**Personalized Medicine in the Adjuvant Chemotherapy of Stage II Colon Cancer—Are We There Yet?**

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Over the past few years, significant efforts have focused on developing and validating molecular biomarkers to better define the subset of patients with stage II disease who might derive benefit from adjuvant therapy.

Despite significant treatment advances over the past 15 to 20 years, colorectal cancer remains a major public health problem in the United States and globally. In 2013, approximately 142,000 new cases of colorectal cancer will be diagnosed, and nearly 50,000 people will die from this disease.[1] Nearly 30% of patients present with stage III disease, and 25% present with stage II disease. For early-stage colon cancer, surgical resection remains the standard treatment approach. While adjuvant chemotherapy improves both disease-free survival (DFS) and overall survival (OS) in patients with stage III colon cancer, the precise role of adjuvant chemotherapy for patients with stage II colon cancer remains a matter of ongoing debate.[2] In the setting of high-risk stage II disease, it is clear that adjuvant chemotherapy provides nearly the same degree of clinical benefit that it does for stage III patients. However, the true clinical benefit of adjuvant chemotherapy in patients with average- or low-risk stage II disease is not quite as definitive.[3-8]

Over the past few years, significant efforts have focused on developing and validating molecular biomarkers to better define the subset of patients with stage II disease who might derive benefit from adjuvant therapy. Further identification of key prognostic and predictive biomarkers would then allow adjuvant therapy to be personalized for individuals with stage II disease. In this regard, the review by Mettu et al[9] provides a timely overview of the various molecular biomarkers that may be used for prognosis and/or prediction in early-stage colon cancer. As presented in the authors’ Table 2, the main biomarkers that have been well characterized to date include microsatellite instability (MSI), loss of heterozygosity (LOH) at chromosome 18q21 (involving the DCC gene region), p53, KRAS, BRAF, thymidylate synthase (TS), ERCC1, and multigene assays. LOH 18q21, p53, KRAS, BRAF, TS, ERCC1, and MSI have all been shown to provide important prognostic information that can identify patients with an increased risk of disease recurrence and worse clinical outcome. Of these biomarkers, however, MSI status has emerged as the only prognostic biomarker that can be used in daily clinical practice. In particular, a large body of evidence has nicely documented the important role of MSI-high (MSI-H) status as a favorable prognostic marker that is associated with improved survival.[10-13] In addition to its prognostic value, there is growing evidence that MSI status may play an important predictive role in patients with early-stage colon cancer. Preclinical in vitro studies first showed that human colon cancer cells characterized as being MSI-H were resistant to the cytotoxic effects of DNA-damaging agents, such as fluorouracil (5-FU). Moreover, re-expression of mismatch repair (MMR) function was able to effectively restore chemosensitivity to 5-FU and other anticancer agents.[14,15] In the clinical setting, Ribic and colleagues were the first to demonstrate that 5-FU-based adjuvant chemotherapy benefited stage II and stage III colon cancer patients with microsatellite stable (MSS) or MSI-low (MSI-L) status tumors but not patients whose tumors exhibited MSI-H features.[16] Subsequent retrospective studies confirmed that patients with stage II MSI-H tumors do not derive clinical benefit from 5-FU-based chemotherapy.[17] In a pooled analysis of 1,027 patients from 5 completed, randomized clinical trials, Sargent et al[18] provided further evidence that MSI-H colon cancers have a favorable stage-adjusted prognosis. Moreover, their analysis revealed that adjuvant 5-FU-based chemotherapy significantly improved DFS in patients with MSS and MSI-L tumors. In sharp contrast, patients with MSI-H tumors did not derive clinical benefit from adjuvant therapy. Perhaps raising even greater concern was the fact that treatment of MSI-H patients with 5-FU-based adjuvant chemotherapy was associated with reduced OS.

