

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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IN FOCUS: Colorectal Cancer

Optimizing Oxaliplatin-based Therapy in Metastatic Colorectal Cancer

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H&O What is the background of the recent phase III trial comparing oxaliplatin-based regimens in metastatic colorectal cancer?

JC There was a good amount of data from phase I and II studies suggesting that capecitabine (Xeloda, Roche) would achieve positive results in combination with oxaliplatin (Eloxatin, Sanofi-Aventis) for the treatment of metastatic colorectal cancer. The phase II comparisons of capecitabine plus oxaliplatin (XELOX) with leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX) further suggested that these two regimens have similar efficacy. Additionally, XELOX had demonstrated advantages in terms of patient convenience. The hypothesis that XELOX was equivalent to FOLFOX in the first-line setting was thus tested in a randomized phase III international trial. However, because it is quite difficult to prove equivalency in a clinical trial, the comparison was planned in a noninferiority design. The trial was initially planned to accrue 1,000 patients. After this trial began, the monoclonal antibody bevacizumab (Avastin, Genentech) was approved for the treatment of metastatic colorectal cancer and entered the marketplace. Because this approval made recruitment of patients to the trial difficult, the investigators were compelled to modify the design to a 2 × 2 randomization, XELOX or FOLFOX with or without bevacizumab.

H&O What were the findings of the comparison of XELOX with FOLFOX?

JC No matter how the data from the trial were analyzed and which subpopulations were compared, the noninferiority of XELOX to FOLFOX was demonstrated. We can say with confidence that the two regimens have essentially identical efficacy outcomes. The side effect profiles, however, are not identical. Compared to the alternate regimen, FOLFOX is associated with greater neutropenia and XELOX is associated with greater diarrhea. The rates of neuropathy are similar with each regimen, and capecitabine is associated with hand-foot syndrome. The toxicities profiles are such that the regimens are interchangeable insofar as each one has expected toxicities; neither should be considered superior in terms of toxicity.

H&O How do the regimens compare in terms of patient convenience?

JC At my institution, XELOX is considered the default regimen largely because it is easier to administer. Patient management requires fewer resources. Lines and pumps are not needed in most cases, and the amount of time spent with the intravenous-infusion management team is lessened with XELOX. The financial burden associated with XELOX is thus lower than that associated with FOLFOX. When choosing which regimen to administer to a given patient, clinicians should not give XELOX to a patient who has previously experienced severe diarrhea. Similarly, patients with problems related to sepsis or wound healing should not receive FOLFOX because

of the increased risk of neutropenia. Clinicians can therefore tailor the treatment based on specific patients' clinical pictures.

H&O How did the addition of bevacizumab affect the outcomes with XELOX and FOLFOX?

JC For both XELOX and FOLFOX, the addition of bevacizumab conferred a statistically significant increase in the outcome parameters, particularly progression-free survival. Bevacizumab can thus be considered to confer a positive benefit in addition to that seen with oxaliplatin-based chemotherapeutic regimens. It was already known that bevacizumab increases the benefit of irinotecan-based regimens, but this trial was the first phase III demonstration of its benefit in combination with oxaliplatin-based regimens.

H&O What side effects were associated with the administration of bevacizumab?

JC Bevacizumab has its own toxicity profile, including hypertension, proteinuria, problems with wound healing, and some thromboembolic events. These events occur at low rates, and in this trial, these events occurred at lower rates than had been reported in the literature previously with administration of bevacizumab. Clinically, the addition of bevacizumab does not significantly change the safety picture because these events are relatively insignificant and do not occur often.

H&O Which patients should not receive bevacizumab in this setting?

JC There are some patients for whom bevacizumab confers unwanted risk. Patients who have recently experienced myocardial infarctions, who have recently undergone surgical correction of fistulas, or who have problems with wound healing would not be candidates for therapy with bevacizumab. These contraindications, though, may be more theoretical than real. Patients with recent myocardial infarctions were excluded from the trial, so the safety of bevacizumab in this setting is unknown. There have been some patients treated with bevacizumab fairly recently after surgery who did not experience any untoward toxicities. But it seems prudent not to expose patients to the extra risk that may be associated with bevacizumab, in particular by allowing at least 6 weeks of postsurgical recovery before initiation of therapy. Early on in this research with bevacizumab, questions arose as to whether

it was safe to administer this agent in the presence of a central venous catheter. Many clinicians were apprehensive about the safety of bevacizumab in this setting. With increased experience, however, it has become apparent that it is safe to begin the administration of this agent on the same day the catheter is placed.

H&O What are the next steps of research with oxaliplatin-based therapy?

JC There are three directions of research in the near future. First, XELOX is under evaluation in the adjuvant setting in the XELOX-A trial. This trial has finished recruitment, and the safety outcomes have been presented. The efficacy outcomes are expected soon. The community expects XELOX to be found effective in the adjuvant setting. A trial has commenced evaluating a shortened duration of chemotherapy in the adjuvant setting, comparing a 3-month to a 6-month schedule. Clearly, shortening the duration of chemotherapy would have a major impact in terms of quality of life, cost, and side effects. Second, researchers hope to investigate the optimal duration of the administration of biologics, including bevacizumab, in the setting of metastatic colorectal cancer, both in the advanced-disease and adjuvant settings. Trials are ongoing in patients with advanced disease, and trials are planned in the adjuvant setting. A question to answer might be whether the administration of bevacizumab for 2 years is necessary. Finally, researchers are wondering whether a combination of bevacizumab, cetuximab (Erbix, Bristol-Myers Squibb/Merck/ImClone), irinotecan, and oxaliplatin would be useful in patients whose disease would benefit from downstaging prior to resection. There is a small group of patients whose disease is considered borderline resectable. In these patients, if the malignancy can be shrunk, surgery may become more feasible.

Suggested Readings

- Carrato A, Gallego-Plazas J, Guillén-Ponce C. Capecitabine plus oxaliplatin for the treatment of colorectal cancer. *Expert Rev Anticancer Ther.* 2008;8:161-174.
- Cassidy J, Clarke S, Díaz-Rubio E, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. *J Clin Oncol.* 2008;26:2006-2012.
- Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol.* 2007;25:1670-1676.
- Saltz LB, Clarke S, Díaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol.* 2008;26:2013-2019.