Oxaliplatin in the Adjuvant Treatment of Colon Cancer

Updated results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trial evaluating the addition of oxaliplatin to fluorouracil (5-FU) and leucovorin in the adjuvant treatment of patients with colon cancer confirmed previous findings of a strong disease-free survival (DFS) advantage. The findings, however, showed no advantage in overall survival (OS) for the entire cohort.

Greg Yothers, PhD, research assistant professor in biostatistics at the University of Pittsburgh and associate director of the NSABP Biostatistical Center in Pittsburgh, Pennsylvania, and colleagues recently published this first report of OS and updated DFS data, as well as an exploratory analysis of patient subsets of the C-07 trial (J Clin Oncol [published online ahead of print August 22, 2011]. doi: 10.1200/JCO.2011.36.4539).

The addition of oxaliplatin to 5-FU and leucovorin has been established as a standard of care for the adjuvant treatment of patients with colon cancer mainly by 2 phase 3 trials: one titled “Fluorouracil Plus Leucovorin With or Without Oxaliplatin in Treating Patients With Stage II or Stage III Colon Cancer” (the NSABP C-07 trial) and another titled “The Multicenter International Study of Oxaliplatin/SFU/Leucovorin in the Adjuvant Treatment of Colon Cancer” (MOSAIC) (N Engl J Med. 2004;350:2343-2351).

“This updated report confirms the durability of the [DFS] effect of oxaliplatin as originally reported for the NSABP C-07 and MOSAIC trials,” Dr. Yothers says.

Questions remain, however, as to patient selection for oxaliplatin in the adjuvant setting. DFS was significantly increased in both trials, and the OS in the MOSAIC trial showed a benefit for the entire cohort. However, on further analysis, the authors of the MOSAIC trial concluded that only patients with stage III disease experienced the OS benefit (J Clin Oncol. 2009;27:3109-3116).

A more recent phase 3 study comparing 5-FU and leucovorin with oxaliplatin and capecitabine (XELOX) for the adjuvant treatment of colon cancer has also been reported, with a clear DFS benefit noted with the oxaliplatin regimen (J Clin Oncol. 2011;29:1465-1471). After 5 years, OS was not found to be increased in this trial, but longer follow-up is planned.

DFS Remains Significant

In the NSABP C-07 trial, 2409 patients with resected stage II (29%) or stage III colon cancer were randomized to receive a bolus 5-FU and leucovorin regimen given for 6 consecutive weeks with 2 weeks of rest (FULV) or the same regimen plus oxaliplatin given on days 1, 15, and 29 of each cycle (FLOX). Three 8-week cycles were planned. (In the MOSAIC trial, 5-FU was given as a continuous infusion.) Demographics and disease characteristics were well balanced between the 2 study arms.

There was a nonsignificant trend toward improved OS noted in the FLOX arm for the entire study population, with a hazard ratio (HR) for FLOX versus FULV of 0.88, corresponding to a 12% relative reduction in the risk of death. OS estimates at 5 years were 78.4% for the FULV regimen and 80.2% for the FLOX regimen.

DFS was found to be significantly better in the FLOX group (P = .002). The HR for FLOX versus FULV was 0.82, an 18% relative reduction in the risk of disease recurrence or death. Overall DFS estimates at 5 years were 64.2% for the FULV regimen and 69.4% for the FLOX regimen.

Age-Related Differences in Outcome

Multivariate modeling was performed with the following factors to assess benefits for specific subgroups: chemotherapy regimen, age (< 70 years vs ≥ 70 years), gender, number of positive lymph nodes (0 vs 1-3 vs ≥ 3), depth of invasion, and location of the tumor (right vs left). In this analysis, only the age-treatment regimen interaction was significantly different between groups, suggesting that the addition of oxaliplatin in patients aged younger than 70 years was different from those aged 70 years or older. Because of this significant interaction, the researchers analyzed outcomes separately by age group. OS was found to be significantly improved with FLOX versus FULV for patients aged younger than 70 years (HR, 0.80; P = .013). The 5-year OS estimates were 78.8% for the FULV regimen compared with 81.8% for the FLOX regimen. No significant difference was noted between treatment.
groups for those patients aged 70 years or older, but the OS rate was 4.7% worse with FLOX in the older age group. DFS results showed a trend toward a difference with regard to the effect of oxaliplatin in patients aged younger than 70 years compared with those aged 70 years or older, but the interaction was not significant.

Patients aged 70 years or older in the FULV arm had a grade 4 or 5 toxicity rate of 13%, while those in the FLOX arm had a grade 4 or 5 toxicity rate of 20%. In the patients in the younger age group, these rates were 9% and 10%, respectively, for the FULV and FLOX regimens. The cumulative dose of oxaliplatin was approximately 25% lower in the older age groups, but dose intensity was similar between the age groups, suggesting that older patients more often withdrew from oxaliplatin therapy before the planned 6 months of treatment.

“This update of the NSABP C-07 trial does not change clinical practice,” says Axel Grothey, MD, professor of oncology at the Mayo Clinic in Rochester, Minnesota. “The adjuvant treatment of colorectal cancer in the United States is dominated by the oxaliplatin-containing regimens, though this update and other recent data questions the use of oxaliplatin in older patients and it has never shown a survival benefit in stage II patients.”

Clinical Application

The NSABP C-07 trial showed only a trend toward improved OS with oxaliplatin, with a HR of 0.88 ($P = .08$). This finding is not very different from the MOSAIC trial’s statistically significant HR of 0.84 for OS, favoring oxaliplatin. Taken together, the 2 trials show an approximately 15% reduction in the hazard of death for all participants.

The NSABP C-07 trial also demonstrated a significant OS advantage in the younger age group but not in the patients aged 70 years and older. “There is some evidence from NSABP C-07 that patients over age 70 experienced poorer OS and DFS outcomes when oxaliplatin was added to a 5-FU chemotherapy regimen as compared to patients treated with fluoropyrimidine therapy alone,” Dr. Yothers says.

The authors suggest that when making treatment decisions regarding the addition of oxaliplatin to 5-FU and leucovorin for the adjuvant treatment of colon cancer, age should be just one of the factors considered. “We do not encourage the use of chronologic age 70 as a rigid threshold for a decision to use oxaliplatin. The patient’s overall state of health should be considered, and frail patients under 70 should perhaps not get oxaliplatin while robust patients over age 70 perhaps should get it,” Dr. Yothers says. The authors also noted in the study that previous trials have shown that elderly patients with colon cancer benefit from adjuvant 5-FU and leucovorin (N Engl J Med. 2001;345:1091-1097).

According to Dr. Grothey, once the decision is made that a patient should receive adjuvant chemotherapy for stage III colon cancer, oxaliplatin-containing regimens are standard unless the patient is not thought to be able to tolerate it. Other issues such as better patient selection for adjuvant therapy using molecular testing and potentially using shorter durations of therapy are currently being addressed in numerous clinical trials, he says. Dr. Grothey says he hopes this ongoing work will help achieve a more individualized approach, causing less toxicity and maximizing benefit.