 200 mg/m² daily for five days, and the National Surgical Adjuvant Breast and Bowel Project (NSABP) CO-3 study compared 5-FU plus leucovorin with a regimen of methyl-lomustine (CCNU), 5-FU, and vincristine. The CO-3 study used 5-FU at 500 mg/m² and leucovorin at 500 mg/m² weekly for six-week cycles with

### Table 3

| Regimen | Total Patients Accrued | ≥ Three-Year DFS (%) | ≥ Three-Year Survival (%) | Trial |
|---------|------------------------|----------------------|--------------------------|-------|
| Surgery+5-FU/LV | 239 | 74 | 81 | Francini³⁶ |
| Surgery alone | 60 | 64 | |
| Surgery+5-FU/LV | 309 | 77 | 75 | NCCTG³³ |
| Surgery alone | 64 | 71 | |
| Surgery+5-FU/LV | 1,081 | 73 | 84 | NSABP³⁴ |
| Surgery+MOF | 64 | 77 | |
| Surgery+5-FU/LV | 1,526 | 71 | 83 | IMPACT³⁵ |
| 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.
two-week breaks, resulting in 48 weeks of therapy. In the other studies, adjuvant chemotherapy was administered for approximately six months.

As was the case with 5-FU plus leucovorin in advanced colorectal cancer, differences in leucovorin dosing schedules were not associated with significant differences in efficacy. In the three studies that used surgery-only controls, all 5-FU-plus-leucovorin regimens increased survival compared with surgery alone. [Note: 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, along with the older report from INT-0035 indicating that 5-FU plus levamisole was effective therapy, led to the design of clinical trials comparing 5-FU plus levamisole with 5-FU plus leucovorin as the next logical step. This strategy, pursued by both the INT and NSABP trial groups with results reported in 1997 and 1998, is discussed later in this review, in the section on current recommendations for adjuvant therapy (see page 210).

**Portal Vein Infusion**

Portal vein infusion of chemotherapy has been explored as an adjuvant therapy for colon cancer for at least two decades. 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. Effective cytotoxic therapy delivered into the portal system, therefore, could destroy microscopic metastatic disease in the liver. If this hypothesis is correct, patients treated with effective adjuvant therapy through the portal vein should have a decrease in liver metastases along with an increase in overall survival.

The first study to spark interest in portal vein infusion was published by Taylor et al initially in 1977 and updated in 1985.19 A decrease in liver metastases was noted in 127 patients randomized to receive 5-FU plus heparin by the portal vein compared with 117 patients who were treated with surgery alone. Additionally, patients receiving intraportal therapy experienced a significantly increased five-year survival rate (p=0.002). Interestingly, the benefit achieved with portal vein infusion of chemotherapy in the study appeared to be limited to patients with stage II colon cancer and was not apparent in stage III cases.

The Taylor study led to other phase III studies aimed at confirming the benefit of portal vein infusion of fluorinated pyrimidines. Table 4 lists pertinent data from a number of these studies. As can be seen, with the exception of the NSABP24-25 and Swiss Group for Clinical Cancer Research (SAKK)27 studies, most clinical trials enrolled 200 or fewer patients per treatment arm. Also, the results, in terms of overall benefit and decrease in liver metastases, were mixed.

The NSABP study (CO-2) is of interest because it demonstrated both an increase in disease-free survival and, in the most recent report, an overall increase in survival.25 Nevertheless, this study showed that portal vein infusion did not decrease liver metastases. It has been suggested that fluorinated pyrimidine has a systemic adjuvant effect but not a significant impact on hepatic metastases. The clinical benefit seen in the CO-2 trial may be related, therefore, to the fact that the adjuvant 5-FU was given immediately postoperatively rather than 30 to 40 days postoperatively. It is possible that the intraportal route of therapy is irrelevant to any beneficial effects of treatment and that the timing of administration, namely in the immediate postoperative period, is the important factor. This concept (i.e., immediate postoperative delivery of chemotherapy) is being tested in INT-0136, a phase III study in which seven days of 5-FU administered by continuous intravenous infusion are initiated within 24 hours of surgery and compared with a
standard 5-FU-plus-levamisole program started within 35 days of colon resection.

