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## **Individualization of Therapy Based on Clinical and Molecular Parameters**

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Colorectal cancer (CRC) is the third most commonly diagnosed cancer in both men and women in the United States with a predicted 149,000 new cases this year. Since the 1960s, 5-fluorouracil (5-FU) has remained the mainstay of therapeutic options in the treatment of advanced CRC, with response rates of 20% to 25%. The introduction of newer agents such as oxaliplatin and irinotecan in combination with 5-FU have increased response rates to 40% to 50% in advanced disease and have improved survival. The use of monoclonal antibodies targeting the epidermal growth factor receptor (EGFR) or vascular endothelial growth factor (VEGF) has demonstrated additional clinical benefit for patients with metastatic disease. However, many patients succumb to their disease and a significant proportion will experience severe chemotherapy-associated toxicities while deriving little or no benefit. In order to improve the treatment of CRC, efforts must be directed toward the identification of patients likely to respond to a specific therapy, those who will experience severe toxicities, and those who will benefit from chemotherapy in the adjuvant setting. However, the utility of individual markers of response, toxicity, and disease recurrence remains in question, and efforts are under way to develop multimarker profiles that can more accurately predict disease response.

Selection of the most beneficial treatment regimens in CRC remains a challenge and is hindered by the lack of predictive and prognostic markers. In addition, the occurrence of drug resistance in colorectal tumors, either intrinsic or acquired during treatment, remains a major stumbling block to effective cancer treatment. Over recent years, studies on a global scale have attempted to define subsets of biochemical markers that may predict response to treatment (evaluated through clinical response, toxicity, and time to disease

progression), and prognostic markers, which are equally as important in determining the aggressiveness of the disease (generally evaluated in terms of overall survival) and the likelihood of recurrence after surgery. The science of pharmacogenomics is emerging as an increasingly useful molecular tool to investigate the disparity in drug efficacy by analysis of variations such as genetic polymorphisms in drug targets, metabolizing enzymes, transporters, and influential receptors. Consequently, the identification of accurate and validated predictive and prognostic markers combined with an increasing arsenal of therapeutic agents will provide the clinician with the knowledge and the means of tailoring a targeted and effective therapy to the molecular profile of the patient while minimizing life-threatening toxicities.

The use of pharmacogenetic profiling in CRC to predict clinical response and identify those patients susceptible to increased toxicity is still a developing field. To make progress, there must be more complete evaluation of these markers before genetic information can become part of routine clinical practice. Retrospective analyses have clearly demonstrated the proof of principle in this approach. However, the design of new prospective trials must encompass a more comprehensive and disciplined approach with defined protocols, primary end points, and increased statistical power. Only when this approach is adopted will the ambiguity be replaced with more definitive answers regarding the predictive and prognostic value of these markers and their clinical implementation. Follow-up studies are also required to identify the functional significance of the many mutations and polymorphic variants that exist in the patient population; such functional information will inevitably assist in unraveling the complex and multi-faceted mechanisms of drug metabolism and cytotoxicity. Markers of response to novel therapeutic drugs including bevacizumab, cetuximab, and panitumumab must also be identified and rigorously validated so that these agents can be targeted to those who will derive greatest benefit.

The rejuvenation of the cancer stem cell hypothesis is another exciting area of research. A growing body of evidence suggests that cancers develop from a small subset of cells with self-renewal properties (analogous to organ stem cells), that acquire epigenetic and genetic changes required for tumorigenicity, or that may represent proliferative

progenitors that acquire self-renewal capacity. If the cancer stem cell model is correct and if such cells retain the hallmarks of tissue stem cells in being rare and infrequent in replication, they may represent a population of cells intrinsically resistant to conventional therapies and possessing potent tumor-forming capacity. If proven correct, the cancer stem cell hypothesis requires a transformation in tumor diagnosis and treatment in the clinic. Future therapies would therefore require objective targeting of the minority stem cell population that fuels tumor growth and regeneration, and not the bulk of highly proliferative tumor cells. Indeed, once functional assays are developed to identify possible stem cell populations in solid tumors, including CRC, it will be equally important to identify markers unique to the cancer stem cells to confirm their presence and to assist the development of realistic therapies. Analysis of the potential tumor stem cell population may be the most important prognostic marker in deciding which treatment route to pursue in the clinic. A recent workshop convened by the American Association for Cancer Research (AACR) and attended by a wide variety of cancer biology experts highlighted the importance of pursuing this promising field, and as such, is forming a task force dedicated to expediting progress in cancer stem cell research. Such research offers a real possibility of identifying novel targets that could overcome drug resistance, improve therapeutic efficacy, and potentially make cancer treatment curative while preventing adverse toxicities.

### **Present and Future**

To identify patients who will benefit most from chemotherapies (chance of cure, response): (1) Molecular markers should be included in all clinical trials to establish predictive and prognostic markers as well as surrogate markers, and validate target inhibition. (2) The selection of new combinations should be based on molecular targets identified in tumor. (3) Pharmacogenomics should be included early in drug development to understand drug metabolisms and avoid life-threatening toxicities.

### **Challenges**

Validation of the association of molecular markers with clinical outcome in prospective trials is needed. It is encouraging to note that these efforts are already under way. Other

challenges are as follows: (1) Refining of technologies and statistical methods in order to accommodate the complexity of the molecular map that may determine outcome. (2) Standardization of testing methods, and of interpretation of results. (3) Adaptation of these findings and methods to every-day practice, especially in the community.