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Notes From the 2009 ASCO Gastrointestinal Cancers Symposium

Welcome to Conference Coverage Highlights presented by ReachMD radio on XM160. Conference Coverage Highlights features the latest clinical information and research findings presented during the 2009 American Society of Clinical Oncology Gastrointestinal Cancer Symposium, which took place on January 15 through 17 at San Francisco, California. Your host for this presentation of Conference Coverage Highlights will be Phil Duncan and Su Byrd.

PHIL DUNCAN:

Universal gene testing of patients with metastatic colorectal cancer could save more than 600 million dollars a year on unnecessary treatment costs. That was the conclusion of researchers at Northwestern University in Chicago and their colleagues. The test in question looks for mutations in the gene K-ras. People with normal versions of K-ras tend to respond better to the drug rituximab, a monoclonal antibody that targets the epidermal growth factor receptor. Patients who have mutations in the K-ras gene do not seem to benefit from the drug. Investigators used a novel economic model to evaluate the cost savings. About 60% of patients with metastatic colorectal cancer have the normal form of the K-ras gene. To come up with their findings, the researchers used estimates of the number of annual cases of metastatic colorectal cancer and the cost of treating patients with cetuximab. This gene test could spare thousands of people with colorectal cancer the side effects of treatments that are highly unlikely to improve their health and at the same time it would save the healthcare system substantial amounts of money. A significant number of hospitals and institutions are incorporating K-ras testing to guide treatments with cetuximab, but it's not universally used. The test could also be used to guide treatment with a drug panitubimab, another EGFR-targeted therapy that is approved for metastatic colorectal cancer. The researchers planned to use their model to account for the treatments and hospitalization cost associated with side effects caused by these drugs in patients whose tumors have K-ras mutations. In a related development, The American Society of Clinical Oncology released its first provisional clinical opinion on the use of K-ras testing in patients with metastatic colorectal cancer. The Society recommended testing all patients who are candidates for anti-EGFR therapy. Those with the muted form of the K-ras gene should not receive the therapy. ASCO's provisional clinical opinions reflect expert consensus. They are meant to help physicians in their critical decision-making and identify questions and settings for future research.

SU BYRD:

A prophylactic and preemptive skin treatment could allow cancer patients who receive the anti-EGFR therapy panitubimab to avoid some of its side effects. Skin toxicities are the most common adverse effects related to panitubimab. The toxicities can include erythema, dermatitis, pruritus, pustules, rash, and hair and nail changes. Many patients must discontinue using the drug because the side effects are too serious. Researchers at Jefferson Medical College of Thomas Jefferson University and Northwestern University's Feinberg School of Medicine studied 95 patients with metastatic colorectal cancer who were receiving panitubimab in combination with irinotecan-based chemotherapy. The patients were randomized to receive skin toxicity treatments at different times. One group received a preemptive skin treatment 24 hours before the first dose of panitubimab then given daily through week 6. Another group received a reactive skin treatment after the skin toxicity developed. The skin treatment included moisturizers, sunscreen, topical steroids, and oral doxycycline. The investigators looked for grade 2 or higher skin toxicities during the 6-week skin treatment period. The incidents of these toxicities were reduced by more than 50% in the group that received preemptive treatment. Quality of life was

also assessed. The patients who received the preemptive skin treatment reported an improved quality of life even around week 3. Around the same time, the reactive skin treatment group reported grade 2 or higher skin toxicity. Investigators concluded their study supports the notion that it is more advantageous to treat side effects of cancer therapies prophylactically rather than wait for side effects to fully develop. The study also showed that treating skin toxicity early does not affect the benefit received from panitumab.