A meta-analysis published in 1997 evaluated results from 10 randomized studies of portal vein infusion involving about 4,000 cases. Analyses at five years revealed only a minimal overall survival benefit, approximately 4%, for patients treated with portal vein infusion. The authors of the meta-analysis suggested that this survival benefit, although statistically significant, was “not statistically secure” and called for randomized studies “involving several thousand more patients.”

Additional concerns about the questionable benefit of portal vein infusion were voiced in a careful analysis of published studies by Crowley. This analysis noted that most phase III studies of portal vein infusion had significant flaws in design and execution, such as being underpowered to detect realistic levels of treatment effect; frequent use of subset analysis; and high numbers of ineligible cases. He pointed out that although a meta-analysis may indeed show statistically significant results, the flawed nature of the component studies requires caution before applying the results to clinical practice or clinical research. Portal vein infusion should be considered, therefore, an investigational approach to adjuvant treatment of colon cancer rather than a standard approach.

### Table 4
Portal Vein Infusion Trials

| Case Characteristics | Treatment                  | Number of Patients | Decrease in Liver Metastases? | Increased Survival? | Trial          |
|----------------------|----------------------------|--------------------|-------------------------------|---------------------|---------------|
| Dukes A, B, and C; Colon and Rectal | 5-FU/heparin | 127                | Yes                           | Yes                 | Taylor et al 19 |
|                      | Control                 | 117                |                               |                     |               |
| Dukes A, B, and C; Colon | 5-FU/heparin | 442                | No                            | Yes                 | NSABP CO-224,25 |
|                      | Control                 | 459                |                               |                     |               |
| Dukes A, B, and C; Colon and Rectal | 5-FU/mitomycin/heparin | 236                | Yes                           | Yes                 | SAKK22        |
|                      | Control                 | 233                |                               |                     |               |
| Dukes A, B, and C; Colon and Rectal | 5-FU/heparin | 103                | No                            | No                  | Fielding et al 26 |
|                      | Control                 | 145                |                               |                     |               |
| Dukes B2 and C; Colon and Rectal | 5-FU/heparin | 110                | No                            | No                  | NCCTG23       |
|                      | Control                 | 109                |                               |                     |               |
| Dukes A, B, and C; Colon and Rectal | 5-FU/heparin | 99                 | Yes                           | No                  | Wereldsma et al 21 |
|                      | Urokinase                | 103                |                               |                     |               |
|                      | Control                 | 102                |                               |                     |               |

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

Immunotherapy of cancer has always been an intriguing concept. Effective mobilization of host immune mechanisms to destroy malignant disease is an intrinsically attractive strategy. Several compounds with immunomodulatory properties have been proposed for the adjuvant therapy of colon cancer, and a few, such as levamisole (a pharmacologic modulator), 17-1A (a murine monoclonal antibody), and interferon-alpha (a cytokine), have been tested in clinical trials.

**Levamisole**

Levamisole was initially of interest in colon cancer partly because it was thought to be a nonspecific immunomodulator. Although animal studies and in vitro analyses suggest that levamisole does exert an immunomodulatory effect, clinical studies have shown mixed results in regard to immunomodulation. The mechanism for the benefit of levamisole when combined with 5-FU as adjuvant therapy—in view of the former drug’s demonstrated lack of consistent clinical immunomodulatory activity—is unclear, and it is possible that any immunomodulatory effects of levamisole are irrelevant to its role as part of an active therapy in resected colon cancer.

**MONOCLONAL ANTIBODIES**

Some investigators are enthusiastic about evaluating the 17-1A monoclonal antibody as adjuvant therapy for colon cancer, based on results of a small (fewer than 200 patients) German phase III trial reported by Riethmüller et al. 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 and rectal cancer in the German study. The benefits of 17-1A therapy—as measured by freedom from relapse and survival—were of the same order of magnitude as the benefits seen with 5-FU plus levamisole in the INT-0035 study.

An update of Riethmüller’s phase III study was published recently and confirms the survival benefit of 17-1A therapy. Of interest, local recurrence was not decreased by use of the monoclonal antibody, and all of the decrease in relapse resulted from prevention of distant metastatic disease.

