Systemic Therapy for Metastatic Colorectal Cancer

Presented by Leonard Saltz, MD

Abstract

In the treatment of advanced colorectal cancer (CRC), the addition of so-called “targeted” agents to irinotecan- and oxaliplatin-based regimens has resulted in statistically significant—but often clinically modest—improvements in progression-free and overall survival. This is true for the most recent additions to the treatment armamentarium, regorafenib and ziv-aflibercept. In his recent presentation at the NCCN 18th Annual Conference, Leonard Saltz, MD, reviewed the landmark trials establishing targeted agents as effective in metastatic CRC. However, he also noted that statistical significance does not necessarily equal clinical significance, and indicated that clinicians should consider the differential toxicity profiles of the regimens when individualizing treatment. (JNCCN 2013;11:649–652)

“Overall, progress in metastatic colorectal cancer (CRC) has been real, but modest, while hype and cost increases have been substantial,” said Leonard Saltz, MD, Chief of the Gastrointestinal Oncology Service at Memorial Sloan-Kettering Cancer Center, New York.

The backbone of treatment is still 5-fluorouracil [5-FU], which was patented in 1957 and remains “arguably the single best drug we have in CRC,” he noted. “ Virtually every drug since then has been a relative failure in terms of its intention to replace 5-FU.” Instead, new drugs have found a role in combination therapy, he added, as none have been effective enough as single agents.

In this regard, FOLFOX (leucovorin, fluorouracil, oxaliplatin) and FOLFIRI (leucovorin, fluorouracil, irinotecan) produce essentially the same outcomes in terms of response rates, time to progression, and overall survival (OS). Dr. Saltz further noted that due to its neurotoxic potential, FOLFOX’s place as the preferred initial regimen in the United States may be somewhat misguided. Instead, he suggested that clinicians consider and discuss with their patients the toxicity profiles of both regimens and together choose between FOLFOX and FOLFIRI according to the patient’s preferences and tolerance for the associated potential adverse events.

Updated results from the MOSAIC trial of FOLF- OX confirmed that approximately one fourth of patients have some degree of peripheral neuropathy (primarily, but not limited to, grade 1) 1 year after treatment. At 4 years, residual symptomatic neuropathy (probably permanent) still exist for more than 10% of patients.1 “This is a reason we need to think about reducing the patient’s exposure to oxaliplatin,” he said.

The OPTIMOX1 study defined standard practice by showing that a “stop and go” approach to giving oxaliplatin could be as effective as continuous treatment, with less neurotoxicity.2 CapeOx (capecitabine, oxaliplatin) is also an option, he said, but he cautioned that oral agents are not the right choice for some patients. Continuing an oral regimen, especially one containing an emetogenic agent such as oxaliplatin, is a large responsibility to give to some patients. Appropriate patients for consideration of oral agents are those who are both highly motivated and capable of accurately adhering to a complicated oral schedule.

Presented by Leonard Saltz, MD, Chief of the Gastrointestinal Oncology Service at Memorial Sloan-Kettering Cancer Center, New York, New York.

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Highlights of the NCCN 18th Annual Conference

Saltz

**Bevacizumab**

The initial bevacizumab study, which evaluated the benefit of adding the drug to IFL (irinotecan, bolus fluorouracil, leucovorin), found a 4.7-month OS improvement \( (P = .00003) \) with bevacizumab. This is the largest survival benefit yet seen in any randomized metastatic CRC trial.\(^3\) The results led experts to consider whether bevacizumab could enhance the effect of any chemotherapy regimen; however, subsequent trials with oxaliplatin-based regimens produced less robust differences. Although the difference in progression-free survival (PFS) was statistically significant in the NO16966 study, for example, it was for more modest benefit, in that it was only 1.4 months \( (P = .0023).\)\(^4\)

“This was the first in a series of 1.4-month improvements in the clinical trials, and this was sobering,” Dr. Saltz said. “It speaks to the difference between statistical significance and clinical significance and can lead clinicians to overstate the benefits of our treatments to ourselves and to our patients.”

Interestingly, another 1.4-month improvement—in OS— was found when patients continued bevacizumab beyond progression in the recent TML Trial.\(^5\) Patients received chemotherapy (irinotecan- or oxaliplatin-based) plus bevacizumab for first-line treatment; on progression, they switched to either the alternate regimen or to the alternate regimen plus bevacizumab. Median OS was 11.2 months in the bevacizumab arm and 9.8 months in the chemotherapy alone arm \( (P = .0062 \text{ unstratified}) \) and median PFS was 6.7 versus 4.1 months \( (P < .001).\)

**Epidermal Growth Factor Receptor Inhibitors**

Inhibitors of the epidermal growth factor receptor (EGFR) signaling pathway are important agents in metastatic CRC. The European BOND trial confirmed previous studies in the United States and led to FDA approval of cetuximab.\(^6\)

The CRYSTAL trial, however, produced statistically significant but clinically disappointing results with cetuximab plus FOLFIRI. In this study, the authors noted a 0.8 month (25-day) difference in PFS \( (P = .048) \), but subanalysis revealed that the benefit was limited to patients with KRAS wild-type tumors.\(^7\) The 1-year PFS was 43% with cetuximab and 25% without it, but the PFS difference patients with KRAS wild-type tumors of 37 days “was hardly a grand-slam,” Dr. Saltz noted. He did note a survival benefit in excess of 3 months in the group with KRAS wild-type tumors, but also noted that similar survival benefits had been noted for cetuximab in the last-line NCIC CO-17 study.

