ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Section Editor: Clifford A. Hudis, MD

Colorectal Cancer In Focus

# Adjuvant Therapy for Stage II and III Colon Cancer

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**H&O** How is stage II colon cancer different from stage III colon cancer?

**JM** Stage II and III colon cancer patients both have staging scans and surgical exploration that do not show evidence of disease spread outside the local colon cancer. In stage II colon cancer, the disease has grown through the muscle layer to the subserous layer (T3) or beyond, including adhesion to other organs or penetration through the parietal peritoneum (T4), but no local lymph nodes have disease involvement. Conversely, stage III patients have positive lymph nodes and can present with T1–T4 disease. From a prognostic standpoint, stage II patients generally have a better prognosis than stage III patients, which translates to a lower recurrence rate. However, there are some stage II patients that have a higher recurrence rate than stage III patients.

Patients with stage III colon cancer should be treated with adjuvant therapy after surgery. Adjuvant treatment for stage II colon cancer is controversial, primarily due to the lack of definitive data demonstrating a clear benefit; the evidence to date is either inadequate in power or is mixed in terms of potential benefit. Good-risk stage II colon cancer patients have an 80% or higher cure rate with surgery alone, so giving chemotherapy in 100 patients means that 80 or more of those patients do not even need it. Furthermore, even for stage II patients who receive chemotherapy, the absolute benefit is assumed to be only between 0% and 5%.

**H&O** What are some factors oncologists should consider before treating stage II patients with adjuvant therapy?

**JM** There are multiple prognostic factors that appear to have an effect on prognosis, such as bowel perforation, clinical bowel obstruction, T4 disease, poorly differentiated histology, and an inadequate number of lymph nodes. However, there are no definitive data confirming that patients who have these poor prognostic factors will benefit from adjuvant therapy. Therefore, while these factors are prognostic, they are not necessarily predictive. However, because there is a lack of data or inadequate sample sizes in subgroup analyses to provide a definitive correlation, the prognostic factors are often used to determine who should be considered for adjuvant therapy. In patients who do not have these factors, it has been more difficult to determine an appropriate treatment course.

Other factors that are considered when determining treatment are molecular markers. Microsatellite instability and 18q loss of heterozygosity are 2 molecular markers that have received the most attention in colon cancer, with microsatellite instability being the more readily examined marker. Most studies have shown that patients with microsatellite instability have a more favorable prognosis. However, the data are mixed on whether microsatellite instability is a predictive marker for adjuvant therapy. Retrospective studies have demonstrated that patients with stage II or III disease and microsatellite instability who receive adjuvant 5-fluorouracil (5-FU) chemotherapy after surgery have no benefit from such therapy, or may even have an inferior outcome, compared to surgery. However, not all studies have confirmed this association, and data remain retrospective at this point. There are no data to date regarding 5-FU and oxaliplatin combinations. As a result, there is some hesitancy in adopting microsatellite instability testing on all stage II

and III patients due to the retrospective nature of the data and the lack of data with oxaliplatin-based regimens. It is evident that this is an area which needs further research in order to determine whether microsatellite instability, as well as other molecular factors, could help determine who should be given adjuvant therapy.

**H&O** What are some challenges that are seen when treating stage II/III colon cancer patients?

**JM** One challenge is who should get therapy. The other challenge is establishing the best therapy. The chemotherapy treatment options for colon cancer patients are fluoropyrimidine, which could be given as intravenous 5-fluorouracil (5-FU), plus leucovorin or oral capecitabine, or a combination regimen of 5-FU, oxaliplatin, and leucovorin (FOLFOX).

Issues have also been raised in the treatment of stage III colon cancer patients. One debate is the use of oxaliplatin in older patients; there have been some analyses in patients older than 70 years that have shown no additional benefit to oxaliplatin compared to fluoropyrimidine alone, but one recent study contradicted this finding. All of these data are retrospective subgroup analyses and, ultimately, a prospective study may be important to mount. However, it is likely that numeric age alone should not be the basis of choice of treatment in elderly patients; assessments of function as well as performance status are being actively studied to determine better ways to develop a treatment program for an elderly patient.