PHIL DUNCAN:

New research has linked esophageal cancer with reflux disease and gene mutations, specifically certain mutations in the epidermal growth factor gene are associated with a significant increased risk in esophageal cancer in individuals with gastroesophageal reflux disease or GERD. The findings come from a study conducted in approximately 300 esophageal adenocarcinoma patients and a similar number of healthy controls. It is the first study to examine EGF mutations as predictors of esophageal cancer risk in patients with GERD. Investigators at the University of Toronto, The Harvard School of Public Health and their colleagues collected DNA samples from these individuals and analyzed their genotypes and their GERD history. They found that patients who had the mutated EGF gene variant called GG and experienced symptoms associated with GERD more than once a month were at 10-fold increased risk of esophageal cancer compared with those who had a normal AA variant and did not have GERD. The risk of esophageal cancer increased among patients with mutations who suffered from GERD more frequently or for more than 15 years. Risks to patients who had GERD and the genetic variant called AG were intermediate. The findings indicate that performing epidermal growth factor genotype for patients with severe long-standing GERD can help identify individuals at greatest risk for esophageal cancer. GERD is a common condition, so the ability to single out patients at high risk of cancer could lead to better outcomes and significant cost savings.

SU BYRD:

A drug used to treat pituitary gland disorders may help patients with rare malignant neuroendocrine tumors of the midgut. The drug is called octreotide LAR. It's a peptide that mimics the hormone somatostatin. Somatostatin regulates the endocrine system and also effects self proliferation and neuro-communication. Researchers in Germany enrolled 85 patients with newly diagnosed malignant neuroendocrine tumors to receive either octreotide LAR or placebo. Most of the patients had already undergone surgery to remove their primary tumor. Most had liver metastasis as well. After 6 months, the researchers observed stable disease in 64% of patients treated with octreotide LAR compared with about 37% of placebo patients. They also found that the median time to tumor progression was significantly longer in the octreotide LAR group. The median time to progression was just over 14 months in these patients compared with 6 months in patients in the placebo group. The study also revealed that certain patients seemed to respond better to the drug. The patients with localized disease tended to have a better response than patients with multiple metastases. Treatment side effects included diarrhea, fatigue, fever, and bile stones. The findings bring very good news for patients. For patients with malignant midgut tumors that are still localized, the median survival is more than 10 years. For patients whose tumors have metastasized, median survival is about 5 years. Investigators say their study could change the way that malignant neuroendocrine tumors of the midgut are treated. Now individuals with this rare disease who are not cured with surgery have a drug option. The researchers are studying the molecular makeup of these tumors to determine why some patients do not respond to the drug. In addition, they plan to evaluate octreotide LAR's ability to slow cancer progression in pancreatic and another neuroendocrine tumors.

PHIL DUNCAN:

Certain gene variations may be able to predict treatment response and survival in patients with pancreatic cancer. That was the conclusion of the first study to look at the role of variations in genes responsible for DNA mismatch repair in pancreatic cancer outcomes. The study included 154 patients with potentially operable pancreatic adenocarcinomas who are already enrolled in trials that were testing the benefits of preoperative radiation and chemotherapy with gemcitabine. A team of researchers from The University of Texas, MD Anderson Cancer Center analyzed DNA from samples of patient's blood. They examined 15 different genotypes or single nucleotide polymorphisms in various genes. The genes encode DNA mismatch repair proteins to help repair DNA damage caused by cancer treatment and allow cancer cells to become resistant to therapy. Unfavorable genotypes were identified based on patient's poor response to therapy and reduced survival. Researchers found that survival times decreased as patient's number of unfavorable

genotypes increased. Patients with 2 unfavorable genotypes lived an average of 36 months. Patients with 6 to 7 unfavorable genotypes lived only about 8 months. Eighty percent of patients with 0 or only 1 unfavorable genotype were still alive 3 to 5 years after being diagnosed. The researchers also identified specific combinations of mismatch repair gene variations that increased the likelihood that tumors could be treated effectively with surgery, chemotherapy, or radiation. Pancreatic cancer has proven very difficult to treat and 5-year survival is just 5%. There have been no biomarkers for pancreatic cancer used in the clinic to predict response. Variations in DNA repair genes might be a predictor to treatment responses or prognosis factor for patient's survival. These findings could have profound affect on how pancreatic cancer is treated. Having established biomarkers like abnormal mismatch repair genes could make choosing which patients might benefit from certain therapies much easier.

