Adjuvant Therapy of Colon Cancer: Current Status and Future Developments

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ABSTRACT

Options for the adjuvant therapy of resected stage III colon cancer have expanded beyond the previously well-accepted standard of 5-fluorouracil (5-FU) combined with leucovorin. The Xeloda in Adjuvant Colon Cancer Therapy (X-ACT) study confirmed that capecitabine (Xeloda) is at least as effective and is less toxic than a bolus 5-FU and leucovorin regimen for patients with stage III colon cancer. This study, in addition to National Surgical Adjuvant Breast and Bowel Project (NSABP) C-06, which demonstrated the equivalence of tegafur-uracil (UFT)/leucovorin with 5-FU/leucovorin, provides support for use of oral fluoropyrimidines for adjuvant therapy. Support for use of multi-agent chemotherapy has been provided by the European MOSAIC study, which demonstrated a significant improvement in 3-year disease-free survival for the addition of oxaliplatin (Eloxatin) to infusional 5-FU and leucovorin (FOLFOX). Although adding irinotecan (Camptosar) to a bolus 5-FU and leucovorin regimen did not improve outcome in the adjuvant setting, the PETACC studies are evaluating the combination of infusional 5-FU, leucovorin, and irinotecan. In contrast to agreement on the appropriateness of therapy for stage III colon cancer, adjuvant therapy for patients with stage II disease remains controversial. Future advances in adjuvant therapy may include targeted therapies. Based on data demonstrating efficacy for the monoclonal antibodies bevacizumab (Avastin) and cetuximab (Erbix) in the metastatic setting, clinical trials adding these agents to standard chemotherapy have been initiated in the adjuvant setting. Specifically, one U.S. cooperative group trial will evaluate the addition of bevacizumab to chemotherapy, a second will assess the addition of cetuximab, and a third trial will evaluate FOLFOX, infusional 5-FU/leucovorin (FOLFIRI), and FOLFOX followed by FOLFIRI. Finally, a study for patients with stage II disease and adverse prognostic factors will open. An important consideration in the new clinical trials is an assessment of molecular markers that either predict response or resistance to therapy or provide other prognostic information.

KEYWORDS: Colorectal neoplasm, neoplasm metastasis, colorectal neoplasm drug therapy, colorectal neoplasm therapy

Objectives: Upon completion of this article, the reader should be able to understand: (1) major clinical studies underlying current recommendations for adjuvant therapy for colon cancer; (2) more recent studies that suggest that further modifications of current therapy will yield better outcomes; and (3) clinical trials of novel agents for the treatment of colon cancer.

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Colorectal cancer presents as localized disease (stage I and II) in 36.6%, as regional disease (stage III) in 45.2%, and as distant disease (stage IV) in 18.2% of patients.¹ The problem of residual micrometastatic disease is highlighted by the 5-year stage-specific survivals of 93.2% for stage I but 82.5% for stage II and only 59.5% for stage III disease.² Adjuvant therapy is delivered with the intention of destroying the micrometastases that are below the level of detection. In this article, we discuss the major clinical studies underlying current recommendations for adjuvant therapy, the more recent studies that suggest that further modifications in the established therapies will yield better outcome and tolerability, and the clinical trials of novel agents that we hope will improve results in the future.

HISTORICAL PERSPECTIVE

The first generation of adjuvant clinical trials in the late 1950s through mid-1970s with single agents (thiotepa, FUDR [floxuridine], and 5-fluorouracil [5-FU]) were generally considered negative, although two studies did suggest small benefits for 5-FU therapy compared with surgery alone.^{3,4} The next generation of studies in the late 1970s and early 1980s used multiagent chemotherapy and/or immunotherapy with levamisole or bacillus Calmette-Guérin (BCG). In National Surgical Adjuvant Breast and Bowel Project (NSABP) C-01, the combination methyl-CCNU (semustine), vincristine, fluorouracil (MOF) provided statistically significant disease-free and overall survival (OS) compared with the observation group,⁵ the first prospective randomized trial to do so. NCCTG 78-48-52 reported that fluorouracil plus levamisole provided a disease-free survival (DFS) benefit compared with observation in the subgroup of stage III patients.⁶ A national Intergroup study confirmed the DFS and demonstrated an OS benefit for 5-FU plus levamisole.^{7,8} Nonetheless, the actual mechanism of levamisole was never entirely clear and biochemical modulation of 5-FU with leucovorin to create a ternary complex with greater inhibition of thymidylate synthase was more scientifically appealing. Therefore, even before the Intergroup study was reported, studies of 5-FU and leucovorin (LV) were begun. NSABP C-03 demonstrated that 5-FU/leucovorin improved survival compared with the MOF regimen.⁹

