Current Strategies in Previously Untreated Advanced Colorectal Cancer

In the past 5 years, the treatment of metastatic colorectal cancer has seen unparalleled advances. Median overall survivals reported in phase III trials have almost doubled and are poised to break the 2-year barrier very soon, perhaps as early as this year. This has been made possible through the introduction of a variety of active agents into the treatment of this disease.

Several Key Points

- Combination regimens with 5-FU/leucovorin plus either irinotecan or oxaliplatin have emerged as standard of care for first-line chemotherapy. There is truly no need to discuss this further.

- Bolus 5-FU/leucovorin protocols are obsolete.[1] It has been clearly shown that both the Mayo Clinic and Roswell Park protocols are associated with inferior safety profile and lower efficacy compared with infusional 5-FU/leucovorin or capecitabine (Xeloda), in particular when used as the backbone for combination protocols with irinotecan and oxaliplatin. Thus iFL, the combination of bolus 5-FU/leucovorin plus irinotecan, should be abandoned in clinical practice and replaced by FOLFIRI. Based on the available data, it is conceivable that purely infusional oxaliplatin- or irinotecan-based regimens, ie, protocols that omit any bolus 5-FU application completely, confer an even better safety profile.

- While capecitabine can already be considered a superior substitute for bolus 5-FU/leucovorin, it is not yet clear if it can replace infusional 5-FU/leucovorin in combination regimens. The results of ongoing clinical trials will clarify if capecitabine/irinotecan and capecitabine/oxaliplatin regimens will be able to replace FOLFIRI and FOLFOX in the future.

- Patients should receive all available active drugs in the course of their disease to maximize their overall survival. While the optimal sequence of chemotherapy regimens is debatable, it is clear that patients benefit from active second- and presumably thirdline therapies.[2]

- The high efficacy associated with modern combination protocols has turned advanced colorectal cancer into a chemosensitive disease in which innovative therapeutic strategies with curative intent have emerged. In patients with disease limited to the liver (perhaps even with additional potentially resectable lung metastases), secondary surgery for metastases after downstaging should be considered an integral part of the therapeutic strategy. No
patient should be denied the only potentially curative chance he might have in the course of his disease.[3]

- Bevacizumab (Avastin) and cetuximab (Erbitux), the two monoclonal antibodies both approved for the treatment of advanced colorectal cancer in February 2004, constitute a great challenge. What is the best way to integrate these agents into current clinical practice? Fortunately for now, both drugs are approved for very different clinical settings.

Cetuximab
Because cetuximab was mainly developed as salvage therapy for patients that have progressed on conventional, irinotecan-based therapy, the approval follows this label exactly. It has to be emphasized, however, that the actual clinical activity of cetuximab is quite impressive. As monotherapy, it is able to generate a response rate of around 10% in patients refractory to irinotecan- and oxaliplatin-based therapy. In combination with irinotecan, the response rate is in the range of 20%. This compares very favorably to the efficacy reported for FOLFOX after IFL (10% response rate).[4,5] 

Bevacizumab
Based on the convincing proof of efficacy when added to IFL and bolus 5-FU/leucovorin as first-line treatment, bevacizumab has been approved for the use in the first-line setting in combination with any intravenous 5-FU-based therapy.[6] This label opens the door for a combination that has not yet been tested in first line: FOLFOX plus bevacizumab. While safety data on FOLFOX plus bevacizumab have become available through an interim analysis of the second-line Eastern Cooperative Oncology Group trial E3200, it is an open question if bevacizumab will add significant efficacy to FOLFOX in the same way it did to less active cytotoxic regimens (IFL and bolus 5-FU/leucovorin). However, not least based on the molecular mechanism of action of bevacizumab, it is conceivable its enhancement of activity is independent of the cytotoxic combination partner used. Thus, the clinical approach to combine the best available cytotoxic protocol with the best available biologic agent in the first-line setting makes sense. In fact, as of the time of this writing (April 2004), about 40% of all bevacizumab is used in combination with FOLFOX-in the absence of confirmatory data! If we postulate that bevacizumab will add a similar incremental benefit to FOLFOX as it did to IFL-in particular, in terms of time to tumor progression- a distinct clinical problem emerges: Hypothetically, the median time on treatment could now exceed 12 months. However, 12 months of therapy with FOLFOX would mean a cumulative oxaliplatin dose of over 2,000 mg/m^2 if FOLFOX were used continuously. It is quite obvious that this cumulative dose is not tolerable by most patients. Thus, innovative treatment strategies have to be developed. The most promising approach to solve this problem has already been studied in the OPTIMOX trial.[7] It has been shown that it is clinically feasible, and does not compromise overall efficacy, to stop oxaliplatin after a certain number of induction cycles up to a predefined cumulative oxaliplatin dose. The achieved response or stable disease can then be maintained by a non-oxaliplatin-containing regimen. This concept, though, will have to be validated in a randomized trial under inclusion of bevacizumab.

Conclusions
In view of the great variety of therapeutic options in advanced colorectal cancer, the key question for all clinical trials has moved from, "What is the best X (first-, second-, etc)-line therapy?" to "What is the best overall treatment strategy?" If we make use of all available resources and treatment modalities, we will turn metastatic colorectal cancer into a chronic disease; there will be significant (positive) implications for patients, but also pharmacoeconomic consequences that we are only beginning to understand. Along this way, we as medical oncologists will have a lot to learn for the benefit of our patients.

Disclosures: The author receives research support from Sanofi-Synthelabo and Roche. He is on the speaker's bureaus of Sanofi-Synthelabo, Genentech, Roche, and Bristol-Myers Squibb.

References:


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