Options Updated for Adjuvant Colon Cancer Tx

BY DIANA MAHONEY
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HOLLYWOOD, FLA. — New guidelines have broadened the options for adjuvant chemotherapy in colon cancer patients who are at high risk of recurrence to include the alkylating agent oxaliplatin and the antimetabolite drug capecitabine.

In the adjuvant setting, patients with stage III colon cancer (tumor-node-metastasis T1-3, N1-2 [any lymph node involvement], M0) should receive oxaliplatin with 5-fluorouracil (5-FU) and leucovorin (the FOLFOX regimen); or capecitabine (Xeloda); or 5-FU and leucovorin without oxaliplatin, Paul Engstrom, M.D., said when presenting the updated guidelines at the annual conference of the National Comprehensive Cancer Network (NCCN).

The updates reflect large-scale clinical trial findings, said Dr. Engstrom, chair of the NCCN colon cancer guideline panel.

The oxaliplatin recommendation is based on findings from the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) study in which investigators compared the toxic effects and efficacy of the three-drug FOLFOX regimen against that of the 5-FU/–leucovorin regimen. The study, which included about 2,200 patients with resected stage II or stage III colon cancer randomized to 6 months of treatment with one of the two regimens, showed stage III patients receiving FOLFOX had a 24% reduction in their relative risk of disease recurrence after 3 years, compared with the non-oxaliplatin group.

The data showed a significant disease-free survival benefit for stage III patients, but not for stage II patients, said Dr. Engstrom of the Fox Chase Cancer Center, Philadelphia.

Additional options for adjuvant colon cancer treatment have fueled optimism. Still, the choice of regimen should depend on the risk to the patient.

Given the incidence of oxaliplatin-associated toxicities—41% of patients experienced neutropenia higher than grade III, and 12.4% experienced reversible grade III peripheral sensorial neuropathy—the new guidelines do not recommend the FOLFOX regimen for most stage II patients, Dr. Engstrom said.

The oxaliplatin-containing regimen may be an option for patients with stage II colon cancer who are considered to be at high risk for cancer recurrence based on primary tumor staging, the guidelines state.

The capecitabine recommendation reflects the findings of the Xeloda in Adjuvant Colon Cancer Therapy (X-ACT) trial of nearly 2,000 patients with stage III disease randomized to receive capecitabine or intravenous 5-FU/leucovorin following tumor resection. Taken orally, capecitabine is converted by the body into 5-FU. The X-ACT results showed capecitabine had better disease-free survival and overall survival rates than the 5-FU/leucovorin regimen and caused significantly fewer serious side effects, although hand-and-foot syndrome was significantly more common in the capecitabine group, he said.

The added options for adjuvant colon cancer therapy have contributed to a sense of optimism in treatment. Because the guidelines give equal weight to the adjuvant therapy recommendations, the choice of which regimen to use should depend on the risk to the patient, he said.

Last updated in 2004, the colon cancer guidelines also include these changes:

► Distinctions between three levels of stage III disease (stages IIIA, IIIB, and IIIC) to better target therapeutic decisions.

► The recommendation that radiotherapy be considered for use in combination with 5-FU/leucovorin for patients with advanced stage III disease with tumors that have invaded other organs or structures or have perforated the visceral peritoneum, and those with one or two regional metastases.

► The inclusion of a restructured treatment algorithm that includes chemotherapy with bevacizumab (Avastin) for patients with advanced colon cancer, giving equal weight to all of the commonly used regimens, including FOLFOX, FOLFIRI (5-FU/leucovorin/irinotecan), irinotecan and bolus 5-FU/leucovorin—all with or without bevacizumab—and 5-FU/leucovorin with bevacizumab.

► A recommendation that computed tomography be explored in the surveillance period for those at high risk of recurrence.

► A suggestion that laparoscopic surgery be considered instead of open surgery for resection of limited disease.

► A recommendation that staging of disease following primary resection of the tumor should be based on results from sampling a minimum of 12 lymph nodes.

► The addition of a section regarding risk assessment for stage II disease that recommends physician/patient discussion about treatment options and factors to consider when determining whether adjuvant therapy should be administered.

The NCCN is an alliance of 19 institutions designated comprehensive cancer centers by the National Cancer Institute. ■

Radiofrequency Thermal Ablation Useful for Colorectal Liver Metastases

BY DOUG BRUNK
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Laparoscopic radiofrequency thermal ablation appears to be a useful adjunct to chemotherapy for treating colorectal liver metastases. The survival benefit conferred by the technique is associated with three factors—serum carcinoembryonic antigen less than 200 ng/mL, dominant lesion less than 3.0 cm in diameter, and having one to three tumors vs. more than three tumors—results from a prospective study have shown.