Levamisole-containing regimens, with some exceptions,¹⁰ fell out of favor when it was shown to add no additional benefit to 5-FU and leucovorin. For example, the North Central Cancer Treatment Group–National Cancer Institute of Canada (NCCTG–NCIC) trial¹¹ demonstrated no additional benefit of levamisole. Similarly, in the Intergroup 0089 study, 3759 high-risk stage II and stage III patients were randomly assigned to one of four treatment arms: 5-FU plus levamisole for 12 months, 5-FU plus high-dose LV (Roswell Park

Regimen, weekly for 6 of 8 weeks for four cycles), 5-FU plus low-dose LV (Mayo regimen, daily for 5 days every 4 to 5 weeks for six cycles) and 5-FU plus low-dose FA plus levamisole.¹² The only groups that differed in OS or DFS were FU/LDLV (low-dose leucovorin)/levamisole versus FU/levamisole; all others had similar 5-year DFS and OS (60% and 66%), suggesting that the 12-month 5-FU/levamisole regimen is inferior and that either of the 5-FU/LV regimens can be the standard therapy for stage III colon cancer. This also shows that 6 months of systemic 5-FU and leucovorin is as effective as 12 months of therapy. Because the Mayo regimen resulted in more stomatitis and neutropenia, the Roswell Park regimen became preferred. The lack of benefit for levamisole was confirmed by the QUASAR-1 study, in which 4927 patients were randomly assigned in a 2 × 2 design to 5-FU with high-dose or low-dose leucovorin (FU/LV) and either levamisole or placebo.¹³ Three-year survival with levamisole trended toward inferiority (69.4% compared with 71.5% with 5-FU/LV alone; $p=0.06$). There was no survival difference between high- and low-dose LV regimens.

Although the foregoing clinical trials demonstrated benefits for systemic chemotherapy, meta-analyses have given a better picture of the absolute benefits. In the meta-analysis of seven phase III trials that compared chemotherapy (five had 5-FU/leucovorin and two had 5-FU plus levamisole) with surgery by Sargent and colleagues,¹⁴ the 5-year OS was 71% for those who received adjuvant therapy compared with 64% for those who did not. Recurrence-free survival was improved as well. Notably, this study demonstrated that toxicity, in general, was not greater among the elderly patients (age > 70 years), except for leukopenia in one study, and the survival benefits were found across all age groups. Available data for long-term follow-up beyond 5 years are limited. NSABP C-01 reported 10-year results, at which point no difference in 10-year DFS or OS was observed between patients in the chemotherapy group (MOF) and those in the surgery-alone group.¹⁵ Because other chemotherapy regimens appear superior to MOF in terms of DFS and OS, the long-term results from other studies will be important for interpreting these data.

RECENT CLINICAL TRIALS SUGGEST CHANGES TO THE STANDARD OF CARE

Oral Agents

The search for an oral alternative to 5-FU has been long standing. Oral 5-FU achieves erratic blood levels because of the presence of the metabolizing enzyme dihydropyrimidine dehydrogenase (DPD) in the gastrointestinal tract. Solutions have included attempts to inhibit DPD

(uracil or eniluracil) or to use orally bioavailable agents that mimic the functions of 5-FU or can be converted into the active derivative of 5-FU (capecitabine). Capecitabine is converted by thymidine phosphorylase into fluorouracil, and because tumor tissue expresses higher levels of thymidine phosphorylase than normal tissues, capecitabine tends to be activated to a greater extent in tumor.

