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How Can We Use Molecular Biology to Develop New Adjuvant Strategies?

Heinz-Josef Lenz, MD

USC/Norris Comprehensive Cancer Center

Los Angeles, California

The goal is to identify patients who would benefit most from adjuvant therapy and patients who would respond better to one regimen versus another. Prognostic molecular markers that predict tumor behavior as well as host/tumor interactions could be helpful in risk stratification and in restriction of treatment to patients who would benefit most.

There are several examples of identified genes, including microsatellite instability (MSI), deleted in colon cancer (DCC), thymidylate synthase (TS), transforming growth factor- β (TGF- β), p53, p27, K-ras, and others. The most important markers are MSI, DCC, TS and TGF- β . Analysis of pooled data from published studies by Popat et al reveals that CRCs with MSI have a better prognosis (hazard ratio [HR] 0.65, 95% confidence interval [CI], 0.59 to 0.71). MSI tumors appeared to derive no benefit from adjuvant 5-FU, but the data are limited with HR of 1.24 and a 95% CI of 0.72 to 2.14. The Eastern Cooperative Oncology Group E5202 is a planned prospective randomized trial that assigns patients with stage II colon cancer to a high- or low-risk category based on the presence of 18q deletion and MSI. More recently, low TS expression assessed by immunohistochemistry in tumors from 1,326 patients with stage II and III colorectal cancer was found to be a statistically valid independent prognostic factor. While the prognostic value of TS has been established, its role in predicting benefit from adjuvant 5-FU based chemotherapy has been somewhat controversial. There is a clear need for technologic advances that would define a more comprehensive molecular fingerprint to identify patients who benefit from adjuvant chemotherapy. Using Affymetrix GeneChip U133A, Wang et al reported a 23-gene signature that predicted recurrence in Dukes' B colon cancer patients. This provocative data, if validated, could serve as a way to "upstage" some patients with Dukes' B colon cancer to receive adjuvant chemotherapy.