Role of Biologics in Colon Cancer: Still Not Clear

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Patients with metastatic colorectal cancer are living more than a year longer today than they did one decade ago. Because progress has been made in almost every aspect of cancer care over that time period, it is difficult to isolate the factors most responsible for these improvements. However, drug development for colorectal cancer has certainly contributed.

Irinotecan and oxaliplatin became available in approximately 2000 and jumpstarted the notion that metastatic colorectal cancer was a treatable disease. The approval of the first three biologics with activity in metastatic colorectal cancer—bevacizumab, cetuximab, and panitumumab—followed and led to a series of combination studies of chemotherapy and biologics that have defined the current standards. In this issue of *Journal of Oncology Practice*, Mahipal and Grothey[1] offer the chronology, data, and case-based recommendations regarding how to deploy these agents in first-line treatment of metastatic colorectal cancer.

It is important to put this subject into context. The biologics in first-line treatment are added to chemotherapy, which is the mainstay in the management of metastatic colorectal cancer. The term biologics was coined to represent substances that were expected to affect biologic pathways without off-target toxicities, and in an ideal world, their use would be informed by companion biomarkers. However, there are no positive predictive biomarkers (yet) for these biologics in metastatic colorectal cancer.

This may explain why patients with metastatic colorectal cancer have derived less benefit than was expected from biologic agents. When cetuximab was approved by the US Food and Drug Administration, for example, tumor expression of the epidermal growth factor receptor (EGFR) was thought necessary. We soon learned that the presence of the receptor (at least as receptor density could be measured) is not necessary for patients to accrue benefit from agents that target EGFR (cetuximab or panitumumab).[2]

These observations were the preamble to a retrospective series suggesting that mutations in the *KRAS* gene at exon 2 confer resistance to EGFR antibodies.[3] Subsequent research suggested that mutations in *KRAS* exon 3 and exon 4 hotspots as well as parallel mutations in *NRAS* are also associated with a lack of benefit from EGFR antibodies.[4] These recent additions shrink the number of patients previously eligible to receive cetuximab or panitumumab by approximately 20%, and because these mutations are also prognostic, survival results have become inflated for the all-*RAS* wild-type cohort (while the excluded patients experience relatively poorer results). Moreover, higher sensitivity assays are detecting *KRAS*-mutant clones in tumors previously classified as *KRAS* wild type, which, depending on the *RAS* mutation detection threshold used to exclude use of EGFR antibodies, may also seem to improve survival.[4]

The incorporation of these mutational analyses seems to apply equally to cetuximab and panitumumab, which may be interchangeable even though they are different molecules. However, patients who have spent time in the mid-southern United States have a 20% or greater risk of cetuximab-induced hypersensitivity

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reactions. In a classic medical sleuthing story, a pre-existing immunoglobulin E antibody related to environmental exposure explains this regional variation.[5]

Our disappointment that biomarkers tell us only when not to use EGFR antibodies must be balanced by the complete lack of biomarkers to inform the role of bevacizumab. After more than a decade of searching, bevacizumab use is still based solely on patient characteristics and clinical risk factors.[6] It is hoped that this could change with the recent observation of the differential activity of biologics based on the side of the colon primary cancer. For example, it is clear that patients with right-sided primary tumors derive no benefit from cetuximab regardless of *RAS* status, whereas the activity of bevacizumab seems similar across the colon.[7] Sidedness is assumed to be a surrogate for molecular characteristics that are nonrandomly distributed through the colon, and we hope to uncover the explanation from the analyses of specimens in CALGB/SWOG 80405.

The need for predictive biomarkers goes beyond the obvious goal of optimizing patient clinical outcomes. With biologics costing more than $5,000 per dose, the value of their addition to more effective and much less expensive chemotherapies needs to be scrutinized. As detailed in the accompanying review by Mahipal and Grothey,[1] biologics have a place in the algorithm for the management of metastatic colorectal cancer even though the average benefit to patients has been less than expected. We can only hope that ongoing correlative research can help us decipher the role of biomarkers in metastatic colorectal cancer and make biologics both effective and cost effective. JOP

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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