The efficacy of capecitabine in stage III colon cancer was assessed in the Xeloda in Adjuvant Colon Cancer Therapy (X-ACT) trial, which was recently reported.¹⁶ Chemotherapy-naïve patients (1987) with resected Dukes C (stage III) colon cancer were randomly assigned to capecitabine 1250 mg/m² orally twice a day on days 1 to 14 every 3 weeks for a total of 24 weeks or the Mayo Clinic regimen of bolus fluorouracil/leucovorin (5-FU 425 mg/m² and leucovorin 20 mg/m² given on days 1 to 5 as intravenous boluses every 4 weeks, also for 24 total weeks). The primary endpoint of the study was to demonstrate that both arms had equivalent disease-free survival. The patients in each arm were well balanced with similar percentages with regard to performance status, degree of tumor differentiation, and percentage with T3 tumors. The therapy was completed by similar percentages of patients in each arm (84% for capecitabine and 88% for 5-FU). Similar percentages of patients required dose reductions (42% capecitabine, 44% bolus 5-FU/LV), but capecitabine was generally better tolerated with fewer patients experiencing nausea and vomiting, mucositis, diarrhea, and leukopenia. Capecitabine was associated with more hand-foot syndrome. The study met its endpoint in that capecitabine was at least as effective as 5-FU/LV. In fact, relapse-free survival (RFS) was superior for capecitabine (3-year RFS: 65.5 versus 61.9%, HR 0.86; 95% confidence interval [CI] 0.74 to 0.99; $p = 0.0407$) and there was a trend toward better DFS (3-year DFS: 64.2% versus 60.6%; HR 0.87; 95% CI 0.75 to 1.00, $p = 0.0528$) and OS (81.3% versus 77.6%; HR 0.84; 95% CI 0.69 to 1.01; $p = 0.0706$). To counter possible criticisms, it has been pointed out that the Mayo regimen performed in this study exactly as it had in prior studies with similar 3-year DFS. Also, the results seen in the entire population were maintained in patients 70 years and older. One major caveat with the study when translated to clinical practice is that the starting dose on the study is higher than most clinicians generally prescribe. Also, the Mayo Clinic regimen is acknowledged to be more toxic than other 5-FU-based regimens and therefore is not generally considered the standard of care. Whether toxicities would have varied with the Roswell Park weekly 5-FU regimen is not known.

Another oral combination of tegafur-uracil (UFT) plus leucovorin has also been tested against 5-FU and leucovorin. UFT consists of tegafur, a prodrug of 5-FU combined with uracil (to inhibit DPD) in a 1:4

molar ratio. In NSABP C-06,¹⁷ 1608 patients with stage II and III colon cancer, stratified by nodal status, were randomly assigned to the Roswell Park weekly bolus 5-FU/LV regimen (for three cycles) or UFT/LV (300 mg/m²/day by mouth with leucovorin 90 mg/day by mouth for 28 days followed by a 1-week rest period for five cycles). There was no difference in RFS, DFS, and OS. There were similar toxicities between the two arms, and there were no differences in quality of life on the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) instrument, which is designed for colon cancer. One instrument suggested greater fatigue with UFT, but three other instruments showed greater convenience and lower prevalence of symptoms with UFT. Unfortunately, UFT was not approved for commercial availability in the United States, but these data do add to those from the X-ACT study showing that an oral fluoropyrimidine regimen is at least as effective as an intravenous regimen. This was confirmed by a Japanese meta-analysis that pooled results from studies comparing surgery with postoperative oral chemotherapy (usually UFT or capecitabine plus MMC [mitomycin C]) in patients with resected stage I, II, III colon cancer and found a reduced risk of recurrence (15%) and improved survival (by 11%) for oral chemotherapy.¹⁸ Patients in all stages of disease appeared to benefit.