International studies are currently evaluating 17-1A in combination with 5-FU-based regimens in patients with stage III colon cancer and are close to completing accrual. Another study being conducted in the United States, by the intergroup mechanism, is testing 17-1A as a single agent in patients with stage II colon cancer, comparing surgery plus 17-1A with surgery alone. This trial, initiated in late 1997, is particularly interesting as a mechanism for evaluating 17-1A because it does not include any chemotherapy. Chemotherapy has the potential to alter immune responsiveness and thus may mask the potential benefit from an immunotherapeutic agent.

**INTERFERON-ALPHA**

Interferon-alpha in combination with 5-FU plus leucovorin has been tested in the NSABP CO-5 trial. The results of this two-armed study of 2,176 patients were reported in abstract form in May 1998. Although the addition of interferon to the standard combination regimen produced no differences in disease-free overall survival, there was a significant increase in toxicity among patients in
the interferon group. The clinical consequence of this increased toxicity was the withdrawal of 22% of patients in the interferon arm, compared with a drop-out rate of 5% for those who received only 5-FU plus leucovorin. The results of CO-5 clearly demonstrate that interferon-alpha has no role in combination adjuvant therapy with 5-FU plus leucovorin for colon cancer.

**VACCINES**

Interesting innovative approaches to immunotherapy, such as the work described by Foon et al., which tested a vaccine concept, are being evaluated in early clinical trials in the United States. The vaccine is an anti-idiotypic monoclonal murine antibody raised against a highly tumor-specific CEA epitope. The aim of immunization with the vaccine is to break specific immune tolerance to the tumor-specific CEA epitope in patients with colon cancer.

This approach has resulted in specific immunization to the target CEA epitopes in 70% to 90% of patients with advanced disease and in 100% of patients undergoing immunization as adjuvant therapy in small pilot studies. It is not yet known, however, whether this approach, namely specific immunization against a tumor-associated antigen in humans, will result in an immunotherapeutic antitumor effect.

A United States cooperative group is considering a large-scale clinical trial of the anti-idiotypic vaccine as adjuvant therapy.

**Standard of Care for Patients with Resected Colon Cancer**

A most important clinical question for oncologists with respect to adjuvant therapy for colon cancer has been the delineation of the relative roles of active therapies. Understanding the risks and benefits of available therapies will allow definition of the standards of care for the large number of patients affected with colon cancer each year.

Important questions include: Is there still a role for 5-FU plus levamisole or is 5-FU plus leucovorin the therapy of choice? Are there differences in toxicity and efficacy among available therapies that would impel a clinician to choose one regimen over the other? Finally, what is the role of chemotherapy in resected stage II colon cancer? Recently published results of large studies conducted by cooperative clinical trials groups have helped answer these important clinical questions.

Table 5 shows the schemata of INT-0089, NSABP CO-4, and NCCTG 894651. These studies are all basically similar in that they evaluated 5-FU plus levamisole as a standard therapy compared with a series of 5-FU-plus-leucovorin regimens.

**INT-0089**

In the largest study, INT-0089, which involved 3,759 patients, 80% had stage III colon cancer. 5-FU plus levamisole, considered the “control” arm, was administered for 12 months; the 5-FU/low-dose leucovorin/levamisole program was given for six months; and the weekly high-dose 5-FU-plus-levamisole regimen was given as four six-week cycles. INT-0089 was designed as a comparative study, and mature results reported in 1998 have demonstrated that there were no differences in efficacy among prospectively planned comparisons of the following regimens: (1) 5-FU plus high-dose leucovorin and 5-FU plus low-dose leucovorin; (2) 5-FU plus levamisole and 5-FU plus high-dose leucovorin; (3) 5-FU plus low-dose leucovorin and 5-FU plus low-dose leucovorin plus levamisole; (4) 5-FU plus levamisole and 5-FU plus low-dose leucovorin; and (5) 5-FU plus levamisole and 5-FU plus low-dose leucovorin.

The complete and mature results of INT-0089 showed that the five-year disease-free (56% to 60%) and overall (63%...
to 67%) survival rates for patients with high-risk stage II (obstructing and/or perforating node-negative lesions) and stage III colon cancers are not different for the various 5-FU-plus-leucovorin and the 5-FU-plus-levamisole strategies and schedules. Also, the percentages of disease-free and overall survival for patients treated on all the arms of INT-0089 were comparable to those achieved with 5-FU plus levamisole in INT-0035. In general, most clinicians prefer to use 5-FU plus leucovorin, which is given for only six months, over 5-FU plus levamisole, which must be given for one year.

