Combining Molecular Markers With the TNM Staging System to Improve Prognostication in Stage II and III Colon Cancer: Are We Ready Yet?

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In this issue of the Journal, Roth and colleagues (1) report a study entitled “Integrated Analysis of Molecular and Clinical Prognostic Factors in Stage II/III Colon Cancer.” The study population consisted of participants in a randomized adjuvant therapy trial (PETACC-3) that evaluated 5-fluorouracil and leucovorin alone or combined with irinotecan in curatively resected stage II and stage III colon cancer patients. In prospectively collected tumor tissue from a subset (420 stage II; 984 stage III) of the overall cohort well-characterized high-intermediate-risk tumors can provide the answer to the question that we have been trying but have failed to answer for more than 30 years.

References


Notes

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(N = 3278), molecular markers, including microsatellite instability (MSI), BRAFV600E and KRAS mutation status, chromosome 18q loss of heterozygosity (LOH), and SMAD4 protein expression, were analyzed and their association with clinical outcome was determined. Importantly, all biomarker assays were performed in the same laboratory. Biomarkers were chosen based upon promising data for their potential prognostic impact in nonmetastatic colon cancer patients. To date, none of the biomarkers evaluated in this study are considered to have been sufficiently validated for prognostication in routine clinical practice. The primary objective of the study by Roth et al. (1) was to determine whether any of these five biomarkers can refine the established TNM staging system by identifying prognostic subgroups that may improve upon the accuracy of TNM staging to predict clinical outcome.

Prior reports from the PETACC-3 biomarker cohort (2) and other retrospective studies (3) have shown that MSI-high (MSI-H) stage II and stage III colon cancers are associated with more favorable survival than MSI-low (MSI-L) and microsatellite-stable (MSS) cancers. Most MSI-H colorectal cancers are sporadic and show epigenetic inactivation of the MSH1 gene and carry mutations in the BRAFV600E oncogene in up to 50% of tumors that are mutually exclusive with KRAS mutations (4). Studies examining the prognostic impact of BRAFV600E or KRAS mutations in nonmetastatic colon cancer patients have produced inconsistent results (2,5,6). Conflicting data also exist for chromosome 18q LOH in stage II and stage III colon cancer patients treated in adjuvant chemotherapy trials, with studies showing a null effect (7) or worse survival compared with tumors retaining both 18q alleles (8). The SMAD4 gene, located on chromosome 18q21, encodes the SMAD4 protein that is a tumor suppressor and important mediator of intracellular transforming growth factor β signaling. Recent evidence indicates that SMAD4 loss is associated with increased Wnt/β-catenin target gene expression and increased tumor burden (9). Loss of SMAD4 expression occurs in a subset of colorectal cancers, and limited data suggest an association with inferior outcomes (10).

In the PETACC-3 biomarker cohort, demographic and clinicopathologic features and patient survival rates were shown to be similar to the overall study population. Consistent with prior studies, a higher prevalence of MSI-H was found in stage II vs stage III tumors (11). Conversely, both 18q LOH and SMAD4 expression showed a strong trend toward a higher frequency in stage III vs stage II tumors, with statistical significance defined as a P value less than .01. As previously reported in this cohort (2), the presence of MSI-H exerted a strong protective effect, with the finding of a statistically significant improvement in relapse-free survival (RFS) and overall survival (OS) rates compared with MSI-L and MSS tumors. A clear survival advantage for MSI-H tumors vs MSI-L and MSS tumors was observed in the study cohort despite a lack of benefit for the addition of irinotecan and data from other studies demonstrating that any benefit from adjuvant 5-fluorouracil is restricted to MSI-L and MSS colon cancers (12). SMAD4 was strongly prognostic for RFS and OS univariately, with focal loss of expression being associated with adverse outcome. Although SMAD4 resides on 18q21, 18q LOH was not prognostic. Regarding discrepant results for SMAD4 and 18q LOH, Alażouzzi et al. (10) failed to detect differences in SMAD4 expression based upon 18q21 LOH, suggesting that additional mechanisms of SMAD4 downregulation appear to be responsible. The lack of prognostic impact of KRAS exon 2 mutations in the PETACC-3 cohort was previously reported and discussed (2).

