HEM/ONC News

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BRAF Mutation Is Associated With Worse Survival in Metastatic Colorectal Cancer

At the 2010 American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO GI), Dr. Eric Van Cutsem presented an analysis of tissue samples from patients in the CRYSTAL (Cetuximab Combined With Irinotecan First-Line Therapy for Metastatic Colorectal Cancer) trial. The study found that BRAF mutant patients (n=59) responded much worse to 5-FU, leucovorin, and irinotecan (FOLFIRI) with and without cetuximab (Erbitux, ImClone Systems Inc) compared with BRAF wild-type patients (n=566), suggesting that BRAF mutation status is of prognostic value. This analysis showed that mutations of the BRAF gene resulted in shorter progression-free survival (PFS) and overall survival (OS) compared to wild-type BRAF, even in patients with KRAS wild-type status. The median PFS and OS in patients with KRAS wild-type/BRAF wild-type tumors was 10.9 and 25.1 months, respectively, for those receiving cetuximab plus FOLFIRI and 8.8 and 21.6 months, respectively, for those on FOLFIRI alone. However, in patients with KRAS wild-type/BRAF mutant tumors, median PFS and OS were 8 and 14.1 months, respectively, in those receiving cetuximab plus FOLFIRI and 5.6 and 10.3 months, respectively, in those receiving FOLFIRI alone. Overall response rates were also higher in those patients with wild-type KRAS and BRAF tumors compared to those with wild-type KRAS/mutant BRAF tumors. Although a significant prognostic value was observed in BRAF, the study was too small to make definitive conclusions on the efficacy of cetuximab plus FOLFIRI versus FOLFIRI alone. Additional studies are warranted to confirm the prognostic importance of BRAF in colorectal cancer.

Researchers Identify Cause of Chronic Leukemia Progression

Researchers at the Ohio State University Comprehensive Cancer Center discovered that chronic myeloid leukemia (CML) progresses when immature white blood cells lose a molecule called *miR-328*. When miR-328 is lost, cells are trapped in a quickly growing immature state. The cells fill the bone marrow and leak into the bloodstream, resulting in the blast crisis stage of CML. In the March 5 issue of *Cell*, researchers suggested that maintaining the level of miR-328 may signify a novel therapeutic strategy for patients with blast crisis CML who do not benefit from tyrosine kinase inhibitors such as imatinib (Gleevec, Novartis) and dasatinib (Sprycel, Bristol-Myers Squibb). The study findings also showed that microRNA molecules can bind directly to protein molecules and modify their function: miR-328 binds to a protein that prevents maturation in immature blood cells. It was found that during CML progression from chronic phase to blast phase, the level of miR-328 dropped, thereby preventing leukemic white blood cells from maturing. The researchers believe that these findings may aid in the discovery of novel pathways and more effective treatments for patients with CML.

Proton Therapy Achieves Local Control in Patients With Sinonasal Cancer

A retrospective analysis of 99 patients with locally advanced cancer of the sinus or nasal cavity found that proton beam therapy produced an 87% rate of local control at 5 years. The findings were presented by Dr. Annie Chan at the 2010 Multidisciplinary Head and Neck Cancer Symposium. Dr. Chan and colleagues conducted a retrospective analysis of outcomes in 99 patients who underwent proton beam therapy (total radiation dose 70 GyE) at Massachusetts General Hospital between 1991 and 2003. Patients received combined proton and photon therapy: protons for the sinus area and upper neck, and photons for the lower neck. Two-thirds of patients had stage T4b disease with sinonasal undifferentiated carcinoma/squamous cell carcinoma and neuroendocrine tumor/esthesioneuroblastoma as the most common tumor types. One-third of patients underwent a biopsy and the rest had a partial or gross total resection. Of all patients, 27% received chemotherapy. The analysis found that at a median follow-up of 5.3 years among all patients (8.5 years among living patients), the 5-year local and regional control rates were 87% and 89%, respectively. The rate of local control did not significantly differ by tumor type, extent of surgery, type of surgical approach, or T stage. The first site of failure most commonly observed was a distant site (26% of

patients); local site (11%) and regional site (8%) were also observed. An increased risk in distant metastases was seen in patients who had a primary tumor in the sphenoid or ethmoid sinuses compared to those who had tumors in the maxillary sinuses or nasal cavity. The most commonly reported adverse events grade 3 or higher was soft tissue toxicity. Although proton beam therapy demonstrated positive outcomes in this retrospective trial, multicenter, prospective studies are needed to corroborate these findings.