**H&O** What studies have changed adjuvant therapy from just a fluoropyrimidine alone?

**JM** There have been 3 trials performed in stage II and stage III patients in which oxaliplatin was added to fluoropyrimidine. The MOSAIC (Multi-Center International Study of Oxaliplatin/5-fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer) trial compared FOLFOX versus infusional 5-FU plus leucovorin and found a statistically significant improvement in disease-free survival and overall survival in the combined stage II and III patients. Both endpoints were also significant in the stage III-only cohort. The analyses did suggest that high-risk stage II patients may benefit from FOLFOX compared to fluoropyrimidine alone, although the benefit was not statistically significant because the sample size was small. However, the low-risk stage II patients had no benefit from the addition of oxaliplatin to 5-FU and leucovorin in these analyses. The second trial was the National Surgical Adjuvant Breast and Bowel Project (NSABP) 07 trial. This study compared a bolus regimen of 5-FU, leucovorin, and oxaliplatin versus 5-FU and leucovorin. The third trial was a European trial that looked at capecitabine plus oxaliplatin versus intravenous 5-FU plus leucovorin. The latter 2 trials demonstrated similar findings to the MOSAIC study.

The duration of therapy has been debated in stage II and III patients. All the oxaliplatin-based regimens that have been investigated to date have been administered for 6 months. There are currently 4 ongoing trials—3 in Europe and 1 in the United States—looking at the duration of adjuvant therapy. Two of these trials include stage II and III patients and the 2 other trials include only stage III patients. These protocols are evaluating 3 months versus 6 months of adjuvant FOLFOX. The data analysis, pooled from all 4 studies, will examine the noninferiority of a shorter course of treatment duration.

**H&O** Why are there drugs that are beneficial in some patients with metastatic colorectal cancer but not beneficial in adjuvant therapy?

**JM** There are currently 3 drugs that have been utilized in metastatic colorectal cancer that have demonstrated no benefit when tested in the adjuvant setting: irinotecan, bevacizumab (Avastin, Genentech), and cetuximab (Erbitux, Bristol-Myers Squibb/ImClone; in KRAS wild-type patients). There have been 3 studies comparing irinotecan to fluoropyrimidine plus irinotecan, and none of them established a statistically significant benefit in disease-free survival. There was a trial in the United States that studied cetuximab limited to KRAS wild-type patients, which did not produce a benefit in cetuximab-treated patients. There is also a European trial looking at cetuximab that is fully enrolled, for which we do not yet have results. Furthermore, there are 2 trials with bevacizumab in stage III colon cancer patients that also have not demonstrated a benefit to bevacizumab compared to FOLFOX alone. It is not clear why these drugs that have efficacy in the metastatic setting do not seem to produce any response in the adjuvant setting, but we hope that the ongoing trials that are examining molecular features of colon tumors will provide an explanation.

**H&O** What is the best treatment approach in a patient who presents with stage II/III colon cancer?

**JM** The best approach is to first review all the pathologic features of the patient's tumor, the performance status, the comorbidities, and the age of the patient, and consider those in the decision-making process. For patients who have higher risk features, one has to realize that those are prognostic and not necessarily predictive of a benefit from chemotherapy. In patients who have low-risk stage II disease, there should be a discussion with the patient about the unclear benefit of chemotherapy and about

the justification of using a combination regimen versus fluoropyrimidine alone. For stage III patients, one should offer adjuvant chemotherapy. It is still important to consider comorbidity and functional status of the patient, but in general, an oxaliplatin/fluoropyrimidine-based regimen would be appropriate. For these patients, enrollment in a clinical trial is strongly recommended. There is an ongoing Cancer and Leukemia Group B/Southwest Oncology Group trial 80702; it is comparing the duration of FOLFOX (either 3 or 6 months), and second randomization to celecoxib, a cyclooxygenase 2 (COX-2) inhibitor, versus placebo for 3 years. The latter hypothesis is based on the strong evidence of a protective benefit of aspirin and COX-2 inhibitors in preventing polyps and colorectal cancer, as well as observational data demonstrating improvement in disease-free survival in colorectal cancer survivors that regularly used aspirin or COX-2 inhibitors.

## Suggested Readings

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