Multiagent Chemotherapy

Because of the survival benefit in the metastatic setting for multiagent chemotherapy using newer agents, such as irinotecan and oxaliplatin, over fluorouracil and leucovorin, it was appropriate to test such combinations in the adjuvant setting. In the European MOSAIC study,¹⁹ 2248 patients with completely resected stage II (40%) or III (60%) colon cancer were randomly assigned to receive LV5FU2 (leucovorin 200 mg/m² as a 2-hour infusion d1,2, 5-FU 400 mg/m² bolus and 600 mg/m² 22 hours CI, d1-2) or FOLFOX (LV5FU2 + oxaliplatin 85 mg/m² d1) bimonthly for 12 cycles. Overall 3-year DFS was 78.2% versus 72.9% with 3-year DFS for stage II 87% versus 84.3%, and for stage III, it was 72.2% versus 65.3%; grade 3, 4 neutropenia was 41% versus 4.7% but only 0.7% and 0.1% developed febrile neutropenia; less than 11% diarrhea; grade 3 neurotoxicity occurred in 12% of those receiving the oxaliplatin combination but by 1 year of follow-up, only 1% continued to have grade 3 symptoms. Nonetheless, some degree of neuropathy was present in more than 30% at 1 year. Chemotherapy-related mortality was low at 0.5% for each arm. An OS benefit has not been established yet, but 4-year DFS continues to show a benefit in continuing analysis of the study.²⁰

Furthermore, Sargent and colleagues reported that a 3-year DFS benefit for patients receiving adjuvant therapy did predict survival benefit.²¹ On November 4,

2004, the U.S. Food and Drug Administration approved oxaliplatin for injection in combination with infusional 5-FU/LV for adjuvant treatment of stage III colon cancer patients who have undergone complete resection of the primary tumor. These data support use of a multiagent, oxaliplatin-based regimen for resected stage III disease.

Another study evaluating the oxaliplatin combination is NSABP C-07, which randomly assigned patients with stage II and III colon cancer to the Roswell Park bolus 5-FU/high-dose LV regimen for three cycles or 5-FU/LV/oxaliplatin (with bolus 5-FU). The HR was 0.79 (CI 0.67, 0.93) and the 3 year DFS was 76.5% versus 71.6% in favor of the oxaliplatin containing regimen.^{21a} Whether multiagent chemotherapy should also supercede single-agent capecitabine is not known, but the following facts emerge from the completed clinical trials. The MOSAIC study showed that the 3-year DFS for FOLFOX was 71%, whereas it was 61% for capecitabine in the X-ACT study. Although differences between study populations could account for differences in results between the two studies, it is also possible that the multiagent chemotherapy is superior to the oral agent as well as intravenous 5-FU in DFS. Whether certain populations such as older patients or those with poorer performance should be considered for the less aggressive regimens is also less clear. In the metastatic setting, FOLFOX remained active in patients older than 75²² and was active in performance status 1, 2 patients.²³ Therefore, most individuals could be considered candidates for oxaliplatin-containing regimens.

Irinotecan-containing regimens have also been studied in the adjuvant setting. Unfortunately, CALGB C89803 did not show a benefit for the bolus 5-FU/LV irinotecan regimen.²⁴ A total of 1260 patients with stage III disease were randomly assigned to the Roswell Park 5-FU/LV bolus regimen or the irinotecan plus fluorouracil/leucovorin (IFL) regimen. There was no benefit in DFS or OS for the IFL regimen, and there was more 60-day mortality in the IFL arm (2.5 versus 0.8%) because of gastrointestinal or vascular toxicity. One criticism of this study is that the IFL regimen is not the standard of care and is likely to be inferior to infusional fluorouracil-containing regimens. Therefore, the PETACC-3/EORTC study treated patients with one of two different infusional 5-FU/leucovorin regimens (the LV5FU2 and the AIO regimens at the investigators discretion) with or without irinotecan for 6 months. The HR for DFS was 0.89 (0.77–1.03) ($p = 0.107$) with a three-year DFS of 62.9 for the irinotecan containing arm vs. 59.9% for the control arm and the HR for RFS was 0.87 (0.75–1.02) ($p = 0.076$) with a three-year relapse free survival of 65.1 vs. 61.8% in stage III pts. The HR for DFS for the pooled stage II/III population was 0.87 (0.76–0.99) ($p = 0.038$). The irinotecan containing therapy had slightly more toxicity.^{24a} In

