

Can we personalize drug therapy in colorectal cancer patients?

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For the treatment of metastatic colorectal cancer, the practicing physicians have available a large armamentarium of therapeutic options. The last decade has seen significant advances in survival of metastatic cancer patients compared to the era of single-agent therapy with 5-fluorouracil, mainly due to the approval of novel therapies. Today, clinicians can rely on the use of 4 classical cytotoxic agents (5-fluorouracil, capecitabine, irinotecan, and oxaliplatin) and 3 targeted therapies (bevacizumab, cetuximab, panitumumab).

These drugs have a wide variety of antitumor activity and toxicity, and are usually given in combination. For any given patient, the selection of the best therapy is based upon the analysis of risk/benefit for that patient, and takes into account several factors, including tumor histology, pathological features, stage, comorbidities, age, performance status, and other features. This evaluation is the traditional way of choosing cancer therapy, but is far from optimal. Many (and in most cases the majority) of treated patients do not have significant benefits from the treatment while they often experience moderate to severe toxicities. The outcome of colorectal cancer patients needs to be improved by using strategies aiming to minimize the risk of toxicity and maximizing the efficacy of the treat-

ment. Finding markers that can guide the selection of the best therapy for each patient is a step forward towards the application of personalized medicine. As the cost of the newer therapies is high, the use of molecular markers can improve the affordability of expensive therapies that are indicated for certain patients.

By having access to the germline DNA of patients and from the primary tumor, we can now use markers to select drug therapy. For example, immunochemical analysis of tissue slides of the primary tumor is performed to screen for the expression of EGFR in tumor cells; cetuximab, a monoclonal antibody against EGFR, is indicated for patients who are EGFR positive by staining. However, recent data indicate that tumors positive for the K-ras mutation do not benefit for EGFR blockade with cetuximab and panitumumab, and wild-type K-ras colorectal cancer patients have better clinical response in terms of prolonged progression-free survival and overall response rates when compared to mutant K-ras. Germline DNA information is now used to predict the patients who are at high risk of severe neutropenia from irinotecan; the UGT1A1 test for the *28 polymorphism is now included in the "black box" warning of the package insert of irinotecan in the USA.