New Approaches to the Adjuvant Therapy of Colon Cancer

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Key Words. Colon cancer • Adjuvant chemotherapy • Stage II • Stage III

Learning Objectives

After completing this course, the reader will be able to:

1. Discuss clinical trial and SEER data for patients with stage II colon cancer and describe the impact of adjuvant therapy.
2. Discuss clinical trial data supporting the use of adjuvant therapy for stage III colon cancer, including recent trial results with oxaliplatin and irinotecan.
3. Discuss whether stage II colon cancer patients should receive adjuvant chemotherapy and describe the new clinical trial design that integrates molecular marker data.

Abstract

Analysis of data from patients treated outside clinical trials suggests that adjuvant chemotherapy for stage II colon cancer provides less than a 3% absolute improvement in survival at 5 years. This is remarkably close to the small degree of benefit suggested by controlled studies. An overview of the data suggests that surgery alone cures approximately 75% of stage II patients. Between 20% and 25% of patients experience disease recurrence despite surgery and adjuvant chemotherapy, whereas adjuvant chemotherapy cures between 1% and 6%. In stage III patients, the benefit of adjuvant therapy is greater overall. The extent of benefit relates to tumor grade, invasion, and nodal involvement. Incorporation of molecular markers in the design of current trials may enable us to refine our identification of patients at highest risk of recurrence and hence those standing to gain most from adjuvant therapy. The Oncologist 2006;11:973–980

Introduction

Of the 152,000 cases of colorectal cancer (CRC) in the United States in 2003, 55% were either stage II or stage III disease and therefore eligible for adjuvant chemotherapy [1–3]. This represents 83,000 people each year.

Stage II disease can be divided into IIA (T3N0M0) and IIB (T4N0M0), whereas stage III disease includes IIIA (T1-2N1M0), IIIB (T3-4N1M0), and IIIC (TanyN2M0) [4]. Understanding the significant differences in survival among subsets is important when considering individual patient treatment options and clinical trial design.

Five-year disease-free survival (DFS) decreases with higher T stage, greater extent of nodal involvement, and high grade of tumor. However, Gill et al. have produced estimates suggesting that the addition of adjuvant chemotherapy to surgery can improve rates of DFS in all groups (Table 1) [5].

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The Oncologist 2006;11:973–980 www.TheOncologist.com
The largest adjuvant colon cancer trial in the U.S., Intergroup study 0089, which accrued 3,759 high-risk stage II or III patients for 3.5 years, investigated the effect of adding biochemical modulation to 5-fluorouracil (5-FU) in the adjuvant setting [6, 7]. This study compared 5-FU + low-dose leucovorin (LV), versus 5-FU + high-dose LV, versus 5-FU + levamisole, versus 5-FU + levamisole + low-dose LV. Combining high-risk stage II and III patients, five-year overall survival (OS) was 64% in the group treated with 5-FU plus levamisole alone, 66% in the groups which had either high- or low-dose LV added to 5-FU, and 68% in the group that had received 5-FU plus low-dose LV plus levamisole. Toxicities were related to gender and age. The risks of stomatitis and leukopenia were greater in females than in males and were greater among patients aged over 70 years than in those who were younger. The incidence of diarrhea was significantly greater in women than in men.

In the Intergroup study 0153, patients who had had surgery with curative intent were randomized to levamisole plus 5-FU administered either by bolus (according to the Mayo Clinic regimen) or by continuous infusion (Fig. 1) [8]. The bolus group also received LV. The overall conclusion of the study was that treatment with infusional 5-FU was as effective as 6 months’ treatment with bolus 5-FU/LV. The infusional regimen was associated with lower toxicity and with less impairment of quality of life.

A Review of the Adjuvant Trials

The largest adjuvant colon cancer trial in the U.S., Intergroup study 0089, which accrued 3,759 high-risk stage II or III patients for 3.5 years, investigated the effect of adding biochemical modulation to 5-fluorouracil (5-FU) in the adjuvant setting [6, 7]. This study compared 5-FU + low-dose leucovorin (LV), versus 5-FU + high-dose LV, versus 5-FU + levamisole, versus 5-FU + levamisole + low-dose LV. Combining high-risk stage II and III patients, five-year overall survival (OS) was 64% in the group treated with 5-FU plus levamisole alone, 66% in the groups which had either high- or low-dose LV added to 5-FU, and 68% in the group that had received 5-FU plus low-dose LV plus levamisole. Toxicities were related to gender and age. The risks of stomatitis and leukopenia were greater in females than in males and were greater among patients aged over 70 years than in those who were younger. The incidence of diarrhea was significantly greater in women than in men.

