New First-line Option for Advanced Colorectal Cancer

Roxanne Nelson | January 14, 2015

Adding oxaliplatin to a chemotherapy regimen already used in combination with bevacizumab (*Avastin*) for the treatment of metastatic colorectal cancer has been shown to double the 5-year survival rate.

The latest results from the TRIBE trial, conducted in 34 oncology units in Italy, show that the new chemotherapy combination known as FOLFOXIRI (folinic acid/leucovorin, fluorouracil, oxaliplatin, and irinotecan) is superior to the standard chemotherapy regimen of FOLFIRI (folinic acid/leucovorin, fluorouracil, and irinotecan) when both are used with bevacizumab.

FOLFOXIRI extended overall survival by about 4 months, and doubled the 5-year overall survival rate seen with FOLFIRI (24.9% vs 12.4%). However, it also increased adverse events. FOLFOXIRI had a greater incidence of grade 3/4 diarrhea, mucositis, neuropathy, neutropenia.

Therefore, it might not be suitable for all patients, said lead author Chiara Cremolini, MD, a medical oncologist at the Tuscan Tumor Institute in Pisa, Italy.

"I see this as a new first-line regimen for patients with metastatic colorectal cancer who are able to tolerate this kind of treatment," she explained during a press briefing held in advance of the 2015 Gastrointestinal Cancers Symposium in San Francisco.

"There was an increase in adverse events, but patients were able to tolerate it for the most part," she told *Medscape Medical News*. "It is important to manage the treatment with dose reductions, but overall, this is a manageable and reasonable regimen in most settings."

Not for Everyone

"This study clearly demonstrates that FOLFOXIRI plus bevacizumab is a safe and effective option for patients with metastatic colorectal cancer who can tolerate a triple chemotherapy regimen," said presscast moderator Smitha S. Krishnamurthi, MD, from the Case Western Reserve University School of Medicine in Cleveland,.

"We have to consider that 90% of the patients in the study were asymptomatic at the time of enrollment, and those over the age of 75 were not eligible, so this isn't for everyone," she added. "But for the right patients, this is one of the most active regimens, with an impressive almost 25% survival rate at 5 years."

Details of the Updated Results

The most important aspect of the study is the fact that we "have been able to prove that FOLFOXIRI plus bevacizumab provides a significant survival benefit," said Dr. Cremolini.

"In the preliminary analysis, there was only a trend toward statistical significance, but now the data are much more clear and mature," she told *Medscape Medical News*.

In a previous analysis of the TRIBE data, first-line FOLFOXIRI plus bevacizumab was shown to significantly prolong progression-free survival (the primary end point), compared with FOLFIRI plus bevacizumab (*N Engl J Med*. 2014;371:1609-1618).

Of the 508 patients with metastatic colorectal cancer involved in the TRIBE study, 252 were randomized to receive FOLFOXIRI plus bevacizumab and 256 were randomized to receive FOLFIRI plus bevacizumab. Both treatments were given for up to 12 cycles, and followed with fluorouracil, leucovorin, plus bevacizumab until disease progression.

About 80% of the patients were not candidates for surgical resection. However, after the chemotherapy regimen, 15% of the FOLFOXIRI group and 12% of the FOLFIRI group were able to undergo radical resection.

At a median follow-up of 48.1 months, there were 174 deaths in the FOLFOXIRI group and 200 in the FOLFIRI group.

Median overall survival was significantly better in with FOLFOXIRI than with FOLFIRI (29.8 vs 25.8 months; hazard ratio [HR], 0.80; *P* = .030).

Table. Survival Rates

Years of Survival	FOLFOXIRI Group, %	FOLFIRI Group, %
3	40.0	34.5
4	27.3	22.9
5	24.9	12.4

Progression-free survival was also better in the FOLFOXIRI group (12.3 vs 9.7 months; HR, 0.77; *P* = .006).

The treatment effects were consistent in all of the subgroups analyzed in the study.

On univariate analysis, prognosis was found to be negatively affected by an Eastern Cooperative Oncology Group (ECOG) performance status of 1 or 2, a right-sided primary tumor, synchronous metastases, disease not confined to the liver, an unresected primary tumor, and a high Kohne score.

After adjustment for these variables, the hazard ratio for effect on overall survival was 0.77 (95% confidence interval [CI], 0.61 - 0.96; *P* = .02).

Follow-up Study Underway

The phase 3 TRIBE-2 study is being launched by the same group. It will involve 654 patients randomized to either first-line FOLFOXIRI plus bevacizumab followed at disease progression by a reintroduction of FOLFOXIRI plus bevacizumab, or to FOLFOX plus bevacizumab followed at progression by FOLFIRI plus bevacizumab.

This study was supported by the Gruppo Oncologico Nord Ovest (GONO), the ARCO Foundation, and a research grant from F. Hoffmann-La Roche. Dr. Cremolini reports serving in a consulting or advisory role for Bayer and Roche, and being on the speakers bureau for Bayer. Several of her coauthors report relationships with industry, as noted in the abstract.

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