Safety

The safety analyses for INT-0089, summarized in Table 6, revealed interesting and clinically important differences among the various treatments’ toxicity profiles. For grade III or worse toxicities,

### Table 5
Multi-Institutional Trials Exploring Postoperative Fluorouracil–Plus–Leucovorin Strategies: Reported 1996 - 1998

| Study                | Number of Patients Accrued | Regimen                                      |
|----------------------|----------------------------|----------------------------------------------|
| NCCTG 894651<sup>32</sup> | 915                        | 5-FU+levamisole (6 or 12 months)             |
|                      |                            | 5-FU+leucovorin+levamisole (6 or 12 months) |
| NSABP CO-4<sup>31</sup> | 2,151                      | 5-FU+levamisole                              |
|                      |                            | 5-FU+leucovorin weekly                       |
|                      |                            | 5-FU + leucovorin+levamisole                |
| Intergroup-0089<sup>30</sup> | 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

### Table 6
Intergroup-0089: Toxicity of Grade III 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
the 5-FU-plus-low-dose leucovorin, with and without levamisole, regimens were associated with significantly higher incidences of stomatitis than were the 5-FU-plus-levamisole or 5-FU-plus-high-dose leucovorin regimens. Conversely, grade III or worse diarrhea was almost three times more common with 5-FU plus high-dose leucovorin than with 5-FU plus levamisole.

Safety analysis of INT-0089 also showed interesting and clinically important differences in qualitative toxicities, according to age and gender. Patients older than 70 years (unpublished data) and females had significantly higher rates of stomatitis and leukopenia. As leukopenia and stomatitis are most commonly associated with low-dose 5-FU-plus-leucovorin regimens, clinicians may wish to carefully consider the use of these programs in women and the elderly.

In summary, it is clear that the mature findings of INT-0089, a very large phase III clinical trial, provided several important pieces of information. First, 5-FU-plus-leucovorin regimens given for six months and 5-FU plus levamisole given for one year appear to be similarly effective. Second, results of the qualitative toxicity analyses provide clinicians with the tools to rationally choose among equally efficacious therapies a treatment regimen tailored to individual patient tolerance.

NCCTG 894651
A second significant clinical trial, NCCTG 894651, reported by O’Connell et al., addressed the important issue of whether 12 or six months of adjuvant therapy were required for patients with resected colon cancer. The trial, which involved 890 eligible patients, compared the following two regimens, both given for six and 12 months: 5-FU plus low-dose leucovorin plus levamisole; and 5-FU plus levamisole.

This study demonstrated that the three-drug regimen—5-FU plus levamisole plus leucovorin—for six months resulted in longer overall survival compared with 5-FU plus levamisole for six months (75% versus 63%; p<0.03). However, 5-FU plus levamisole for 12 months produced survival benefits equal to those of 5-FU plus levamisole plus leucovorin for six months. It was concluded that six months of 5-FU plus leucovorin plus levamisole are equivalent to 12 months of 5-FU plus levamisole.

Together with the results of INT-0089, demonstrating that six months of 5-FU plus leucovorin by either of two schedules is equal to 5-FU plus levamisole for 12 months, it seems clear that

---

**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.**

---

most clinicians and patients would choose six months of a 5-FU-plus-leucovorin regimen without levamisole, over 12 months of 5-FU-plus-levamisole therapy. Additionally, results from the INT-0089 and NCCTG-894651 trials demonstrated that six months of 5-FU plus levamisole do not constitute adequate adjuvant therapy for colon cancer.

NSABP CO-4
In a third randomized study, NSABP CO-4, six cycles of 5-FU plus high-dose leucovorin (each cycle consisting...
of the combination of 5-FU at 500 mg/m² plus leucovorin at 500 mg/m², given weekly for six weeks) was compared with either the standard 5-FU-plus-levamisole regimen or a combination of 5-FU plus high-dose leucovorin plus levamisole. A total of 2,151 patients with stages II and III colon cancers were studied.