A multivariable analysis identified MSI status and SMAD4 expression as statistically significant and independent prognostic variables. Specifically, MSI-H tumors and those with intact expression of SMAD4 were associated with more favorable RFS and OS, whereas MSS and MSI-L tumors or those with loss of SMAD4 were associated with inferior outcomes after accounting for tumor stage and other clinicopathological features. Given the rather arbitrary scoring system used to define focal loss of SMAD4 and the semiquantitative nature of immunostaining, the prognostic impact of SMAD4 expression requires validation in an independent cohort. As previously reported by Roth et al. (2), BRAFV600E mutations were associated with worse OS, but not RFS, in the multivariable analysis. However, the association of BRAFV600E status with survival did not achieve statistical significance, defined as a P less than or equal to .01 to adjust for multiple comparisons. As acknowledged by the authors, the study results are average effects across tumor stages, and the power to detect such differences by stage or treatment was limited.

Within the PETACC-3 biomarker dataset, recursive partitioning models were used to determine whether the addition of MSI status and SMAD4 expression could refine risk estimation within the TNM staging system. In this data-driven analysis using prognostic trees, refinement of risk stratification regarding RFS was accomplished in stage II (T3N0) and stage III (T3N1) patient subgroups by incorporating MSI and SMAD4 data, respectively. Inclusion of MSI status was shown to improve prognostication by T stage (T3 vs T4) in stage II cancers. In stage III cancers and within the T3N1 subgroup, inclusion of MSI status and SMAD4 expression improved prognostication, with the finding that the 11% of tumors showing MSI-H and intact SMAD4 expression had a favorable outcome that was similar to that of stage II tumors. The identification of a stage III subgroup with a prognosis similar to that of stage II patients has important implications for clinical practice. If validated in an independent cohort, these data suggest the potential for a subgroup of stage III patients to potentially avoid the short- and long-term toxicities, inconvenience, and expense of adjuvant chemotherapy.

Roth and colleagues are to be commended for conducting a well-designed study that utilized sophisticated analytical methodology. Nevertheless, important caveats exist. Because the primary study endpoint was RFS and included second primary colon cancer or death as outcome variables, it would have been of interest to examine time-to-recurrence given that data for colon cancer–specific death were not available. The association of MSI-H and 18q LOH with RFS and OS showed clear trends toward differences between stage II and stage III tumors, as shown by interaction P values less than or equal to .05. Furthermore, an interaction between SMAD4 expression and study treatment arm was found for RFS and OS in stage III tumors, but not in stage II tumors. Together, these findings illustrate the multidimensional relationships between the selected biomarkers and clinical outcome when stratifying by stage and treatment. A limitation of recursive partitioning is that tree modeling searches for possible interactions between all biomarkers within a dataset. Thus, the risk group classifications identified in a
tree model can be biased by the strength of the interaction in a particular dataset. Accordingly, the generalizability of the risk groups needs to be determined in an independent cohort (13). Because stage II and stage III colon cancers are known to have different prognoses, the study conclusions could be strengthened if the robustness of the recursive partitioning analysis were to be tested separately within stage II and stage III cancers.

In summary, the prognostic impact of MSI status and SMAD4 expression in stage II and stage III colon cancers from PETACC-3 further demonstrates a survival advantage for MSI-H in patients receiving 5-fluorouracil–based adjuvant therapy and provides prognostic data for SMAD4 from a randomized trial. Prognostic trees suggest that the inclusion of MSI and SMAD4 data can refine prognostication using the TNM staging system. Specifically, the authors found that a subset of stage III (T3N1) colon cancers showing MSI-H and intact SMAD4 expression have a clinical outcome that is similar to that of stage II (T3N0) patients. Although these study results require validation in an independent cohort, they provide evidence, albeit preliminary, to suggest that inclusion of these biomarkers in the TNM staging system has the potential to refine clinical decision making. In this manner, the PETACC-3 data represent a step forward in an effort to bring biomarker data into oncologic practice; however, we underscore the critical role of validation because biomarker data from recent adjuvant trials have yielded inconsistent results in same-stage patients, for which explanations remain elusive.

References


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