Table 1. Estimates of 5-year disease-free survival (%) with surgery plus adjuvant therapy [5]

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Adapted from [5]. Abbreviations: AT, adjuvant therapy; S, surgery.

Edrecolomab, a murine monoclonal antibody to the cell-surface glycoprotein 17-1A, has also been assessed as an adjuvant therapy in colon cancer patients. Two trials randomized North and South American stage III colon cancer patients (trial 157-001, n = 1,839 patients) and European, South African, and Australian patients (trial 157-002, n = 2,763 patients) to three arms: 5-FU/LV plus 17-1A, 5-FU/LV alone, or 17-1A alone [12–14]. In the study carried out in the Americas, the addition of 17-1A increased 3-year OS from 78.9% to 81.6% and 3-year DFS from 66.6% to 67.5% (Table 2). However, the reverse effect was seen in the international study 002: OS was 76.1% with 5-FU/LV and 74.7% with the addition of 17-1A, and DFS was 65.5% compared with 63.8%. Edrecolomab was well tolerated and did not increase the toxicity in combination with 5-FU/LV. However, the addition of edrecolomab to 5-FU/LV as an adjuvant treatment in stage III colon cancer did not improve OS or DFS.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) conducted an adjuvant study in colon cancer patients which assessed the benefit of the addition of interferon alfa-2a (IFN) [15]. Patients with Dukes’ stage B or C cancer (n = 2,176 patients) were entered onto this NSABP C-05 study and were randomly assigned to receive either 5-FU + LV or 5-FU + LV + IFN. No statistically significant difference in either DFS (69% with 5-FU/LV, 70% with 5-FU/LV/IFN) or OS (80% with 5-FU/LV, 81% with 5-FU/LV/IFN) was observed. The addition of interferon to 5-FU/LV had no effect on OS at 4 years (p = .41). Furthermore, there was a higher incidence of ≥ grade 3 adverse events with the 5-FU/LV/IFN arm (72.1% vs. 61.8%).

New Adjuvant Therapies for Colon Cancer

Figure 1. Schema of the INT 0153 study, an adjuvant colon 5-fluorouracil (5-FU) infusion trial [8].
The Cancer and Leukemia Group B (CALGB) 89803 trial addressed the question of the addition of irinotecan to adjuvant treatment of stage III colon cancer by randomizing 1,264 patients to postoperative adjuvant bolus 5-FU/LV or bolus 5-FU/LV plus irinotecan (IFL) [16]. IFL was associated with a 2.5% mortality, produced no DFS benefit, and cannot be recommended for patients with stage III colon cancer.

The role of irinotecan as an adjuvant therapy in colon cancer is addressed further in the PETACC-3 (Pan-European Trials in Adjuvant Colorectal Cancer-3) study [17]. This randomized phase III trial compared irinotecan 80 mg/m² + LV 500 mg/m² + infusional 5-FU 2,000 mg/m² over 24 hours (Group A1) versus 180 mg/m² irinotecan + LV 200 mg/m² + 5-FU bolus followed by 600 mg/m² 5-FU i.v. over 22 hours (Group A2) in stage II/III colon cancer patients. Three thousand two hundred and seventy-eight patients (stage II/III: 945/2,333 patients) were randomized, and of the stage III patients, 2,094 were randomized and treated with 5-FU/LV ± irinotecan. The 3-year DFS was 62.9% for 5-FU/LV/irinotecan versus 59.9% for 5-FU/LV. While patients in the 5-FU/LV/irinotecan group experienced slightly more toxicity, the safety profile was acceptable. In stage III colon cancer patients, irinotecan did not significantly increase the efficacy of 5-FU/LV. However, in the pooled population of stage II/III patients, irinotecan significantly increased the efficacy of 5-FU/LV. OS results are not yet available.