Although earlier studies suggested that radiofrequency thermal ablation (RFA) favorably affected survival in this population of patients, "there are little data on predictors of survival," Eren Berber, M.D., and his associates wrote (J. Clin. Oncol. 2005;23:1358-64). "The aim of this study was to determine factors that might predict survival at the time of RFA in patients with colorectal liver metastases."

Dr. Berber and his associates studied 135 patients with primary or metastatic liver tumors who underwent laparoscopic RFA in the department of general surgery at the Cleveland Clinic Foundation. The patients were not candidates for resection, and 80% had intrahepatic tumor progression despite chemotherapy. Their mean age was 62, and most (85) were men. The mean number of liver tumors was 3.2; the largest tumors had a mean diameter of 4.1 cm.

Investigators performed triphasic CT scans of the liver within 1 week before surgery. After undergoing laparoscopic RFA, most patients were kept in the hospital overnight for observation and sent home the next morning. CT scans and lab tests were repeated at 1 week and every 3 months postoperatively.

Median survival for all patients was 28.9 months after RFA and 44.9 months after the diagnosis of liver metastasis. Patients with a serum carcinoembryonic antigen (CEA) of less than 200 ng/mL at the time of RFA lived a median of 34 months, while those whose CEA exceeded 200 ng/mL lived a median of 16 months. The size and number of tumors also affected survival.

Those with a dominant lesion less than 3 cm in diameter had a median survival of 38 months, while those whose dominant lesions were 3-5 cm had a median survival of 34 months. Patients whose dominant lesions were larger than 5 cm had a median survival of 21 months.

"Survival approached significance for patients with one to three tumors versus more than three tumors (29 vs. 22 months)," the investigators wrote.

"There was no survival advantage based on sex, age, colon versus rectal primary, nodal status at time of diagnosis, metachronous versus synchronous disease, bilobar versus unilobar disease, pretreatment chemotherapy, or documented extrahepatic disease at the time of treatment," they said.

The only significant predictor of mortality by the Cox proportional hazards model was largest liver tumor size greater than 5 cm. Patients whose largest tumor was this size were 2.5 times more likely to die than those whose largest tumor was less than 3 cm.

"Overall, the results of this prospective study are encouraging and suggest a survival advantage when compared with chemotherapy alone," wrote the investigators, who noted that historical survival with chemotherapy alone is 11-14 months. "Although our sample size might be insufficient for making decisive conclusions on the nonsignificance of the potential risk factors, we believe that RFA is a useful adjunct to chemotherapy in this group of patients." ■

Gene Profiling Might Predict Tx Response in Rectal Cancer

Pretreatment gene expression profiles might predict who responds to preoperative chemoradiotherapy in patients with rectal adenocarcinomas, results from a small trial have shown.

The finding is important because the response of individual tumors to adjuvant therapies is not consistent, wrote the investigators, led by B. Michael Ghadimi, M.D., a surgeon at University Medical Center in Göttingen, Germany.

"This poses a considerable clinical dilemma, because patients with a priori resistant tumors could be spared exposure to radiation or DNA-damaging drugs, treatments that are associated with substantial adverse effects, and surgery could be scheduled without delay," they wrote.

Dr. Ghadimi and his associates used microarrays to analyze pretherapeutic biopsies from 23 patients with rectal carcinomas for gene expression signatures.

The patients were enrolled in the phase III German Rectal Cancer Trial and were randomized to receive a preoperative combined-modality therapy that included fluorouracil and radiation (J. Clin. Oncol. 2005;23:1826-38).

After using class-comparison analysis, the investigators identified 54 genes that had significantly different expression levels between responsive and nonresponsive tumors based on T-level downsizing.

Next, they used leave-one-out cross-validation to estimate the response prediction of gene expression profiling and noted that the sensitivity and specificity of the test were 78% and 86%, respectively, while the positive and negative predictive values were 78% and 86%, respectively.

"Our inability to achieve higher accuracy could be due to several reasons, including tumor heterogeneity or the possibility that contamination of these particular biopsies with either normal rectal epithelium or adenomatous or stromal tissue could have partially obscured the detection of gene expression profiles more specific to rectal tumor cells."

They emphasized that larger, multicenter studies will be needed to confirm the findings.

—Doug Brunk