Colon Cancer: The New Chronic Disease

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Thirty years ago, there was 5-FU. Period. The projected life span of the patient with metastatic colorectal cancer (CRC) was indeed dismal. Liver resection was certainly not routine.

Eighteen years ago, the first NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colorectal Cancer appear. Treatment options include 5-FU, leucovorin, and irinotecan, with limited sequential therapy options, and shift median survival to about 1 year.

Ten years ago, oxaliplatin and 5-FU emerge as a standard of care for metastatic CRC, and the era of targeted or biologic therapy begins, solidifying the role of sequential therapy beyond initial treatment.

However, progress in treating CRC has not been limited to advances in systemic therapy for metastatic disease. This progress is exemplified by critical refinements in surgery and radiation oncology, including liver and lung resections for increasing numbers of patients, particularly those who have received neoadjuvant or “conversion” combination chemotherapy; laparoscopic surgery in both colon and rectal cancers; adequate lymph node sampling for prognostication; total mesorectal excision surgery as the standard of care for rectal cancers; and the emergence of neoadjuvant chemoradiation as the preferred approach for locally advanced rectal cancer, and for its effect on local recurrence, including downstaging and sphincter preservation. Pathologic evaluation has played a role with the use of database-driven analyses that demarcate subsets of patients, most notably those with stages II and III CRC, highlighted in the AJCC staging manual who show marked variability in prognosis within a given stage. The past few years have introduced genomic profiles that are important for treatment selection and prognosis: KRAS mutation determination (now extended RAS assessment) before considering anti–epidermal growth factor receptor (EGFR) therapy; BRAF mutation status as a prognostic tool, and microsatellite instability analysis, particularly for patients with stage II colon cancer, as a prognostic indicator and negative predictive marker for use of adjuvant 5-FU. Experts anticipate that, in the future, genomic analyses will be integrated with anatomic staging as a more robust or precise prognostic measure.

For the generation of oncologists who have witnessed this treatment evolution and its impact on survival, both a cause for celebration and a sense of urgency exist. Investigators must further unravel the mysteries of human tumor biology that challenge the ability to select patients most likely to benefit from a given therapeutic approach, and to develop agents that will most effectively “hit the target,” whether as a single drug, in combination, or in sequential regimens.

The continuum of care for metastatic CRC is a strategy of sequential therapy over time using all available drugs cited in the NCCN Guidelines for Colon and Rectal Cancers. We now have multiple lines of therapies (more appropriately stated as “initial therapy and therapy after first, second, and third progression”), with numerous choices of combinations administered in sequence over time.

The most recent first-line randomized phase III trials for metastatic CRC, which were reported at the ASCO and ESMO meetings, illustrate the potential of sequential therapy, the importance of extended RAS determination, the power of prospective tissue acquisition in clinical trials (tissue acquisitions that clearly resulted in the discovery of the KRAS link to anti-EGFR treatment in previous trials), and the reality that much remains about the treatment of CRC that we do not understand.
A series of clinical trials that included cetuximab or panitumumab retrospectively and prospectively evaluated the benefit of an anti-EGFR antibody approach for patients with KRAS exon 2 wild-type tumors. These trials confirmed that patients with mutated KRAS exon 2 tumors would not benefit from anti-EGFR therapy and, in fact, that therapy might be detrimental to those patients. More recently, the patient population with KRAS exon 2 wild-type tumors who had participated in phase III randomized trials, such as PRIME (Panitumumab Randomized Trial in Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy) and PEAK (Panitumumab Efficacy in Combination With mFOLFOX6 Against Bevacizumab plus mFOLFOX6 in Metastatic CRC Subjects With Wild-Type KRAS Tumors), were further assessed in secondary analyses to include extended RAS testing (KRAS exons 2, 3, 4; NRAS exons 2, 3, 4). These trials identified approximately 17% of patients with nonmutated KRAS exon 2 who had other RAS mutations and therefore did not benefit from anti-EGFR therapy.