Cabazitaxel: Possible Second-line Treatment for Metastatic Prostate Cancer

A randomized, phase III trial (TROPIC; Treatment of Hormone-Refractory Metastatic Prostate Cancer Previously Treated with a Taxotere-Containing Regimen) of a novel taxane, cabazitaxel (Sanofi-Aventis), showed improved OS in men with metastatic castration-resistant prostate cancer that had progressed on docetaxel-based therapy, which is the only therapy found to be effective after hormone therapy failure. Study findings were presented by Dr. A. Oliver Sartor at the 2010 ASCO Genitourinary Cancers Symposium. The study enrolled 755 men from 26 countries and randomly assigned them to receive either cabazitaxel 25 mg/m^2 every 3 weeks plus prednisone or mitoxantrone 12 mg/m^2 every 3 weeks with prednisone. Both regimens were given for 10 cycles. The primary endpoint was OS. Patients receiving cabazitaxel lived a median of 2.4 months longer compared with patients receiving mitoxantrone. Furthermore, at a median follow-up of 12.8 months, OS was longer in the cabazitaxel arm (15.1 vs 12.7 months). Median PFS in patients on the cabazitaxel arm was 2.8 months compared to 1.4 months for patients on the mitoxantrone arm. The drug was manageable in terms of safety, with neutropenia, febrile neutropenia, and infections reported as the most frequent grade 3/4 hematologic toxicities.

Mitotic Index, Tumor Size, and Small Bowel Location Are Predictors of Relapse in Gastrointestinal Stromal Tumor

A retrospective multivariate analysis of data from a phase III, double-blind, placebo-controlled study of 700 patients with localized, primary gastrointestinal stromal tumor (GIST) found that high mitotic rate, tumor size, and small bowel location were predictors of relapse and thus should be examined before choosing appropriate therapy. These prognostic factors were discussed by Dr. Martin Blackstein at the 2010 ASCO GI. The study enrolled patients with KIT-positive primary GIST and randomized them to either adjuvant imatinib (n=359) or placebo (n=354) for 1 year. Both arms were similar at baseline. Mitotic scoring was performed retrospectively in tumors from 620 patients. The researchers used the Miettinen classification system to classify patients as being at low, medium, or high risk for relapse. In the 270 low-risk patients, relapse rates were similar between imatinib and placebo. In the 148 moderate-risk patients, the relapse rates showed a trend, albeit nonsignificant, favoring imatinib (14% with placebo vs 5% with imatinib; hazard ratio, 3.183; P=.0509). However, in the 201 high-risk patients, there was a major benefit for patients receiving imatinib (47% with placebo vs 19% with imatinib; hazard ratio, 3.108; P<.0001).

DNA-based Blood Test Can Track Tumor-specific Markers After Therapy

Researchers have discovered a new way to track cancer by using DNA-based blood tests to examine individualized biomarkers after treatment of solid tumors, a method that can be used to detect cancer recurrence. This test, Personalized Analysis of Rearranged Ends (PARE), is described by Dr. Victor Velculescu in the February 24 issue of *Science Translational Medicine*. Dr. Velculescu and colleagues used 6 sets of tissue samples from 4 patients with colorectal cancer and 2 patients with breast cancer to record the number of gene sequences in each patient. They first identified regions in which the number of DNA sequences was more or less than expected and where sections of different chromosomes fused together. Afterward, the researchers evaluated the regions to classify DNA sequences that displayed incorrect ordering, orientation, or spacing. This analysis demonstrated an average of 9 rearrangements in each of the 6 samples. Researchers then looked for the same changes as shed from the tumor into patients' blood and found that the fraction of mutant DNA in the blood decreased after surgery and fell even more after chemotherapy and removal of metastatic lesions. The researchers determined that PARE was successful in detecting residual tumor DNA. There were limitations in this study and with this method; there is a possibility that some rearranged genetic sequences could be lost during tumor progression, and the very high cost of the assay makes it too expensive for widespread use. Despite these challenges, Dr. Velculescu and colleagues believe that PARE has great potential as a tool to detect tumor-free surgical margins, analyze regional lymph nodes, and measure circulating tumor DNA after surgery, radiation, or chemotherapy.