In the French ACCORD adjuvant trial, 400 patients with high-risk disease (i.e., N2 or N1 with occlusion or perforation) were randomized to 5-FU/LV with or without the addition of irinotecan [18]. Adjuvant 5-FU/LV + irinotecan was associated with significantly more grade 3–4 neutropenia and diarrhea, compared with 5-FU/LV alone. Furthermore, the preliminary results showed no significant DFS improvement between the two arms. This might in part be explained by the low-dose intensity of 5-FU and irinotecan in the triple combination arm, with more dose reductions and cycle delays due to neutropenia. Thus, there are now three adjuvant trials that have not shown a significant DFS advantage when irinotecan is added to either bolus or infusional 5-FU regimens.

In NSABP protocol C-06, patients with resected stage II and III colon cancer were stratified according to number of positive nodes and then randomized to either 5-FU/LV or uracil/torafur (oral tegafur)/LV [19–22]. Both regimens had manageable safety profiles, similar toxicity, and comparable efficacy.

In NSABP protocol C-07, the same population of patients (i.e., stage II and III colon cancer) were randomized after stratification to either 5-FU/LV or 5-FU/LV + oxaliplatin [19, 23]. The study arm containing oxaliplatin + weekly bolus 5-FU/LV had a significantly improved 3-year DFS (76.5% vs. 71.6%, an absolute difference of 4.9%, with a hazard ratio of 0.76, p = 0.008). A higher incidence of neurosensory toxicity and diarrhea occurred in the oxaliplatin-containing regimen.

The treatment arms in MOSAIC (Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer) consisted of infusional 5-FU2/LV with or without the addition of oxaliplatin (FOLFOX4) [24–26]. At 4 years, analysis of the entire cohort of patients (2,246 stage II and III patients) showed that those who had received FOLFOX4 were significantly more likely to be disease-free (75.9% vs. 69.1%, an absolute difference of 6.8%, with a hazard ratio of 0.76, p = .0008). This difference was also statistically significant when stage II patients were considered alone (DFS 69.7% with FOLFOX4 vs. 61% with 5-FU/LV alone). However, it was not significant for stage II patients (DFS, 85.1% vs. 81.3%). In the FOLFOX arm of the trial, 176 patients (15.7%) died, and in the control arm, 194 patients (17.3%) died. The

<p>| Table 2. Edrecolomab (17-1A) alone or in combination with fluorouracil and folinic acid in the adjuvant treatment of stage III colon cancer: Efficacy analysis of the randomized trials (157-002 vs. 157-001) [12, 13] |
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|                                | International study (002) |                    | Americas study (001) |                    |</p>
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<td>Overall survival (%)</td>
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<td>2-year</td>
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<td>3-year</td>
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<td>Disease-free survival (%)</td>
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<td>3-year</td>
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Abbreviations: 5-FU, 5-fluorouracil; ED, edrecolomab (17-1A); LV, leucovorin.
probabilities of surviving to 4 years were 84% and 82.4%, respectively (i.e., an absolute difference of 1.6%). The principal toxicity associated with the addition of oxaliplatin was grade 3 neuropathy, experienced by 137 patients. However, this condition had resolved in more than 60% of cases by 1 month and in all but approximately 5% by 1 year.

The results from the NSABP Protocol C-07 study and the MOSAIC trial each demonstrate that the addition of oxaliplatin to either infusion or weekly bolus 5-FU/LV significantly improves 3-year DFS.

**Should Stage II Patients Have Adjuvant Chemotherapy?**

The INTERGROUP-0035 trial [27–29], which randomized stage II patients to either follow-up only or 5-FU plus levamisole, found that 7-year survival was 72% in both groups.

INT-0089 showed that the 5-year OS of high-risk stage II patients (T4 lesion, perforation, or obstruction) was similar among the four regimens used: 75% with 5-FU + high-dose LV, 75% with 5-FU + low-dose LV + levamisole, 77% in the 5-FU + levamisole arm, and 77% in the 5-FU + low-dose LV arm [7].

In the 4-year update in the MOSAIC study, the DFS in stage II patients was 85.1% with FOLFOX4 and 81.3% with LV5FU2 [24–26].

Whereas the benefit from adjuvant chemotherapy in stage III colon cancer has been clearly proven, the same is not well established in patients with stage II disease.

The IMPACT (International Multicentre Pooled Analysis of Colon Cancer Trials Investigators) project pooled adjuvant data from trials conducted by Italian, Canadian, French, and U.S. trial groups across the studies. The population as a whole, 5-FU/LV was associated with a clear improvement in DFS and OS. However, when analyzed according to stage, Dukes’ B patients show no benefit from treatment in either event-free or overall survival. In contrast, 5-FU/LV appears to improve both outcomes among stage C patients.

