Commentary

Biomarkers and stage II colorectal cancer therapy

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According to the American Cancer Society, colorectal cancer (CRC) is the third leading cause of cancer related death in the United States among men and women. Despite a steady decrease in mortality rates, CRC is still estimated to result in 49,190 deaths during 2016 (1).

The management and survival rates of colon cancer differ by stage. About 80% of all cases of stage II colon cancer are cured by surgical resection of the tumor and local lymph nodes. Because of this surgical effectiveness, the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) do not support routine use of chemotherapy for stage II disease. However, they state that adjuvant chemotherapy may be utilized in "higher risk" patients. Stratification factors associated with high risk include poorly differentiated tumor histology, localized perforation, bowel obstruction, positive surgical resection margins, T4 tumors, perineural invasion and presence of lymphovascular spread (2,3). Lymph node assessment plays a major role in determining further management. It defines staging and assists in risk stratification. In an effort to standardize pathological assessment, it has been suggested that a minimum of 12 lymph nodes be assessed. Cases where less than 12 lymph nodes are sampled are consequentially deemed as high risk (4). Despite the presence of the criteria above, the identification of CRC patients with stage II disease who are most likely to benefit from chemotherapy is an ongoing challenge.

The QUASAR trial was conducted to determine any survival benefit associated with chemotherapy in stage II colon cancer. Assuming that 5-year mortality without chemotherapy was 20%, patients with stage II disease that received 5-fluourouracil and leucovorin had an absolute improvement in survival of 3.6% (95% CI, 1.0–6.0%) (5). On the other hand the MOSAIC trial compared the use of 5-fluorouracil and leucovorin (LV5FU2) with 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX4) in stage II and III patients. The clinical benefit of FOLFOX4 compared with LV5FU2 in terms of 6-year overall survival (OS) and 5-year disease free survival (DFS) reached statistical significance and clinical relevance only among stage III patients. For stage II patients, there was no statistically significant improved 5-year DFS and 6-year OS (6). In stage II disease, enduring the toxicity of chemotherapy has not always translated into survival benefit. Despite the identification of regimens with greater activity and in some cases less toxicity, the risk-benefit ratio for treatment is not straightforward, as most patients with early stage disease will not suffer post-operative recurrence and therefore would be at risk for side effects from treatment without commensurate benefit.

Development of colorectal carcinoma involves a multi-step accrual of genetic abnormalities (7). Based on this concept, we can speculate that genetic markers used as tools for risk assessment and better treatment decisions can be informed by tumor specific gene expression characteristics. A host of molecular and genetic markers in tumor, lymph nodes and blood have all been proposed as potential candidates to identify high, or at least higher risk patients (8-10).

Microsatellite instability (MSI), when present in colon cancer, can be classified as high (MSI-H) or low (MSI-L) depending on the degree of instability. MSI-H has been associated with good prognosis when compared to MSS (stable microsatellite) and patients do not benefit from adjuvant chemotherapy (11). Defective DNA mismatch repair (MMR) attenuates protein expression and leads to MSI-H. Defective MMR is associated with improved prognosis when compared to proficient MMR and MSS. KRAS mutation does not vary with stage and is more frequent in low grade tumors. Its value as a prognostic

marker has been disputed; some report that it is associated with poor prognosis and increased cancer recurrence while others state that KRAS mutation has no prognostic value for OS or relapse free survival (RFS). BRAF mutation has shown no statistically significant difference in RFS but was prognostic for OS in stage II and stage III combined (12-15). ColoPrint, the colon cancer recurrence score, ColDx and Oncotype Dx are a few validated multi-gene assays that may be used to predict recurrence of disease. However, their benefit as predictive assays has been deemed as questionable by the NCCN (3,16-19). Without defined utility, the future of predictive assays has been uncertain.

The recent paper published in the *New England Journal of Medicine* by Dalerba and colleagues took a different, pragmatic approach to identify a genetic risk stratification marker. In this report, the investigators collected about 2000 stage II and III CRC cases from several databases. Each was retrospectively assayed for expression of caudal-type homeobox transcription factor 2 (CDX2), a marker of gastrointestinal cell differentiation. The authors selected this biomarker based on a search intended to identify candidate markers of colonic epithelial differentiation for which there already existed a standardized diagnostic test (immunohistochemistry in this case). Based on their analysis, they report that lack of CDX2 expression was associated with lower 5-year DFS. Further, patients with CDX2 negative cancers who received adjuvant chemotherapy had improved 5-year DFS compared to those who did not (20).

However, this report also provides a lesson on how hard it is, and will be, to identify clinically useful biomarkers. Resources for the collection and analysis of the multiple microarray datasets for this effort were substantial. Most biomarker candidates identified by the team were discarded because no "off the shelf" diagnostic test existed to look for the marker in large numbers of samples. Large sample sizes are almost always required because marker expression, or lack of expression, may not be a common event. In this study, lack of CDX2 expression was seen in only 4% of the colon samples. Given this relative infrequency, despite proof of principle, the overall clinical impact of this observation is probably very small. From a practical perspective, it is unlikely that CDX2 assay will become a standard part of the CRC pathology workflow, recognizing the challenges surrounding incorporation, for example, of MMR analysis for all CRC specimens.

Equally important is the challenge of optimal conduct of any clinical trial. Regardless of the clinical scenario or the variables in question, all retrospective cohort studies are prone to the same concerns about internal validity and causation. With a hard outcome like CRC and a moderate effect size (in this study, for CDX2 negative samples a hazard ratio for DFS of 3.44 (95% CI, 1.60–7.38)], there is little concern regarding observation bias or chance, respectively. However, confounding is a real concern both for the primary outcome of 5-year disease survival, and also for the secondary outcome of benefit from chemotherapy. In terms of 5-year DFS, the authors report no imbalance in factors like age, sex or tumor stage. However, it is unclear if there was a difference between groups in other "higher risk" factors noted above such as lymphovascular invasion or clinical presentation. Most cases of stage II colon cancer, based on standard criteria, do not receive chemotherapy. Hence, a retrospective analysis of cases where chemotherapy was administered suggests this group of patients might not represent the norm.

Of course, CDX2 is a biomarker and not a literal cause of CRC. However, as a proxy to identify higher risk groups, it is reasonable to question the strength of the association between lack of CDX2 expression and poorer outcome. The association itself while statistically significant is not terribly strong. Assignment of CDX2 positive/negative status was based on immunohistochemistry. The authors demonstrate good reproducibility amongst readers, but some misclassification may have occurred. This is important because so few cases were CDX2 negative. The lower bound of the 95% CI was 1.6. Misclassification and confounding could alter this result.

The toxicity associated with current chemotherapy for CRC is substantial. Tools to identify patients most likely to benefit are sorely required. CDX2 expression as such a marker has biological plausibility and previous studies to support its potential role. However, the challenges (at the molecular and the study design levels) faced by investigators in the hunt for potential biomarkers with substantial clinical impact are great and major contenders remain unidentified.

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Footnote

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called Targeted Diagnostics and Therapeutics, while Dr. Olszanski has the following relationships to declare: he serves on Advisory Panels for Merck, BMS, Takeda, with honoraria. He also receives research funding (paid to Fox Chase Cancer Center) from Amgen, Advaxis, BMS, Lilly, EMD Serono, Ignyta, Immunocore, Incyte, Kyowa, Merck, Novartis, Takeda, Mirati, Pfizer. In his opinion none of these relationships poses an obvious conflict, but for transparency he feels it is appropriate to disclose them.

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