Results showed that 5-FU plus leucovorin was superior in disease-free (64% versus 60%; p<0.05) and overall five-year survival (74% versus 69%; p<0.05) to 5-FU plus levamisole. The three-drug regimen, 5-FU plus leucovorin plus levamisole, was intermediate in efficacy and was not significantly different from either of the other two regimens. This study suggested that 5-FU plus high-dose leucovorin for six cycles was superior to the standard of 12 months of 5-FU plus levamisole. This result contrasted somewhat with that of INT-0089, which showed that 5-FU plus high-dose leucovorin was not superior but rather equivalent to 5-FU plus levamisole. It is important to remember that more 5-FU-plus-leucovorin therapy (six cycles, or 48 weeks) was given in the NSABP CO-4 trial, whereas only four cycles (32 weeks) of the same regimen were given in the INT-0089 trial.

CURRENT RECOMMENDATIONS

Stage III Colon Cancer

The clinician treating a patient with stage III colon cancer not in a clinical trial may choose a variety of regimens administered for durations of six to 12 months (Table 7). 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. As the INT-0089 trial has shown that either one of two 5-FU-plus-leucovorin regimens given for approximately six months is equal to 5-FU plus levamisole for 12 months, there is little reason outside a clinical trial for a clinician to use 5-FU plus levamisole.

Stage II Colon Cancer

It is still unclear whether adjuvant therapy offers any significant benefit to patients with stage II colon cancer. Although the NSABP clinical trials CO-1 through CO-4 suggested that adjuvant chemotherapy can be effective in patients with stage II disease, the INT-0035 trial failed to show a positive effect in these patients. More recent adjuvant therapy studies (Table 5) are of no help in defining efficacy because, while many included stan-
standard or high-risk stage II cases, none utilized untreated control groups.

**MOLECULAR GENETIC FACTORS**

In an attempt to define subsets of patients with stage II disease that may benefit from adjuvant therapy, a major effort is being made to define molecular genetic factors (tumor ploidy and mutations/alterations in proto-oncogenes and tumor suppressor genes) that may increase risk of relapse. Such ancillary biologic studies are part of all currently active adjuvant therapy clinical trials. It should be emphasized, however, that although initial results suggest that molecular genetic abnormalities—for example, chromosome 18 deletion—are associated with increased risk of relapse, no information is available about what effects such abnormalities may or may not have with respect to response to adjuvant chemotherapy.

The fact that molecular genetic abnormalities may affect the potential benefit of adjuvant therapy should be carefully considered when therapy decisions are made for stage II patients with “high risk” molecular genetic abnormalities outside of a clinical trial. Patients should be made aware that it is unknown whether molecular genetic abnormalities will alter clinical benefit from postoperative chemotherapy.

**COST ISSUES**

The cost effectiveness of any widely applied therapy is of increasing importance. Postoperative adjuvant therapy of colon cancer is now a mature and widely accepted standard of care for patients with resected large bowel tumors, and adjuvant therapy for stage III colon cancer has also been shown to be highly cost-effective.

The cost of 5-FU plus levamisole as the reference regimen, it is clear that 5-FU plus leucovorin given for six months should be at least equally, if not more, cost-effective.

**Future Directions**

The clinician treating a patient with colon cancer at the present time has several options for adjuvant therapy. In patients with stage III colon cancer, therapy with 5-FU-based regimens clearly increases overall and disease-free survival. It is also apparent that the results that have been obtained thus far with these regimens are not perfect. Therefore, patients should always be offered the option of participating in a clinical trial. Many such trials are available, and Table 8 lists currently active cooperative group studies in the United States.

**FLUORINATED PYRIMIDINES**

Although most active clinical trials for resected stage III colon cancer are testing permutations of intravenous 5-FU, a number of new agents of interest are being, or will be, evaluated in clinical trials. A series of new orally administered fluorinated pyrimidine compounds, for instance, are of particular interest in colon cancer. One such compound, an orally administered combination of the fluorinated pyrimidine Tegafur, the dihydropyrimidine dihydrogenase (DPD) inhibitor uracil, and leucovorin, is currently being tested in the NSABP CO-6 trial. This oral fluorinated pyrimidine compound (UFT) is being compared with the standard regimen of 5-FU and high-dose leucovorin, as was used in previous NSABP studies.

