Editorial

Challenges toward personalized treatment of localized colorectal cancer

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J Gastrointest Oncol 2010; 1: 74-75. DOI: 10.3978/j.issn.2078-6891.2010.023

Colorectal cancer is the third most common cancer and the second leading cause of cancer death in the United States. In 2010, it is estimated that there will be 142,570 new cases and 51,370 will die from the disease (1). Because of earlier diagnosis through screening and more effective treatment modalities including surgery, chemotherapy and radiation, over the past 30 years, mortality from colorectal cancer has decreased. Fluoropyrimidines have remained the backbone of standard therapy for colorectal cancer. Common toxicities include diarrhea, stomatitis, and hand-foot syndrome with diarrhea being a dose limiting toxicity in clinical trials. Being able to predict which patients will have more toxicity or which patients will have less benefit from treatment is the first step toward personalized medicine.

In the last decade progress has been made in oncology successfully tailoring treatments based on molecular markers. In breast cancer patients, overexpression of the HER2/neu protein is associated with more aggressive growth but also predicts response to trastuzumab therapy. In non small cell lung cancer, EGFR mutation is predictive of response to erlotinib therapy and in colon cancer, K-ras mutation predicts response to monoclonal antibodies to EGFR. Historically, the pharmaceutical companies developed medications based upon empiric observations, thereby subjecting all patients to the toxicities of the medication. Now in the era of genomic research, technologies have been developed to probe the cancer genome searching for the driving mechanisms of cancer growth. And yet, currently we only have a few predictive markers of treatment response.

Many studies have been published examining biomarkers and confusion often arises between prognostic and predictive biomarkers. Prognostic markers assess the risk of disease recurrence and outcome for marker positive versus negative patients independent of the treatment. A predictive marker compares treatment outcome based upon marker positive versus negative. In evaluating the predictive nature of a biomarker, many studies rely on banked specimens, which may lead to selection bias or underpowered analysis. For instance, various studies have shown that patients with cancers overexpressing thymidylate synthase (TS) had a worse outcome compared to those with lower levels of TS. However, results regarding levels of TS as a marker of benefit from adjuvant chemotherapy using 5-FU have been conflicting (2,3). In validating a biomarker, utilization of specimens collected from large phase 3 clinical trials randomizing patients between an experimental therapy versus control treatment helps minimize bias. Ideally a confirmatory trial should be designed testing all patients for the biomarker prior to treatment and then evaluating outcomes based upon therapy.

The study by Katkoori VR et al (4) in the current issue analyzed the predictive value of Bax, Bcl-2, and p53. The BCL-2 family, including its antiapoptotic and proapoptotic members, plays a central role in the regulation of cell death. Bax protein, located in the outer mitochondrial membrane, is a key promoter of apoptosis. Overexpression of Bax induces increased mitochondrial permeability, which leads to the release of cytochrome c. Cytochrome c, together with other effectors, induces cleavage of caspase, which leads to the degradation of the chromosomal DNA and triggers the execution of apoptosis (5). The study by Katkoori VR et al (4) is attempting to determine their association with survival in colorectal cancer patients treated with 5-FU

No potential conflict of interest.

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Submitted Dec 10, 2010. Accepted for publication Dec 16, 2010.
Available at www.thejgo.org

ISSN: 2078-6891

based adjuvant therapy after surgery.

Using immunohistochemical staining and robust analysis, this study demonstrates patients lacking Bax expression in the cancerous tissues or with low Bax/Bcl-2 expression ratios had a better survival when they received 5-FU based treatment. In contrast, patients whose colorectal cancer exhibited high Bax expression had a worse outcome when they received 5-FU based treatment, indicating the treatment might be detrimental. Of note, the study showed that expression levels of Bcl-2 and p53 had no predictive value on survival in colorectal cancer patients with or without chemotherapy. This study was performed on archival tissues from 56 patients that received 1 of 6 different chemotherapy regimens after surgery and 56 patients that received surgery alone for stages I-IV colorectal cancer. Additionally patients that died due to other causes were excluded thus lowering the number of patients in the final analysis. Previous studies evaluating the prognostic and predictive value of Bax in different cancers have shown conflicting results. In patients with breast cancer, although reduced expression of Bax is also found to be associated with a shorter survival, in contrast to the study by Katkoori VR et al, a decreased response to chemotherapy is noted (6). In patients with ovarian cancer, overexpression of Bax is associated with significant higher percentage of complete remission after chemotherapy and the survival is also prolonged (7). In patients with diffuse aggressive non-Hodgkin's lymphoma, low expression of Bax seemingly is associated with a lower survival (8). In patients with hepatic metastases of colorectal cancer, low Bax expression is noted to be an independent negative prognostic marker (9). Apparently, more studies are needed to elucidate the role of Bax as prognostic/predictive markers in various cancers.

For decades, clinical decisions on adjuvant therapy have been determined by the TNM staging system and conventional clinicopathologic factors. Apparently, current therapeutic decision remains suboptimal. With appropriate biomarkers, patients with locally confined cancers who are at low risk of recurrence/metastasis could be spared from the toxicity of systemic treatment. In contrast, patients with early-staged cancer at high risk of recurrence/metastasis could be benefited from known effective treatment. With advances in basic, translational and clinical research, it is believed that validated clinical biomarkers will become a new standard as part of more accurate prognostic systems and form better predictors of response to specific therapies. Efforts are needed to identify predictive markers so that therapeutic decisions may be made with greater precision.

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