The phase III CALGB/SWOG 80405 trial compared FOLFOX or FOLFIRI (physician/patient choice) with the addition of either cetuximab or bevacizumab for patients with KRAS wild-type (exon 2) untreated metastatic CRC (N=1140) in a first report. The initially reported results showed overall survival (OS) to be no different between the 2 arms. The median survival at more than 29 months in both arms is the most significant survival statistic in metastatic CRC reported other than in some subset analyses. The subset of patients who received FOLFIRI and bevacizumab numerically had an improved median OS compared with those who received FOLFIRI and cetuximab (33.4 vs 28.9 months; P=.28); however, this was not statistically significant. No statistically significant difference was found in median OS in the subset of patients receiving FOLFOX either, although in this case a numerical difference favored the cetuximab group (30.1 vs 26.9 months; P=.09). Postprogression therapy was administered to 88% of the patients. Approximately 10% of patients were alive at more than 5 years, reflecting those who underwent surgical resection of metastatic disease. Further assessment is pending, as is the extended RAS analysis.

The German FIRE-3 study, a randomized comparison of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS wild-type metastatic CRC, has now been reported in the population with extended RAS wild-type disease (N=592). No difference was seen in the primary end point of overall response rate or in progression-free survival (PFS). OS significantly favored FOLFIRI plus cetuximab (28.7 vs 25 months; P=.017 for KRAS exon 2 wild-type; 33.1 vs 25.6 months for extended RAS). Postprogression therapy was administered to 67% of patients. These results not only seem to be opposite of those in the CALGB/SWOG 80405 trial arm of FOLFIRI plus cetuximab versus bevacizumab, but also raise intriguing questions as to why no difference was seen in PFS, whereas OS was improved—a phenomenon that was not noted in past metastatic CRC trials. The separation of the curves at approximately 2 years are also puzzling and might reflect the percent of patients exposed to second-line and beyond combination therapy including the available targeted agents.

The optimal combinations and sequences of therapy for metastatic CRC, particularly for the all–RAS wild-type population, remain a work in progress. Planned pooled analyses of data from this worldwide portfolio of clinical trials perhaps will answer some of the remaining questions, including the impact of offering all available treatment options in sequence whenever possible. Current clinical trials and practice patterns seem to indicate significant variability in the number of patients who are offered and receive subsequent therapy after initial progression. Although it is not the subject of this editorial, significant variability also exists in the number of patients who continue initial therapy or a maintenance therapy program (usually defined as discontinuation of oxaliplatin) before progression, a treatment strategy that has been shown to improve PFS in clinical trials.
Over time, the NCCN Colon/Rectal/Anal Cancers Panel for has consistently and thoroughly monitored the evolution of CRC treatment by assessing the evidence, particularly as it emerges from clinical trials, building on the principles of the continuum of care, and incorporating these principles in the guidelines. Patients with metastatic CRC are increasingly viewed as having a chronic, although usually fatal, disease. That further improvements in outcomes are desperately needed is not in question; however, strategies have evolved, particularly over the past 10 years, that have progressively improved survival and quality of life.

In summary, based on the most recent evidence, the following represent some of the guiding principles to optimize the care of those with metastatic CRC:

- The median survival goal for patients with all–RAS wild-type tumors and for whom intensive therapy is appropriate should be greater than 30 months.
- Extended RAS mutation analysis should be performed in all patients with metastatic disease who are potential candidates for anti-EGFR therapy.
- Initial therapy for patients with all–RAS wild-type metastatic CRC may include either FOLFOX or FOLFIRI with either bevacizumab or cetuximab/panitumumab, and this should be viewed as a choice after discussion of potential toxicities; maintenance therapy improves PFS and should be considered as a strategy for first-line therapy, particularly for those receiving oxaliplatin.
- Sequential therapy using all available agents over time should be the initial plan for all appropriate patients.
- BRAF testing provides prognostic information, and for those with mutated BRAF tumors and poor prognosis, initial patient discussion about prognosis and treatment choice would be an important component of the continuum of care.
- Patients who have potentially resectable metastatic disease should be evaluated by a surgeon at the time of initial assessment as an opportunity to improve survival.

References

3. Venook A, Niedzwiecki D, Lent H, et al. CALGB/SWOG 80405: phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC) [abstract]. J Clin Oncol 2014;32(Suppl):Abstract LBA3.