This two-arm study, having an accrual goal of over 2,100 patients, is of great importance because, as an oral therapy, UFT would be preferred to current intravenous regimens for patients with resected colon cancer if it is shown to be active and well-tolerated.
At least two other fluorinated pyrimidines are currently in clinical trials and are likely to be included in future studies of adjuvant therapies. One of these therapies is the combination of oral 5-FU and the DPD inhibitor 776C85. The compound 776C85 significantly differs from uracil in its biologic effect upon DPD because 776C85 is an irreversible inactivator of the enzyme, whereas uracil is a competitive inhibitor. 776C85 is capable of very complete inactivation of DPD, making small oral doses of 5-FU clinically effective.

For example, in a phase I study of 5-FU and 776C85 given on a 28-day schedule, the effective oral dose of 5-FU was found to be only 1.15 mg/m²/day. The 776C85/5-FU combination is currently being widely tested in advanced gastrointestinal cancers, and in the near future, will be compared with continuous infusion 5-FU in a phase III metastatic colon cancer study being conducted by the United States intergroup.

This comparative study is of particular interest because all of the oral fluorinated pyrimidine formulations have pharmacokinetics similar to those of intravenously administered 5-FU by continuous infusion, producing continued low levels of plasma 5-FU. If the oral fluorinated pyrimidines are found to be effective and safe—and particularly if they are judged to be equivalent to low-dose continuous infusion intravenous 5-FU—then they will rapidly replace continuous infusion as a standard of care, eliminating the need for the catheters and pumps required for intravenous continuous infusion therapy.

A final oral fluorinated pyrimidine of interest is capecitabine, which is a prodrug of 5-FU recently approved in the United States for third-line therapy of advanced breast cancer. Capecitabine, a prodrug that depends upon carboxyl esterase and thymidine phosphorylase enzymes for activation, is of interest because it may be preferentially activated in tumors compared with normal tissues. Preferential activation at the tumor cell may increase the therapeutic index by

---

**Table 8**

| Study         | Accrual Goals | Regimen                                                                 |
|---------------|---------------|--------------------------------------------------------------------------|
| 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 | 1,500         | Prolonged continuous infusion 5-FU+levamisole versus Bolus 5-FU, leucovorin+levamisole |
| NSABP CO-6    | 2,100         | 5-FU+leucovorin versus UFT                                               |

5-FU=fluorouracil; NSABP=National Surgical Adjuvant Breast and Bowel Project; UFT=Tegafur+uracil+leucovorin (oral therapy)
producing higher cytotoxicity in colon cancer cells compared with non-neoplastic cells. If it proves effective in advanced colon cancer, capecitabine is certain be tested in the adjuvant setting.

**OTHER DRUGS**

**Oxaliplatin**

Although it has been demonstrated that both cisplatin and carboplatin have no efficacy in advanced colon cancer, oxaliplatin—a neurotoxic platinum analogue with clinically insignificant renal and bone marrow toxicity—does appear to have activity in advanced colon cancer. Oxaliplatin has been shown in European studies to enhance the response rate obtained with 5-FU.

A recent study from France demonstrated that the response rate with 5-FU increased from 26% to 57% with the addition of oxaliplatin. Further studies are underway to confirm the activity of oxaliplatin combined with fluorinated pyrimidines and to define whether any survival benefit results from use of this combination in advanced colorectal cancer. The 5-FU-plus-leucovorin-plus-oxaliplatin regimen is currently slated to be one of the treatment arms in the CO-7 trial, the NSABP’s upcoming large bowel adjuvant therapy study.

**CPT-11**

The only drug other than fluorinated pyrimidines approved in the United States for the treatment of advanced colon cancer is CPT-11. Adjuvant therapy combining CPT-11 with 5-FU plus leucovorin (see Figure) has been proposed, and a trial comparing 5-FU plus leucovorin (high-dose regimen) with 5-FU plus leucovorin plus CPT-11 has been designed. In the 5-FU-plus-leucovorin-plus-CPT-11 arm, the leucovorin dose has been reduced to 20 mg/m² from 500 mg/m² to reduce the potential for serious diarrhea. This study (Figure) will soon be activated as the next major Intergroup adjuvant therapy trial.

