Monoclonal Antibodies: The Foundation of Therapy for Colorectal Cancer in the 21st Century?

Review Article [1] | May 01, 2004
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Drs. Hoff, Ellis, and Abbruzzese have provided a thorough and useful overview of the current status of the two new monoclonal antibodies, cetuximab (Erbitux) and bevacizumab (Avastin), that have recently become available for the treatment of colorectal cancer. In the case of bevacizumab, a very large, randomized, double-blind, placebo-controlled trial has demonstrated that the addition of this monoclonal antibody to a front-line combination chemotherapy regimen resulted in a 4.7-month advantage in median survival.[1] It is noteworthy that this represents the largest median survival advantage that we have seen to date in a randomized trial in this disease, and that the 20.3-month median survival reported for the bevacizumab arm was achieved despite using a bolus fluorouracil (5-FU)-based schedule, and without the general availability of oxaliplatin (Eloxatin) for second-line therapy. Thus, there is cause for optimism that the use of bevacizumab in conjunction with infusional 5-FU-based combinations and with availability of all other active agents in colorectal cancer for second-line salvage treatment could possibly provide even further benefit. Future trials will undoubtedly assess the validity of these hypotheses. Cetuximab has now consistently been shown to achieve a response rate of 22% to 23% in combination with irinotecan (Camptosar) in the salvage setting after failure of irinotecan-, and in most cases, oxaliplatin-based chemotherapies as well.[2,3] This compares favorably with the 15% response rate seen for irinotecan alone after 5-FU failure,[4] and the 10% response rate seen with FOLFOX and the 1% response rate seen with single-agent oxaliplatin after failure on irinotecan plus fluorouracil.[5]

Tempered Enthusiasm
Clearly these new agents are active and important in the treatment of colorectal cancer. Yet our optimism over the relative successes of these agents must be tempered with the realization that, as pointed out in the opening paragraph by Drs. Hoff, Ellis, and Abbruzzese, colorectal cancer is still the number 2 cause of cancer death in the United States and other Western countries. It will remain so despite the availability of these new agents. This is not meant to belittle the contribution of bevacizumab and cetuximab to the field of colorectal cancer. All of us who work in this area appreciate how difficult it is to make any progress against this disease and how hard we have had to fight for every inch of ground. Rather, this sobering statistic is quoted here to emphasize that while we can all feel enthusiastic about the benefits that these new agents will bring to our patients, we must remain focused on the continued need for better therapies. Will cetuximab and bevacizumab be the “foundations for colorectal cancer therapy” in the 21st century? I hope not. Right now the “foundation” of our therapies is still 5-FU, an agent patented in 1957, and one that remains at the focus of virtually all of our front-line regimens almost 50 years later. It is sobering to realize that despite the elegance of the targeted monoclonal antibodies and their considerable usefulness, these agents are given merely in addition to, not instead of, cytotoxic therapies. It is appropriate to recall that the goal of biologic therapies had been to replace cytotoxics, thereby freeing patients from the dangers and discomforts of chemotherapy-associated toxicities. Thus far we have not achieved this goal. As such, the monoclonal antibodies in use today have not yet realized the potentials we had hoped for. They should be viewed as important prototypes, and as something that should be used now as part of stateof-the-art care, while we work to move beyond them and the other available drugs as quickly as we can. Unrealistic Expectations?

One pitfall that we should be careful to avoid is the maintenance of the perhaps unrealistic expectations for these new agents based on preclinical data and preclinical enthusiasm. It had been expected, for example, that these targeted therapies would work on virtually all tumor cells that have the putative target, and would not work on any cells that lack the target. Clearly this was a wishful oversimplification of the reality that has now presented itself. Although we understand that bevacizumab exerts its action by neutralizing VEGF, we have yet to determine any marker-be it in
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Published on Nutritional Outlook (http://www.nutritionaloutlook.com)

serum, on the tumor, or in an imaging study—that can reliably predict who will or will not respond. Similarly, we have no such marker for cetuximab. So wishful have we been for such a marker that we decided, in the absence of data, that an immunohistochemical stain for EGFR, with a somewhat arbitrarily defined cutoff between 0 and 1+, could predict for activity vs inactivity—even to the extent that an EGFR grade of 0 was used as an exclusion for our initial trials. In fact, all of the clinical data to date say just the opposite. The two clinical trials that we have in colorectal cancer have shown the activity to be virtually identical across patients with 1+, 2+, and 3+ positive tumors using these immunohistochemical criteria, a finding that strongly argues against the predictive nature of this marker. What limited data there are in EGFR-negative patients suggest a degree of activity that is not dissimilar from that seen in receptor-positive patients. Thus, none of the clinical data to date suggest that EGFR immunohistochemical staining is an appropriate predictor of activity or failure, and use of this marker to exclude patients from cetuximab therapy is not, in the opinion of this author, appropriate. The lack of a validated predictive marker, however, is not a problem unique to bevacizumab and cetuximab. We do not yet have validated markers for sensitivity or resistance to any of the other drugs that we use routinely in the management of colorectal cancer. Appropriately, although we continue to search for such markers, this lack of predictive markers has not impeded our use of these other agents.

Conclusions

That the monoclonal antibodies bevacizumab and cetuximab have been shown to be active and useful in the management of colorectal cancer is a tribute to the decades of basic science, translational, and clinical research that have ultimately brought these agents to our patients. We can take pride in the accomplishment of adding these agents to our armamentarium. But let's not get too comfortable with these new drugs. They must not be viewed as the end of the story, but rather as an important and hopefully brief chapter along the way. There are, as yet, no laurels to rest on, and we have miles to go before we sleep.

Disclosures: Dr. Saltz has acted as a consultant for Pfizer, Roche, Sanofi, Genentech, Taiho, and Access. He has received research support from ImClone, Bristol-Myers Squibb, Pfizer, Roche, Medimmune, and Fujisawa


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