A pooled analysis of stage II patients from four sequential NSABP trials (C-01, C-02, C-03, and C-04) was undertaken, which compared different adjuvant chemotherapy regimens with each other or with no adjuvant treatment [32]. The trial comparisons included C-01: semustine/vincentrine/5-FU (MOF) versus surgery alone; C-02: perioperative 5-FU versus surgery alone; C-03: 5-FU/LV versus MOF; and C-04: 5-FU/LV versus 5-FU/levamisole (LEV) versus 5-FU/LV/LEV. In all four studies, improvement in DFS and recurrence-free survival was observed in both Dukes’ B and Dukes’ C patients. The conclusion drawn from this pooled analysis was that patients with Dukes’ B colon cancer do benefit from adjuvant chemotherapy and should be offered this treatment option.

The Surveillance, Epidemiology, and End Results (SEER) Medicare Cohort study of 3,444 cases of resected stage II colon cancer distinguishes between the great majority of patients (3,151 in this series) with ‘T3N0 disease and “usual” risk, and a small number (293) at high risk (T4N0 disease, obstruction, or perforation) [33]. Among the usual-risk group, 27% received chemotherapy and 33% high-risk patients were treated. Treatment was started a median of 5.5 weeks from surgery; 62% of patients who started chemotherapy had at least one claim for treatment between 5 and 7 months from their start date. Fifty-one percent of patients who had a consultation with a medical oncologist received adjuvant therapy. Survival curves between treated and untreated patients in this SEER cohort are identical until 3 years from surgery, when the curve for chemotherapy-treated patients starts to diverge. However, the absolute difference in survival at 5 years among this nonrandomized population is only approximately 3%. This is much the same temporal pattern and degree of benefit shown by the IMPACT B2 (International Multicentre Pooled Analysis of Colon Cancer B2 Trials Investigators) study.

Hence, we have evidence that the influence of adjuvant therapy “in the real world” is remarkably similar to that in clinical trials. The absolute improvement in survival is small (at best) and indeed disappears once adjustment is made for the older age of the patients who remained untreated.

Both the cohort data and the outcome of clinical trials conducted to date suggest that a control arm of no treatment continues to be justified in randomized studies of adjuvant therapy in stage II patients. However, the fact that many patients outside trials receive adjuvant therapy indicates that, in practice, it may be difficult to accrue to a study in which one arm involves no treatment. A substantial minority of stage II patients and/or their doctors appear to believe that the possibility of a small increment in the chances of survival justifies the risks and discomforts of adjuvant chemotherapy.

In study INT-0089 of 5-FU–based chemotherapy, there was a substantial variation in the number of lymph nodes removed at surgery, a variation that was significantly associated with differences in survival [7, 34]. Five-year OS was 59% in patients who had had 10 or fewer nodes removed, 73% in those with 11–20 nodes removed, and 79% when more than 20 nodes were removed. The more extensive evaluation of nodes was also associated with improved OS in patients with N1 and N2 disease. American Joint Committee on Cancer recommendations attribute this difference
to increased accuracy of staging, and state: “It is important to obtain 7–14 lymph nodes in radical (curative) colon and rectum resection” [35, 36].

In the Quick and Simple and Reliable (QUASAR) study, following complete resection, doctor and patient decided whether there was a clear indication for adjuvant chemotherapy or an uncertain indication [37]. Patients in whom chemotherapy was clearly indicated were randomized in a two-by-two design to 5-FU plus either high- or low-dose LV and to the addition of either levamisole or placebo. Patients in whom the indication was uncertain were randomized to either an observation-only control arm or chemotherapy. Clinical parameters and age were exactly matched in the chemotherapy and no-chemotherapy arms: in both, 92% of patients were stage II. Five-year survival was 80.3% for those patients who received chemotherapy and 77.4% for those in the observation group. The relative risk associated with chemotherapy was 0.83 (p = .02). An overview of the data suggests that surgery alone cures approximately 75% of stage II patients. Between 20% and 25% of patients experience disease recurrence despite surgery and adjuvant chemotherapy, while adjuvant chemotherapy cures between 1% and 6%.