**Summary**

In summary, adjuvant therapy of colorectal cancer is now a widely accepted standard of care for patients with stage
III disease and is an area of particularly active investigation by clinical and laboratory-based oncologists. The standard of care for patients with resected colon cancer has clearly been significantly improved by the widespread use of 5-FU plus leucovorin. Many exciting areas of investigation remain to be explored in the adjuvant therapy setting, including definition of the roles of new oral fluorinated pyrimidines, evaluation of the value of non-fluorinated pyrimidine drugs, such as camptothecin and platinum analogues, and further study of sophisticated immunotherapies.

Moreover, there is no doubt that therapeutic studies targeting molecular genetic abnormalities of tumor cells will begin in the near future. All of this innovative clinical and basic science focused upon the improvement of adjuvant therapy bodes well for the care of patients with resected colon cancer, now and in the future.

References
1. Landis SH, Murray T, Bolden S, Wingo PA: Cancer statistics, 1999. CA Cancer J Clin 1999;49:8-31.
2. Kokal W, Sheibani K, Terz JR, Harada JR: 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 (suppl) 1992;70:1732-1739.
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 Jr, Hellman S, Rosenberg SA (eds): Cancer: Principles and Practice of Oncology, ed 3. Philadelphia, Lippincott, 1989, pp 895-964.
9. Potter JD, Slattery ML, Bostick RM, Gapstur SM: 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. 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.
12. 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.
13. Moertel C, Fleming T, Macdonald JS, et al: The intergroup study of 5-FU + levamisole and levamisole alone as adjuvant therapy for stage C colon cancer: A final report. Proc Am Soc Clin Oncol 1992;11:161. Abstract.
14. 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.
15. 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.
16. NIH Consensus Conference: Adjuvant therapy for patients with colon and rectal cancer. JAMA 1990;264:1444-1450.
17. Shulman K, Schilsky RL: Adjuvant therapy of colon cancer. Semin Oncol 1995;22:600-610.
18. 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.
19. 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.
20. Gray BN, Dezwart J, Fisher R, et al: The Australia and New Zealand trial of adjuvant chemotherapy in colon cancer, in Salmon SE (ed): Adjuvant Therapy of Cancer V. Orlando, Grune & Stratton, 1987, pp 537-554.
21. Wereldsma JC, Bruggink D, 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.
22. 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.

23. 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.

24. Wolmark N, Rocke 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 C0-2. J Clin Oncol 1990; 8:1466-1475.

25. Wolmark N, Rocke 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 C0-2. Proc Am Soc Clin Oncol 1994; 13:194. Abstract.

26. Fielding LP, Hittinger R, Grace RH, Fry JS: Randomised controlled trial of adjuvant chemotherapy by portal-vein perfusion after curative resection for colorectal adenocarcinoma. Lancet 1992;340:502-506.

27. Riethmüller 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.

28. Foon KA, Bhattacharya-Chatterjee M, Chakraborty M, et al: Murine antiidiotype monoclonal antibody induces specific humoral responses to carcinoembryonic antigen (CEA) in colorectal cancer patients. Proc Am Soc Clin Oncol 1994;13:294. Abstract.

29. 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.

30. Haller DG, Catalano PJ, Macdonald JS, Mayer RJ: Fluorouracil (FU), leucovorin (LV) and levasamisole (LEV) adjuvant therapy for colon cancer: Preliminary results of INT-0089. Proc Am Soc Clin Oncol 1996;15:486. Abstract.

31. Wolmark N, Rocke H, Mamounas EP, et al: The relative efficacy of 5-FU + leucovorin (FU-LV), 5-FU + levasamisole (FU-LEV), and 5-FU + leucovorin + levasamisole (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;15:460. Abstract.

32. O’Connell JM, 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;15:478. Abstract.

33. 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.

34. Wolmark N, Rocke 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 C0-3. J Clin Oncol 1993;11:1879-1887.

35. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT): Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. Lancet 1995;345:939-944.

36. Francini G, Petrioli R, Lorenzini L, et al: Folinic acid and 5-fluorouracil as adjuvant chemotherapy in colon cancer. Gastroenterology 1994;106:999-906.

37. Liver Infusion Meta-analysis Group: Portal vein chemotherapy for colorectal cancer: A meta-analysis of 4,000 patients in 10 studies. J Natl Cancer Inst 1997;89:497-505.