In addition to investigating individual molecular biomarkers to predict disease recurrence in stage II colon cancer, significant efforts have focused on developing gene expression-profiling strategies. As
reviewed by Mettu et al,[9] the Oncotype DX quantitative multigene-expression assay was developed to improve the ability to identify which stage II colon cancer patients are at increased risk of disease recurrence. In the initial developmental phase of this assay, real-time reverse transcriptase polymerase chain reaction (RT-PCR) analyses were performed on tumor samples from a large cohort of nearly 1,900 patients from 4 National Surgical Adjuvant Breast and Bowel Project (NSABP) colon cancer adjuvant clinical trials and one adjuvant study from the Cleveland Clinic.[19,20] Starting with a list of 761 candidate genes, a list of 7 potential recurrence genes was subsequently identified, along with 6 potential treatment benefit genes and 5 internal reference genes. Based on this gene signature, a prespecified continuous recurrence score (RS) was assigned to each patient. This RS was then prospectively validated in the phase III randomized Quick and Simple Reliable (QUASAR) trial conducted in the United Kingdom. A significant correlation between RS as a continuous variable and the likelihood of recurrence at 3 years was identified. The continuous RS was then validated as an independent predictor of recurrence risk for stage II patients in a multivariate analysis that included MMR status, tumor stage, tumor grade, number of nodes examined, and lymphovascular invasion. In contrast to the RS, however, the treatment-benefit gene signature (treatment score; TS) could not be validated in the QUASAR trial as a predictive marker for clinical benefit of adjuvant chemotherapy with 5-FU/leucovorin (LV). This finding is strikingly different from results of the Oncotype DX 21-gene assay in early-stage breast cancer, with which treatment decisions can, in fact, be made.

Venook et al[21,22] conducted a prospectively designed study to determine the relationship between the continuous 12-gene RS and the risk of cancer recurrence in patients enrolled in the Cancer and Leukemia Group B (CALGB) 9581 trial. This study confirmed the performance of the 12-gene RS previously validated in the QUASAR study, and showed that the RS is significantly associated with risk of recurrence beyond the known prognostic factors in stage II colon cancer. Of note, the Oncotype DX Colon Cancer Assay was most helpful in identifying patients with T3 proficient MMR (pMMR) tumors with an increased risk of disease recurrence and for whom adjuvant chemotherapy might be more seriously considered. In a follow-up study, O’Connell et al[23] validated the 12-gene RS in NSABP C-07, a randomized phase III trial investigating the benefit of adjuvant therapy with 5-FU alone vs 5-FU plus oxaliplatin (FLOX). Patients with stage II and stage III colorectal cancer were randomized to receive either 5-FU alone or FLOX chemotherapy. This study confirmed the importance of RS in predicting disease recurrence in patients with stage II colorectal cancer independent of T and N stage, MMR status, number of lymph nodes examined, tumor grade, and treatment.

The precise role of adjuvant chemotherapy in the treatment of stage II colon cancer remains a subject of ongoing discussion. Without question, there is clinical benefit to adjuvant chemotherapy, yet the absolute benefit is relatively small when compared with the effects seen in patients with stage III colon cancer. In medically fit patients, chemotherapy with the cytotoxic chemotherapy regimens, such as LV/5-FU/oxaliplatin (FOLFOX) and/or capecitabine/oxaliplatin (XELOX), should be offered to patients with high-risk clinical features such as obstruction, perforation, T4 tumors, poorly differentiated tumors, inadequately pathologically examined lymph node invasion (< 12 nodes) and extramural venous or lymphatic invasion. For average- and low-risk patients, a discussion of the small benefit of chemotherapy with either infusional 5-FU or oral capecitabine should be conducted, and in this regard it is absolutely critical for the patient to play an active role in the decision-making process. In addition to using clinical features, it would be ideal to be able to incorporate molecular biomarkers in the decision-making process.

So where are we with respect to the concept of delivering personalized medicine to patients with stage II colon cancer, and can molecular biomarkers be used in our everyday clinical practice to identify stage II patients who should receive adjuvant chemotherapy? The clinical data for MSI status are quite strong for this biomarker, providing important prognostic and predictive information. In daily clinical practice, assessment of MSI status should be performed in all patients with stage II disease, as it provides actionable information that has a direct impact on whether adjuvant chemotherapy should be considered. Specifically, patients with MSI-H should not be offered adjuvant chemotherapy, given their overall favorable prognosis and worse clinical outcome when treated with 5-FU-based therapy.

While there is certainly growing interest in incorporating the Oncotype DX Colon Cancer Assay into routine clinical practice, the critical issue is whether this test can provide real actionable information. Based on the available clinical data, this assay does represent an important advance in biomarker development, as it offers additional prognostic information about risk of disease recurrence above and beyond the well-established clinical factors and MMR status. However, it would be important to
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conduct prospective randomized studies to confirm and validate the potential clinical relevance of this test. Perhaps more importantly, additional studies are required to identify a predictive treatment score to determine an optimal treatment regimen for an individual patient. In the absence of such a treatment score to guide therapy, the true utility of the Oncotype DX Colon Cancer Assay in daily clinical practice would appear to be limited. The development of such a treatment score, as well as other predictive molecular biomarkers, will move us away from empiric delivery of adjuvant chemotherapy and ever closer to being able to offer real personalized medicine to patients with stage II colon cancer.

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