a French FNCLCC/FFCD study, high-risk stage III patients (N2 or N1 with perforation or obstruction) are being randomly assigned to infusional 5-FU/LV with or without irinotecan, and again 3-year DFS is the end-point. There was no difference in event-free survival between the two arms of the study and the irinotecan containing arm caused more neutropenia.^{24b} The available data therefore do not currently support use of irinotecan-containing regimens of protocol for adjuvant therapy.

UNCERTAIN BENEFIT OF ADJUVANT THERAPY FOR STAGE II COLORECTAL CANCER

The role of adjuvant chemotherapy in Dukes B (stage II) colon tumors is controversial. Prior attempts to extract data from clinical trials that included stage II and III patients yielded conflicting results. In an analysis combining data from NSABP studies (C-01 to C-04), in which the best arm was compared with the worst arm of the studies, there was a mortality reduction of 30% for Dukes B receiving the best chemotherapy combination.²⁵ This study has been criticized for unorthodox statistics. For example, the survival data for the MOF regimen from NSABP C-01 (which compared MOF with surgery alone) were included in the “best arm” data, but data for the MOF regimen from NSABP C-03 (which compared 5-FU/LV with MOF) were included in the “worst arm” data. IMPACT B2²⁶ was a meta-analysis of data from 1016 patients enrolled in five studies of 5-FU/LV versus observation. The 5-year event-free survival was 73% for controls and 76% for 5-FU/LV ($p = 0.061$) and 5-year OS was 80% versus 82%, which was statistically nonsignificant ($p = 0.057$). The authors concluded that there was no benefit to 5-FU/LV postoperatively for Dukes B. Individual studies have also provided hints of activity of chemotherapy in stage II disease. In the Dutch group’s study of 730 patients (half of whom had stage II disease), adjuvant chemotherapy improved relative survival in this group.¹⁰ At a median follow-up of 4 years and 9 months, 78% of stage II patients treated for a year with adjuvant 5-FU/levamisole were alive, compared with 70% in the control arm. In the QUASAR study, a small survival benefit (1% to 5%) was described for patients with uncertain indications for chemotherapy (91% stage II).²⁷ In the MOSAIC study, stage II patients had a numerically better 3-year DFS (RR [relative risk reduction] for recurrence 20%), although it was not significantly different.²⁸

A meta-analysis²⁹ concluded that adjuvant treatment is associated with a small DFS benefit (5% to 10% across studies), but this was not necessarily associated with an OS benefit. This year, the American Society of Clinical Oncology convened an expert panel that

provided recommendations for stage II adjuvant treatment. They concluded that its routine use was not indicated, but it might be considered for patients with inadequately sampled nodes (<13), T4, perforation, obstruction, lymphovascular invasion, or poorly differentiated tumors.³⁰ These recommendations are sensible, for example, in stage II patients there was better survival if more than 12.5 lymph nodes were examined (128 versus 106 months).³¹ Petersen et al³² have demonstrated that the high-risk factors in stage II disease are serosal involvement, extramural vascular invasion, involved resection margins, and tumor perforation. In contrast, patients with microsatellite instability-high (MSI-H) tumors may have a better prognosis but also may be resistant to 5-FU. Ongoing studies of interest in these patients include PETACC4, which is comparing FOLFIRI versus surgery alone, and the Intergroup study, in which patients are evaluated for allelic loss of 18q and MSI status. Low-risk patients are observed and high-risk patients are randomly assigned to FOLFOX with or without the anti-vascular endothelial growth factor (VEGF) antibody bevacizumab.

