Colorectal Cancer and Molecular Targeted Agents: Progress—With Caveats

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Over the past 10 years, the face of colorectal cancer management has changed due to the addition of new cytotoxic and molecular targeted therapies to the treatment armamentarium. As detailed in the excellent review by Sridharan, Hubbard, and Grothey,[1] the use of new cytotoxic agents, such as irinotecan and oxaliplatin, as well as new molecular targeted agents, such as vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) inhibitors, has resulted in the overall survival of patients with metastatic colorectal cancer (mCRC) increasing from 12 months to more than 30 months. However, it is important to note that: (1) our most effective agent in the treatment of metastatic colorectal cancer remains fluorouracil, and (2) most of the overall survival benefit we have achieved over the past 10 years has come from optimizing the use of traditional chemotherapy agents.

Progress in the area of targeted therapies for colorectal cancer has come slowly and with some difficulty. After the clinical triumph of imatinib in chronic lymphocytic leukemia, there was a great deal of excitement about the promise of molecular targeted therapy. With the oncology community eager to make that promise a reality, molecular targeted therapy became a major research focus in all cancer types. As we have discovered relatively quickly, however, our most common cancers are not driven by single simple mutations, but instead by complex networks of abnormalities that are not easily addressed by one compound. One example of the difficulties encountered with the development of molecular targeted agents is the story of cetuximab, originally approved through the US Food and Drug Administration (FDA)’s accelerated approval program based on radiographic response in mCRC patients whose tumors overexpressed EGFR.[2] Subsequently, EGFR was discredited as a biomarker, and cetuximab was found to be effective only in patients with KRAS wild-type tumors, who made up about 60% of the population. Not only were 40% of these patients not helped by the use of this therapy, but indeed, they may have been harmed.[2] Because of these and other findings, the FDA has indicated its intention to more closely regulate the development of laboratory tests involving molecular targeted agents.[3,4] Now, 4 years later, as is outlined in the Sridharan et al review, we find that 17% of those we thought had KRAS wild-type tumors have other RAS mutations that not only negate the effects of cetuximab, but also potentially further drive the cancer and cause patient harm.[1] Indeed, mechanisms of resistance to cetuximab are only beginning to be elucidated.

There was also a great deal of hope that because molecular targeted agents target only mutated cells or cancer cells, the side effects of these drugs would be much less than those of the old cytotoxic agents. However, there is evidence from a meta-analysis of randomized clinical trials (across cancer types) that patients have experienced more toxicity and death from targeted molecular agents than from classic cytotoxic agents.[5] We thus find ourselves having to rethink our approach to targeted therapy. With cytotoxic agents, adverse events are caused because the target of the therapy is a mechanism within cell turnover, which thus results in harm to both normal cells as well as cancerous cells. With molecular targeted therapies, the goal of therapy is to reverse the mutations that cause the cancer, or in essence to return the cell to normal functioning, restoring the capacity for apoptosis and so forth. However, because other normal cells have the same molecular targets, we are seeing untoward events, much as we do with cytotoxic agents: the molecular targets are causing adverse effects by damaging normal cells. The difference, however, is that because our molecular agents are acting within pathways we have not fully defined, we may inadvertently worsen the cancer by driving pathways we did not intend to affect. Thus, the therapeutic use of molecular agents adds an additional level of complexity to cancer treatment. The other hoped for, theoretical benefit of molecular targeted agents was that there would be
appropriate predictive biomarkers for the targeted therapies. However, as has been outlined in the review, no clinically useful biomarkers have been found for bevacizumab, aflibercept, or regorafenib.[1] Thus, we use these agents indiscriminately without knowing which target populations would benefit most. Furthermore, patients are continued on these agents as maintenance therapy and into second and third lines with what appear to be very small overall survival benefits, but at significant cost to the patient and the medical system. It is problematic that our most expensive therapeutic agents provide the least survival benefit and have no biomarkers to direct appropriate therapy. With regard to EGFR inhibitors, the only molecular targeted agents used in mCRC for which we have biomarkers, the biomarkers were not clearly defined from the beginning of the drugs’ use, and we are finding more mutations further downstream that negate the drugs’ benefits. This has caused overuse of these agents in populations for whom they are not helpful and in whom they may even be harmful, as described above. In general, the benefit of biomarkers for drug development in colorectal cancer has been disappointing.[1]

In a 2010 article in *Clinical Cancer Research*, Fojo and Parkinson asked: “Are we making too much of too little and achieving too little by giving too much?”[2] Although we have clearly improved survival for mCRC patients, our journey has been more of a cautionary tale. As opposed to large-scale trials that result in approval of a therapy based on a minimally statistically significant benefit, we must start to design trials to identify target populations that will either really benefit from the therapies, will not benefit, or will be harmed.[2] This will both better serve our patients in providing personalized care, and also, we hope, minimize the cost of research by decreasing the waste associated with large-scale trials that have negative or only marginally positive results. To truly move into an era of personalized medicine, we must learn how to redefine our study patient populations, and we must be ready to quickly apply new laboratory testing as new biomarker information is discovered.

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**References:**

2. Fojo T, Parkinson DR. Biologically targeted cancer therapy and marginal benefits: are we making too much of too little or are we achieving too little by giving too much? Clin Cancer Res. 2010;16:5972-80.


**Links:**
[1] [http://www.physicianspractice.com/authors/laura-tenner-md](http://www.physicianspractice.com/authors/laura-tenner-md)
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