ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Colorectal Cancer In Focus

Biomarkers to Predict Response to Anti-EGFR Antibodies

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H&O What is the current status of molecular markers in colorectal cancer (CRC)?

ST There are currently very few molecular markers in colorectal cancer, partially because the disease is highly complex, possibly more complex than other tumors that we have seen so far. Several studies have demonstrated that there are different mutations occurring in the various combinations, revealing a diverse gene expression and other heterogeneous patterns. The inability to make robust prognostic signatures means that we do not have a good understanding of this heterogeneity, and the more heterogeneity there is, the more robust and well powered our studies need to be to identify this heterogeneity and overcome it. The low status of molecular markers is due to very low and underpowered discovery efforts. As a community, we need to come together to conduct biomarker validation studies. The problem is that until now, most studies were low-powered discovery studies with a high range of false positive results, which often did not hold up in validation. I think that it is necessary to go back to the drawing board to determine how to perform discovery studies in a well-powered, concerted way. The chance of having good validation studies is there, and we need to use the assessment tools we have to determine the full expression copy number mutation on any type of sample we have.

H&O Are there benefits to using biomarkers in CRC patients?

ST With the negative predictive biomarker KRAS, we exclude half of the colorectal cancer population from anti–epidermal growth factor receptor (EGFR) treatment, and therefore have a very high therapeutic index of anti-EGFR therapies in this population. Thus, compared to other standards of care, it is a very good and competitive biomarker.

H&O What role do biomarkers play in the treatment of CRC?

ST Biomarkers like KRAS allow us to select a population of patients that will derive benefit from targeted therapy such as cetuximab (Erbitux, Bristol Myers-Squibb/Eli Lilly) and panitumumab (Vectibix, Amgen). However, the problem with EGFR antibodies is that we only have negative predictive markers. Hence, this leads to some frustration and a decreased prediction ability. In a positive predictive situation, like with HER2 in breast cancer, one is able to positively select patients who will respond to trastuzumab (Herceptin, Genentech) and to rely on that predictive power: this represents a very satisfactory combination of patient selection and drug efficacy. Conversely, with negative markers, simply removing those patients who will not respond to EGFR inhibitors does not mean there is a positive selection. Strong positive predictors for anti-EGFR therapies have been lacking, and this is where our research efforts should lie.

H&O Because of the discovery of the correlation between KRAS and response, what initiatives have been undertaken in biomarker research?

ST Many initiatives have been undertaken. In 2007, Khambata-Ford and colleagues published a seminal paper describing the results of a prospective analysis of predictive biomarkers in cetuximab treatment. The goal of the study was to identify markers associated with disease control. The study response predictors were analyzed by gene expression profiling, enzyme-linked immunosorbent assay, nucleotide sequence, and DNA copy number analysis. The markers identified in this important study have been used in follow-up trials, and are still being used today.

What we have seen is that it is not easy to bring new biomarkers to the clinic, particularly because a validation study showing the impact of the specific biomarker is needed. There is very little drive to perform these validation studies because it is a large financial decision. Furthermore, assays for the markers also need to be developed, and there is not much interest in doing this kind of research either. Since the research of Khambata-Ford and colleagues in 2007, there has been little movement toward bringing biomarkers to clinical practice. They recently published a paper in the *British Journal of Cancer* in which they again validated the performance of the biomarkers they previously discovered, and provided an assay that can be used in clinical practice.

H&O Are there new methods of biomarker detection being investigated?

ST There is ongoing research into new methods of biomarker detection; however, this is not our major problem. Our main concern is to find novel biomarkers and develop a good understanding of the diversity of CRC molecular subtypes. There are many valid questions that we need answered such as "Do we have to biopsy the liver metastases?" "Do we have to get a biopsy of the primary tumor?" "Can we do it in circulating tumor cells?" "Can we identify it in plasma?" This research is important, but at this point it is not of high priority.

H&O What are some new biomarkers being studied?

ST In their recent publication, Khambata-Ford and colleagues used reverse transcription polymerase chain reaction to test 110 gene expression markers from 144 KRAS wildtype metastatic CRC patients who received cetuximab monotherapy. Some novel markers in combination with EGFR ligands amphiregulin and epiregulin were investigated in this study. These markers are being looked at as positive predictors.

There are a number of potential negative predictors being studied as well, such as NRAS and some PI3 kinase mutations. In a paper published last year by my colleagues and I, we discussed 5 negative predictors that could possibly result in an approximate 10% improvement in prediction of outcome. By contrast, if we had a single positive predictive biomarker, we could have a 90% prediction of outcome. However, conceptually, it should be possible to find a single positive marker reaching 90% outcome prediction. The main challenge is that we keep finding negative predictors, and I believe that we should focus our efforts on identifying positive predictive markers.

H&O What are the goals with the discovery of biomarkers in CRC?

ST Obviously this is a disease that has many faces. Our current clinical classification is not well established, so when we categorize patients by the clinical characteristics of their tumor—its differentiation, nodal state, or stage—we are still left with a heterogeneous group of patients containing very many identities. Our clinical classification does not work, and this has implications for the patient because even though we are using the prognostic markers to characterize the patient either in the adjuvant or the metastatic setting, we are failing. When we enroll patients in trials, they appear to be a homogeneous population, but really they are very heterogeneous, and this hampers a lot of clinical trials because they are underpowered. The main objective is to gain better knowledge on the CRC subgroups, as that would allow us to differentiate patients and conduct trials within these subgroups, giving us a higher chance of getting a response to targeted therapies. If we are able to better classify patients, biomarkers will naturally become evident because once we have subgroups it will be apparent in which patients the drug is working.

Suggested Readings

Baker JB, Dutta D, Watson D, et al. Tumour gene expression predicts response to cetuximab in patients with KRAS wild-type metastatic colorectal cancer. *Br J Cancer.* 2011;4:488-495.

De Roock W, Claes B, Bernasconi D, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. *Lancet Oncol.* 2010;11:753-762.

Khambata-Ford S, Garrett CR, Meropol NJ, et al. Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. *J Clin Oncol.* 2007;25: 3230-3237.