SU BYRD:

African-American patients with colorectal cancer are more likely to have worst pathological features when they are diagnosed compared with Caucasian patients. They are also more likely to have a worse 5-year survival rate. That was the conclusion of a study conducted by researchers at Thomas Jefferson University. The investigators say that socioeconomic factors could be a possible explanation. For example, research has shown that African-Americans are less likely than Caucasians to have health insurance, therefore they may not receive the screening that's needed to detect colorectal cancer at an early stage. The study included data from the tumor registry of Thomas Jefferson University Hospital on 2500 patients treated for colorectal cancer between 1988 and 2007. The researchers compared this data with data obtained from the National Cancer Institute Surveillance, Epidemiology, and End Results database on approximately 245,000 patients with colorectal cancer treated from 1988 to 2005. They analyzed data on location, stage, and histological grade of the cancer. In both patient groups, more African-American patients presented with advanced disease at diagnosis. African-American patients were also more likely to have proximal disease that's found on the right side of the colon, and among patients diagnosed with early stage disease, African-American patients risk for nodal involvement was greater. African-American patients also had a worse 5-year survival, both overall and when stratified by cancer stage. The investigators say that more studies are needed to explain these racial disparities. Future studies should look at prognostic factors related to tumor biology, molecular markers, and genetics.

PHIL DUNCAN:

Investigators at Weill Cornell Medical College in New York report that the incidents of rectal cancer has shifted towards younger individuals. Information in the Surveillance, Epidemiology, and End Result database, rectal cancer incidents rose by about 2.5% each year over the past 3 decades for people under the age of 40. In contrast, the incidents of colon cancer in the same age group decreased by 0.2% each year. Rectal cancer incidents in young people went up in both men and women in all races. The incidents of rectal cancer did not increase in older individuals. More research is needed to determine the reason for this trend. The investigators could not find any explanation by analyzing genetic, clinical, demographic, and lifestyle factors.

SU BYRD:

Researchers have presented promising phase-2 clinical results on the use of RAD001 for the treatment of advanced gastric cancer. RAD001's active ingredient is everolimus. It's an oral inhibitor of mTOR or the Mammalian Target of Rapamycin serine-threonine kinase. mTOR is a protein that regulates tumor cell divisions, cell metabolism, and blood vessel growth. The open label single-arm study was conducted in Japan. It included 54 advanced gastric cancer patients previously treated with chemotherapy. After 8 weeks of daily treatment with 10 mg of RAD001, tumor growth halted in 55% of the patients. In addition, 45% of patients in the study experienced some tumor shrinkage. The median progression-free survival was 83 days. At 4 months, about 30% of patients were still progression free. Median overall survival was not obtained when the data was gathered. The most commonly reported adverse events included stomatitis, anorexia, fatigue, and rash. Serious adverse events included stomatitis and hyponatremia. Gastric cancer is the second leading cause of cancer death worldwide. The majority of cases occur in East Asia. In the United States, Asians and Pacific Islanders have the highest mortality rates. Patients with advanced forms of the disease have very limited treatment options. The investigators say that this study indicates that RAD001 has the potential to provide an effective treatment option for patients. Based on this promising

data, Novartis will initiate a phase-3 clinical trial of the drug for advanced gastric cancer patients. The study will evaluate the efficacy and safety of RAD001 in approximately 500 patients. RAD001 is also being studied for the treatment of other cancers including kidney cancer, breast cancer, and lymphoma.

We thank you listening to the Conference Coverage Highlights of the 2009 American Society of Clinical Oncology Gastrointestinal Cancer Symposium of January 15th to the 17th. Conference Coverage Highlights is a presentation of ReachMD radio broadcast on XM160 and by live stream at reachmd.com.