INCORPORATING BIOLOGIC AGENTS

Although incorporation of more effective chemotherapy agents or improved schedules of delivery may continue to provide small improvements in survival, it is hoped that the new targeted therapies under development will provide greater additional benefits. Early approaches included immunotherapy. Interferons (IFNs) activate immune effectors, upregulate antigen expression on tumors, have antiangiogenic activity, and are able to modulate FU activity as well. Therefore, the addition of IFN to 5-FU has been studied in the adjuvant and metastatic setting. Unfortunately, the addition of IFN to 5-FU/LV in stage II and III colon cancer was more toxic and gave no difference in survival in NSABP C-05.³³

The monoclonal antibody (mAb) edrecolomab (Panorex, 17-1A), a murine immunoglobulin G 2a mAb that recognizes Ep-CAM on tumor cells, has been particularly controversial. Initial studies with 7-year follow-up showed death rate reduced by 32% and recurrence by 23% in Dukes C compared with no therapy. Local recurrence was not affected.^{34,35} Subsequently, for patients with stage III colon cancer who received a 5-FU-based chemotherapy regimen (Mayo 5-FU/LV or 5-FU/levamisole) with or without edrecolomab,³⁶ 3-year OS was significantly different for the combination with edrecolomab (81.6% versus 78.9%; HR 0.785) but the 3-year DFS was not significantly different. In another postoperative therapy study, 2761 patients were randomly assigned to edrecolomab plus 5-FU/LV, 5-FU/LV alone, or edrecolomab monotherapy.³⁷ Three-year OS with combination therapy was no

different from that with chemotherapy (74.7% versus 76.1%). DFS was significantly lower with edrecolomab monotherapy than chemotherapy (53.0% versus 65.5%). In stage II disease, there was no benefit for 17-1A compared with placebo in a study closed early because the interim analysis showed that the futility boundary had been crossed.³⁸ The future development of this antibody is unclear as there are better candidates with proven efficacy in other settings.

Cancer vaccines are also of great interest because of the hope that a lasting anticancer response could be induced with one or a few immunizations. Initially, immunotherapy with a vaccine consisting of autologous colorectal tumor cells plus BCG showed no overall benefit for colon plus rectal patients combined but did have a benefit for the colon subgroups, and it was theorized that the pelvic radiation received by rectal cancer patients might have impaired the immune response.³⁹ A longer RFS was then reported for stage II patients receiving the autologous tumor/BCG vaccine.⁴⁰ A subsequent study reported on surgery followed by autologous tumor + BCG versus observation for stage II and III patients.⁴¹ Overall, there was no survival difference by intention to treat; Nonetheless, the magnitude of the delayed-type hypersensitivity reaction at the injection site correlated with survival. For stage II patients with induration greater than 5 mm to autologous tumor, survival was statistically better than in the observation group; those with greater than 10 cm induration had 85% 5-year survival. Further attempts to test this autologous tumor vaccine approach have been slowed by regulatory issues. There continue to be efforts to develop other cancer vaccines for adjuvant therapy. We completed a phase I study of a vaccine consisting of a pool of tumor peptides (carcinoembryonic antigen, MAGE, HER2/neu) in patients who had completed adjuvant therapy for stage III colon cancer. The vaccine was well tolerated and activated tumor antigen-specific immune responses in the majority of patients.⁴²

The more recently developed targeted therapies are now receiving the greatest attention. For example, because of the efficacy of the anti-VEGF antibody bevacizumab (Avastin) and the epidermal growth factor receptor inhibitory antibody cetuximab (Erbix) in metastatic cancer, it is appropriate to test them in the adjuvant setting. NSABP C-08 will test FOLFOX with or without bevacizumab. An international study (MOSAIC II) will evaluate capecitabine, oxaliplatin, or FOLFOX with or without bevacizumab. The Intergroup N0147 study will compare FOLFOX for 12 cycles versus FOLFIRI for 12 cycles versus FOLFOX for 6 cycles followed by FOLFIRI for 6 cycles. Subsequently, a randomization to cetuximab versus placebo was added. PETACC5 will test 5U/LV + cyclooxygenase 2 inhibitor for stage III.