38. Crowley JF: Perioperative portal vein chemotherapy, in ASCO Educational Book 1994. Chicago, ASCO, 1994, p 171.

39. Davies N, Kynaston H, Yates J, et al: Reticuloendothelial stimulation: Levasamisole compared. Dis Colon Rectum 1993;36:1054-1058.

40. Taylor DD, Gercel-Taylor C, Fowler WC, Weese JL: Enhancement of antitumor effects of combined chemoimmunotherapy. J Immunother 1993;13:91-97.

41. Holcombe RF, Stewart RM, Betzing K, et al: Alteration of lymphocyte phenotype in patients receiving adjuvant 5-FU-levasamisole. Proc Am Soc Clin Oncol 1993;12:295. Abstract.

42. Holcombe RF, Stewart RM, Betzing KW, et al: Clinical outcome in patients with Dukes’ stage C colon cancer correlate with changes in natural killer (NK) cells and CD8+ T-cells during adjuvant therapy with 5-FU and levasamisole. Proc Am Soc Clin Oncol 1994;13:228. Abstract.

43. Schiller JH, Lindstrom M, Witt PL, et al: Immunological effects of levasamisole in vitro. J Immunother 1991;10:297-306.

44. Riethmüller G, Holz E, Schlimok G, et al: Monoclonal antibody therapy for resected Dukes’ C colorectal cancer: Seven-year outcome of a multicenter randomized trial. J Clin Oncol 1998;16:1788-1789.

45. Wolmark N, Bryant J, Hyams DM, et al: The relative efficacy of 5-FU + leucovorin (FU-LV) and 5-FU-LV + interferon alfa-2a in patients with Dukes’ B and C carcinoma of the colon: First report.
of NSABP C0-5. Proc Am Soc Clin Oncol 1998;17:255a. Abstract 981.

46. Clinical Immunology Society: New progress in immunotherapy for colorectal cancer patients. Clin Immunol Spectrum 1994: 6:1.

47. Haller DG, Catalano PJ, Macdonald JS, et al: Fluorouracil, leucovorin and levamisole adjuvant therapy for colon cancer: Five-year final report of INT-0089. Proc Am Soc Clin Oncol 1998;17:256a. Abstract 982.

48. 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, Köln, Germany, January 1995. Abstract.

49. 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.

50. 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.

51. Pazdur R: Phase I and pharmacokinetic evaluations of UFT plus oral leucovorin. Oncology 1997;11(9 suppl 10):35-39.

52. Schilsky RL, Hohenker J, Ratain MJ, et al: Phase I clinical and pharmacologic study of eniluracil plus fluorouracil in patients with advanced cancer. J Clin Oncol 1998;16:1450-1457.

53. Ajani JA: Chemotherapy for gastric carcinoma: New and old options. Oncology 1998;12(10 suppl 7):44-47.

54. Pazdur R, Hoff PM, Medgyesy D, et al: The oral fluorouracil prodrugs. Oncology 1998;12(10 suppl 7):48-51.

55. Schuller J, Cassidy J, Reigner BG, et al: Tumor selectivity of Xeloda in colorectal cancer patients. Proc Am Soc Clin Oncol 1997;16:227a. Abstract 797.

56. O'Dwyer PJ, Johnson SW, Hamilton TC: Cisplatin and its analogues, in DeVita VT Jr, Hellman S, Rosenberg SA (eds): Cancer; Principles and Practice of Oncology, ed 5. Philadelphia. Lippincott-Raven, 1997, pp 418-432.

57. de Gramont A, Figer A, Seymour M, et al: A randomized trial of leucovorin and 5-fluorouracil with or without oxaliplatin in advanced colorectal cancer. Proc Am Soc Clin Oncol 1998;17:257a. Abstract 985.

58. Tanizawa A, Fujimori A, Fujimori Y, Pommier Y: Comparison of topoisomerase I inhibition, DNA damage, and cytotoxicity of camptothecin derivatives presently in clinical trials. J Natl Cancer Inst 1994;86:836-842.

59. O'Connell MJ: Surgical adjuvant therapy of colorectal cancer, in ASCO Educational Book 1994. Chicago, ASCO, 1994. Presentation.