Gill et al. have used a pooled analysis model to study the relationship between the benefit of adjuvant treatment and the degree of nodal involvement [5]. In patients with no positive nodes, the survival benefit is marginal. However, in those with one to four positive nodes and five or more positive nodes, benefit is substantial.

A panel convened by the American Society of Clinical Oncology, in partnership with the Cancer Care Ontario Program in Evidence-Based Care’s Gastrointestinal Cancer Disease Site Group, made recommendations on adjuvant therapy for stage II colon cancer patients, based on a literature meta-analysis that included 37 trials, 11 meta-analyses, and 20,317 patients [38, 39]. The panel concluded that while there was a 5%–10% improvement in the DFS with adjuvant treatment, there was no significant improvement in OS. Thus, the panel did not recommend the routine administration of adjuvant chemotherapy for stage II colon cancer patients.

Buyse and Piedbois have also addressed whether Dukes’ B patients should receive adjuvant therapy, from a statistical perspective [40]. They estimated the absolute reduction in risk achieved by adjuvant chemotherapy in Dukes’ B and Dukes’ C patients at various durations of follow-up, and the number of patients needed to give a trial 90% power to detect treatment benefit using a two-tailed test of significance and a p value of .05. For Dukes’ B, with 80% of patients surviving to 4 years and an absolute risk reduction of 3.3%, a trial would require 5,800 patients. In Dukes’ C, with 58% of patients surviving and a 6% reduction in absolute risk, the figure needed to achieve the required power is 2,800 patients.

With the minimal improvement observed in OS with adjuvant chemotherapy in stage II colon cancer, careful consideration of benefits/risks must be given prior to the administration of adjuvant chemotherapy in this disease. It is possible that new agents will have a much more profound effect on outcome.

**DISCUSSION**

Given these data, we must consider what patients want to know by way of prognostic information and their perception of risks and benefits. It is appropriate to convey that the OS rate in stage II disease is 75%–80% and that any improvement in survival with the addition of chemotherapy is less than 5%.

Pathological factors that appear relevant to prognosis are T and N stage, degree of tumor differentiation, and the presence of lymphatic, neuro-, and vascular invasion. In the future, it is likely that assessment of risk, and therefore choice of therapy, will be influenced by molecular profiling of the tumor and the genotype of the patient (Fig. 2).

In stage III colon cancer, the retrospective analysis by Watanabe et al. has suggested that presence of 18q LOH (loss of heterozygosity) is associated with poorer OS [41]. The presence of microsatellite instability (MSI) on its own was not related to improved survival. However, MSI together with the transforming growth factor–beta 1 RII mutation was associated with improved outcome when compared with presence of MSI without the mutation. The analysis linked the presence or absence of three molecular features to two patient profiles establishing a low-risk group, with an OS rate of 75% at 5 years, and a high-risk group with only a 50% chance of being alive at the same interval.

**Figure 2.** Future model for determining best choice of treatment for each patient.
Intergroup E5202 will assess patients’ risk based on the retention of the 18q allele and the presence of MSI in tumor specimens (Fig. 3). High-risk patients will be randomized to chemotherapy with oxaliplatin and 5-FU/LV with or without the addition of bevacizumab (Avastin®; Genentech, Inc., South San Francisco). Those judged to be at low risk will be observed.

Perhaps the inclusion of the newer active agents and greater patient specificity will result in better efficacy with adjuvant treatment. Results from the next generation of clinical trials will contribute to our understanding of the role of combination regimens, including regimens with bevacizumab and cetuximab, and a host of potential prognostic and predictive markers.

**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**
The author receives grant support from and has acted as a consultant for Pfizer, sanofi-aventis, and Genentech.

**Figure 3.** Eastern Cooperative Oncology Group E5202 study design. Low-risk stage II colon cancer patients will be observed, due to the uncertainty of the significance of the survival benefit of adjuvant treatment in this group of patients (following the results from the U.S. Surveillance, Epidemiology, and End Results Medicare population-based study) [5, 33]. As much as possible, individualization of adjuvant therapy for stage II colon cancer patients is required to balance the risk/benefits of the treatment [5].

Abbreviations: 5-FU, 5-fluorouracil; LOH, loss of heterozygosity; MSI, microsatellite instability; MSI-H, high-frequency microsatellite instability; MSI-L, low-frequency microsatellite instability; MSS, microsatellite stable.

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