CHOOSING ADJUVANT THERAPY BASED ON BIOLOGIC MARKERS

Because only a minority of patients with resected colon cancer actually benefit from chemotherapy (the majority are either cured by surgery or relapse), it would be desirable to know which patients should be treated. Both predictive and prognostic markers are important because we would like to know which patients are at very high risk of relapsing (and who are good candidates for therapy) and which patients are likely to benefit from the adjuvant therapy.

Gill et al⁴³ pooled data from 3302 patients with stage II and III colon cancer from seven randomized trials (all the trials with 5-FU/LV used a Mayo-like regimen) comparing 5-FU/LV or 5-FU/levamisole with surgery alone. Prognostic for DFS were nodal status, number of nodes, deep penetration, and high grade. Tumor location, sex, and age were not independent prognostic factors for DFS. For OS, there were similar prognostic factors except that patients older than 60 had a worse prognosis. Interestingly, there was no statistically significant benefit for treatment in poorly differentiated tumors (only 1% difference for those treated). It is possible that this is due to the greater number of MSI-H patients in the poorly differentiated group. Nonetheless, it was not recommended to treat these patients differently because there was no interaction between grade and treatment effect in their statistical analysis. A significant stage by treatment interaction was present, with treatment benefiting stage III patients to a greater degree than stage II patients. On the basis of these data, they created a model with estimates of survival stratified by T stage, nodal status, grade, and age, which is available at <http://www.mayoclinic.com/calcs>.

Although the most important prognostic markers are found on routine pathologic review (depth of penetration, lymph node status), other markers require measurement by what are currently research assays. The impact of MSI is well established. MSI-H tumors have a better prognosis but do worse with chemotherapy. Specifically, 5-FU benefited stage II and III with low MSI but not high MSI.⁴⁴ If one controls for MSI, other factors emerge. Among patients with microsatellite-stable stage III cancer, 5-year OS after fluorouracil-based chemotherapy was 74% in those whose cancer retained 18q alleles and 50% in those with loss of 18q alleles (relative risk of death with loss at 18q, 2.75; 95% CI, 1.34 to 5.65; $p=0.006$). The 5-year survival rate among patients whose cancer had high levels of MSI was 74% in the presence of a mutated gene for the type II receptor for transforming growth factor $\beta 1$ (TGF- $\beta 1$) and 46% if the tumor did not have this mutation (relative risk of death, 2.90; 95% CI, 1.14 to 7.35; $p=0.03$).⁴⁵ The author concluded that retention of 18q alleles in microsatellite-stable cancers and mutation of the gene

for the type II receptor for TGF- $\beta 1$ in cancers with high levels of MSI result in a favorable outcome after adjuvant chemotherapy with fluorouracil-based regimens for stage III colon cancer. The effect of expression of thymidylate synthase (TS), the target enzyme for 5-FU-mediated antitumor activity, has also been extensively studied. For example, among patients treated adjuvantly with 5-FU, the majority of relapses were in the patients with overexpression of TS.^{46,47} Whether these patients would benefit from a different choice of chemotherapy is not known. An interesting observation with relevance to the targeted therapies is that low VEGF expression by tumors predicts better outcome.⁴⁶ Despite the availability of these and other markers such as expression of K_i-67 and p53, it is generally conceded that thus far none of these markers can be used to determine unequivocally which groups of patients receive the greatest benefit for adjuvant therapy.⁴⁸

SUMMARY

The history of the adjuvant treatment of colon cancer has brought us to the point that systemic chemotherapy, possibly multiagent chemotherapy, is the standard of care for stage III and high-risk stage II patients. It is hoped that further developments in prognostic and predictive markers will identify which patients require or will benefit from therapy. Of course, a test to detect the presence of microscopic disease would be of great interest. Whether proteomic assays that have had the power to detect ovarian cancer may have utility in the future is unknown. The growing list of targeted therapies with clinical activity has also opened up the possibility of preventing recurrences with a combination of chemotherapy and targeted therapy.

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