CRC IN FOCUS

Current Developments in the Management of Colorectal Cancer

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EGFR Inhibition in Colorectal Cancer With Liver Metastasis

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H&O What is the standard course of treatment for patients with metastatic colorectal cancer that has spread to the liver?

AG The first step in managing patients with metastatic colorectal cancer (CRC) who have liver-limited disease is a consultation with a dedicated liver surgeon to see whether the liver metastasis can be resected. After we know that, we can determine the appropriate treatment strategy. Can the liver metastasis be resected right away, do we need to induce an anatomical shrinkage of liver lesions in order to make them resectable, or do we have an unresectable palliative situation from the outset? The medical oncologist and the liver surgeon both need to evaluate the patient and work as a team.

When the liver metastases are resectable, the standard of care is to administer systemic chemotherapy before surgery. Administering chemotherapy at this point lets us know whether the tumor is responsive to medical therapy. This step is especially important if the patient has synchronous metastases.

When the liver metastases are not resectable up front and we need to induce a response, the approach to chemotherapy is different because our goal is not only to evaluate the tumor biology, but also to induce anatomical shrinkage in order to facilitate surgery.

H&O Which perioperative chemotherapy regimens are used in these patients with resectable metastatic CRC?

AG The standard of care for patients whose metastases are resectable up front is leucovorin/5-fluorouracil (5-FU)/oxaliplatin (FOLFOX). This standard is based on data from the original EPOC study (Surgery With or Without Combination Chemotherapy in Treating Patients With Liver Metastases From Colorectal Cancer), also known as EORTC 40983, which was published in the *Lancet* in 2008 by Nordlinger and colleagues. The study showed that the addition of perioperative FOLFOX to treatment of resectable liver metastases, which at that time was defined as up to 4 metastases in the liver, improved disease-free survival compared with surgery alone. The study never showed an increase in overall survival with chemotherapy, likely because it was much too small, with just 364 patients.

For liver metastases that are unresectable up front, we try to make the regimen more active because we are aiming for an anatomical response.

H&O Could you describe the design and the results of the New EPOC study?

AG The New EPOC study (Combination Chemotherapy With or Without Cetuximab Before and After Surgery in Treating Patients With Resectable Liver Metastases Caused By Colorectal Cancer) is a phase 3 study from the United Kingdom. It was designed to build on the results of the original EPOC study by looking at the potential role of endothelial growth factor receptor (EGFR) antibodies, which are antitumor agents that can lead to tumor shrinkage. In New EPOC, researchers wanted to determine whether the addition of cetuximab (Erbitux, Lilly) to FOLFOX and/or other chemotherapies would

benefit patients when used in the setting of liver-limited disease. Although the patients in this study were allowed to have resectable or suboptimally resectable disease, most of them had up-front resectable disease according to our current definition.

A total of 257 patients were enrolled in New EPOC. All patients received perioperative chemotherapy; the most common regimen was FOLFOX, but leucovorin/5-FU/irinotecan (FOLFIRI) and capecitabine/oxaliplatin (CAPOX) were also used. Patients were randomly assigned to receive chemotherapy with cetuximab (n=129) or without cetuximab (n=128).

The data and safety monitoring board halted the study after a median of 21 months because perioperative cetuximab was producing a detrimental effect on progression-free survival (PFS). The interim results, which were published by Primrose and colleagues in *Lancet Oncology* in 2014, found a detriment for PFS with the use of cetuximab, with a hazard ratio of 1.48 (95% CI, 0.86-2.60; *P*=.03). The study also revealed a trend toward worse overall survival with cetuximab, although the difference was not statistically significant. These results were especially surprising because at the same time, cetuximab increased the proportion of patients with a response to treatment.

All the evidence shows that the use of EGFR antibodies in the postoperative setting is not helpful, and is potentially detrimental.

Updated data from New EPOC were published online on January 31 in *Lancet Oncology* by Bridgewater and colleagues after a median follow-up of 67 months. These results showed that the difference in PFS was no longer statistically significant, with a hazard ratio of 1.17 (95% CI, 0.87-1.56; *P*=.304). Perioperative cetuximab had a detrimental effect on overall survival, however. Median overall survival was 55 months with chemotherapy plus cetuximab vs 81 months with chemotherapy alone, for a hazard ratio of 1.45 (95% CI, 1.02-2.05; *P*=.36).

H&O What has been the reaction to these findings?

AG The study was very controversial when it was initially published by Primrose and colleagues in 2014. A letter exchange in the *Journal of Clinical Oncology* went back and forth in late 2014 and early 2015. The investigators who criticized the study thought that the cetuximab may have failed because the surgical approach was inadequate, or because of differences in baseline characteristics between the patient groups.

I personally think that the study was conducted as well as it could have been, with appropriate randomization. It took place at dedicated centers for liver resection in the United Kingdom, and there is no reason to doubt the technical skills of the surgeons involved.

H&O What is your explanation for how cetuximab may have improved response rates but led to shorter PFS and overall survival?