It is important to obtain KRAS genotyping from the primary tumor, both to ensure effective treatment in patients with KRAS wild-type tumors and to avoid harmful treatment in patients with KRAS-mutant tumors, who may actually have worse outcomes with an EGFR inhibitor plus oxaliplatin. In the OPUS trial, cetuximab treatment was associated with a median PFS of only 5.5 months versus 8.6 months without it.\(^8\) In the PRIME trial, patients with KRAS-mutant disease also had worse outcome with panitumumab.\(^9\)

The occurrence of skin rash with EGFR inhibitors has consistently been associated with improved responses, and patients without a rash are unlikely to benefit. The rash can be socially debilitating, however, which, Dr. Saltz noted, is why he prefers to reserve the use of EGFR inhibitors for later lines of therapy. These fairly modest benefits and substantial cutaneous toxicity suggest that these agents might be best employed in later lines of treatment, he suggested. “I virtually never use EGFR agents up front, though it’s an acceptable option in the guidelines,” he noted.

**New Agents in CRC**

Ziv-aflibercept is a fusion protein that, unlike bevacizumab, blocks all human VEGF-A isoforms, VEGF-B, and placental growth factor. “We had hoped this would be the next step forward, but in the registration study it provided, again, only a 1.4 month OS benefit.”

The VELOUR trial evaluated ziv-aflibercept plus FOLFIRI as second-line treatment. It showed an OS improvement from 12.06 to 13.50 months \( (P = .00003) \), and PFS improved from 4.7 to 6.9 months \( (P = .00007) \) with the addition of the drug.\(^10\) A cross-study comparison of VELOUR versus TML showed that when given with second line chemotherapy, bevacizumab and ziv-aflibercept have comparable outcomes; each added 1.4 months of survival time.

However, he added that, while cautioning against the limitations of cross-trial comparisons,
ziv-aflibercept appears to have more toxicity potential than bevacizumab and further defined the main concern with the drug as cost. A 12-week treatment of ziv-aflibercept costs more than $30,000, while a course of bevacizumab treatment (5 mg/kg) costs less than $14,000. “The drugs accomplish more or less the same benefit, but one is double the price. This cost difference was a deal-breaker for our physicians at Sloan-Kettering. We decided we did not see a reason to use ziv-aflibercept at this time.”

He noted, however, that the NCCN Guidelines include ziv-aflibercept as an acceptable regimen when added to FOLFIRI or irinotecan. He further cautioned that no justification is available for using single-agent ziv-aflibercept (or bevacizumab), for using FOLFIRI-aflibercept after failure of FOLFIRI-bevacizumab (or vice versa), or for adding either ziv-aflibercept or bevacizumab to a chemotherapy regimen that has failed in the patient.

The agent regorafenib has also been added to the NCCN Guidelines as a treatment option after first, second, or third progression, depending on previous lines of therapy. In the CORRECT trial, patients with metastatic disease who had good performance status and who had received all available agents experienced a 1.4-month OS advantage with regorafenib (Figure 1).11 This led to the FDA indication for the drug in the refractory setting.

“What interests me more about this drug is that more than half the patients derive no benefit, but the other half may obtain enough benefit to really matter,” he said. Fatigue can be a problem; starting treatment with a 25% dose reduction may be necessary to manage this, he noted, although he also noted that the efficacy of this lower dose has not been established.

**Other Questions to Consider**

For patients presenting with unresectable metastases, resecting the primary lesion or performing a biopsy of liver metastases before starting chemotherapy is generally not necessary. Good concordance has been seen between the KRAS and BRAF status of the primary and metastatic lesions;12 therefore, if adequate tissue exists from an initial biopsy, another biopsy and genotyping are not needed.

Further subdivision by molecular subtypes has been pursued in CRC, but no actionable mutations have been identified. Therefore, molecular subtyping other than BRAF and KRAS mutations should not be done at this time, as it does not influence therapy or outcome. In addition, no indication has been found for using BRAF inhibitors in CRC. Although BRAF has been identified as an indicator of poor prognosis, the BRAF inhibitor vemurafenib
has been shown to not be efficacious against these tumors.\textsuperscript{13} The combination of vemurafenib with an EGFR inhibitor is currently being studied. However, neither safety nor efficacy data are yet available, and such an approach is not recommended outside of a formal clinical trial at this time.

Clinicians also question whether anti-EGFR agents might be useful for patients with the G13D type of KRAS mutation. Although earlier reports suggested that tumors with G13D KRAS mutations may show a very slight benefit from cetuximab, subsequent data do not bear this observation out,\textsuperscript{14,15} and the NCCN Guidelines do not currently support the use of an anti-EGFR agent in patients with G13D mutations. Also promising in early studies but discounted in larger patient populations is the combination of an EGFR inhibitor and anti-VEGF agent (dual antibody treatment),\textsuperscript{16} therefore, these drugs should not be used together.

Appropriate Diagnostic and Monitoring Approaches

The NCCN Guidelines indicate contrast-enhanced CT scans of the chest, abdomen, and pelvis to be the appropriate diagnostic studies for baseline and follow-up imaging for patients with metastatic CRC, Dr. Saltz noted. PET/CT is specifically not recommended for preoperative staging, routine surveillance, or monitoring of therapy, and bone scans are not routinely indicated in the absence of specific signs and symptoms.

References