AG That is the million-dollar question. This is not unheard of; we saw a similar surprise finding in an adjuvant study from the North Central Cancer Treatment Group called N0147 that was conducted in the United States and Canada and published in the *Journal of the American Medical Association* in 2012 by Alberts and colleagues. This study looked at patients with stage III CRC, and studied the addition of cetuximab to FOLFOX in *KRAS* wild-type cancers.

The interesting finding was that adjuvant cetuximab actually had a potential detrimental effect on disease-free survival, with a hazard ratio of 1.21—a 20% increased risk of recurrence, even though the difference was not statistically significant (*P*=.08). This really surprised us. Now that we see the similarities between the New EPOC study and N0147, we have more evidence for the idea that EGFR antibodies have some detrimental effect in a potentially micrometastatic setting.

I still believe that using the EGFR antibody to induce responses in a macroscopically visible tumor can be important in the conversion therapy setting, where we want to obtain anatomical shrinkage of metastases to allow for surgical resection. My hypothesis is that by targeting the EGFR on the surface of tumor cells, we may be altering the tumor's biology so that it develops a more aggressive phenotype. Such a phenomenon could explain the reduction in overall survival observed in New EPOC. In any case, all the evidence shows that the use of EGFR antibodies in the postoperative setting is not helpful, and is potentially detrimental.

I would like to see future studies, especially studies in vitro, that examine the effect of EGFR antibodies on the morphologic phenotype of CRC cells. Do EGFR antibodies induce epithelial-mesenchymal transition, for example? Do they allow cells to convert from an epithelial phenotype to a more-aggressive mesenchymal phenotype?

H&O What has been the effect of New EPOC?

AG Right after the interim New EPOC data came out in 2014, the National Comprehensive Cancer Network (NCCN) changed its guidelines on treating CRC. The NCCN had previously allowed the use of EGFR antibodies and bevacizumab in the neoadjuvant setting for patients with operable resectable liver metastases, but now the guidelines list only chemotherapy—preferably FOLFOX—as neoadjuvant treatment in patients with resectable liver metastases.

H&O When should anti-EGFR agents be used in metastatic CRC?

AG Anti-EGFR agents such as cetuximab and panitumumab (Vectibix, Amgen) remain a standard of care for the management of metastatic CRC. We know that EGFR antibodies should only be used in *RAS* and *BRAF* wild-type left-sided CRC, at least in the first-line setting. We define "left-sided" colorectal tumors as those distal to the splenic colon flexure.

Another factor in choosing treatment is human epidermal growth factor 2 (HER2) status. Patients who have *HER2* amplification or overexpression likely do not benefit from EGFR antibodies, but the data for this are not as solid as they are for *RAS* and *BRAF* status.

Based on the data from the New EPOC study, I am hesitant to use EGFR antibodies in the context of up-front resectable liver metastases. However, if I have a scenario in which liver metastases require anatomical shrinkage to even consider resection, I would not hesitate to use EGFR antibodies. I would therefore use FOLFOX plus panitumumab or cetuximab in left-sided *RAS* or *BRAF* wild-type tumors that are potentially resectable in liver-limited disease. We have seen that when we really throw the kitchen sink at patients with left-sided *RAS* or *BRAF* wild-type tumors, and use both triplet chemotherapy (FOLFOXIRI) and an EGFR inhibitor, the response rates are approximately 90%.

H&O When should physicians conduct molecular profiling in these patients?

AG The panel that every patient should receive before first-line treatment includes microsatellite instability or mismatch repair deficiency, *RAS* mutation status, and *BRAF* mutation status. I think testing these items is the low-hanging fruit.

Additional molecular tests to consider, including in the first-line setting, are *HER2* amplification, *NTRK* fusions, and *RET* fusions. These and other alterations may not necessarily be relevant for the first-line choice of therapy, but they still may be relevant to the choice of second-, third-, and fourth-line treatment options both inside and outside of clinical trials.

H&O What should the next steps be in research?

AG First, we need to dive a bit deeper into the available data and see whether some commonalities exist among the different responses we have seen across trials. For example, the phase 3 CALGB/SWOG 80405 study (Cetuximab and/or Bevacizumab Combined With Combination Chemotherapy in Treating Patients With Metastatic Colorectal Cancer) investigated the use of cetuximab vs bevacizumab in first-line treatment, and several patients in the study underwent liver resection. (This study appeared in the *Journal of the American Medical Association* in 2017, with Venook as the first author.) We need to find additional data to see whether the signal we observed in New EPOC is real or not.

Second, I would like to see some translational research aimed at determining why this is happening. Why do we see a potential detrimental effect from EGFR antibodies in the minimal residual disease or microscopic disease setting, even in *RAS* and *BRAF* wild-type colon cancer?

I hope we can develop some preclinical models that will allow us to figure that out, because this unexpected detrimental effect has occurred in not just 1 but at least 2 studies. We owe it to our patients to learn what is going on so we can avoid similar issues in the future and potentially design trials based on a stronger scientific rationale.

Disclosure

The West Cancer Center has received honoraria from Roche/Genentech, Bayer, Array/Pfizer, and Boston Biomedicals for consulting activities performed by Dr Grothey.

Suggested Readings

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