Clinical Chemistry Trainee Council
Pearls of Laboratory Medicine
www.traineecouncil.org

TITLE: Carcinoembryonic Antigen (CEA) and Cancer Antigen (CA19-9) for Gastrointestinal Cancers

PRESENTER: Yan Zhang, Ph.D.

Slide 1: Introduction

Hello, my name is Yan Zhang. I am Assistant Professor in the Department of Pathology and Laboratory Medicine at the University of Rochester Medical Center and Associate Director of Clinical Chemistry and Toxicology Laboratories at Strong Memorial Hospital. Welcome to this Pearl of Laboratory Medicine on "Carcinoembryonic Antigen (CEA) and Cancer Antigen (CA19-9) for Gastrointestinal Cancers."

Slide 2: CEA and CA19-9

This slide provides a brief history review of CEA and CA19-9.

CEA was first discovered in 1965 by Gold and Freeman, and is also known as the "Gold" antigen. Since it was only detected in cancer and embryonic tissues, it was named carcinoembryonic antigen. CA19-9 was originally discovered in patients with colon and pancreatic cancer in the early 1980s. It was first defined by a monoclonal antibody produced by murine spleen cells that were immunized by a human colorectal cancer cell line, and it was named cancer antigen or carbohydrate antigen (CA) 19-9.

CEA and CA19-9 are both glycoproteins. CEA contains 45-50% carbohydrate with a molecular weight of 150-300 KDa. CA19-9 is a tumor-associated antigen that exists in serum as a mucin, which is a huge glycoprotein complex with a molecular weight of 200-1000 KDa.

CEA and CA19-9 have been used as tumor markers for the management of patients with colorectal cancer and pancreatic cancer, respectively.

Slide 3: Cancer Statistics

According to 2013 cancer statistics, colorectal cancer is the third most common cancer in both men and women, accounting for 9% of total cancer incidences in the United States. It's also the third most common cause of cancer death for both men and women, accounting for 9% of cancer deaths. New cases and mortality have decreased significantly for colorectal cancer since the 1980s due to early detection and increased screening rates using colonoscopy.

Although pancreatic cancer is only the tenth and ninth most common cancer in men and women, respectively, in the United States, it's the fourth most common cause of death for both genders. The five-year relative survival rate, based on 2002-2008 data, was only 6%, while the survival rate based on 1975 and 1987 data were 2% and 4%, respectively. Pancreatic cancer has shown little improvement in survival in the past 30 years.

Slide 4: Specificity of CEA and CA19-9

One of the important facts about CEA and CA19-9 is their low specificities for colorectal cancer and pancreatic cancer.

The serum concentration of CEA and CA19-9 can be elevated in either non-neoplastic conditions or malignancies, as summarized in this table. The non-neoplastic conditions for CEA include cigarette smoking, peptic ulcer disease, inflammatory bowel disease, pancreatitis, hypothyroidism, biliary obstruction, and liver cirrhosis. The malignancies associated with elevated CEA include breast, lung, gastric, pancreatic, bladder, medullary thyroid, head and neck, cervical, and hepatic cancers, lymphoma, and melanoma. CA19-9 can also be elevated in the inflammatory conditions of the hepatobiliary system and many benign conditions such as thyroid disease. Its concentration can also increase in the presence of tumors of the upper gastrointestinal tract, ovarian cancer, hepatocellular cancer, and colorectal cancer.

Slide 5: Analytical Perspectives

CEA reference ranges vary by population. The typical cutoff for non-smokers is 2.5 ng/mL, while for smokers it is 5 ng/mL. A serum CEA level of more than 10 ng/mL is very rarely seen in the benign diseases that are listed in the previous slide.

The upper reference limit of CA19-9 is 37 U/mL, which was determined by the 99^{th} percentile of CA19-9 values from normal subjects. CA19-9 can reach very high levels in colorectal cancer; however, it rarely reaches levels higher than 1000 U/mL in individuals with the benign conditions listed above.

The next few slides will discuss the clinical utilities of CEA and CA19-9 for colorectal and pancreatic cancer, respectively.

Slide 6: CEA Utilities – Colorectal Cancer

In general, it is not recommended to use CEA for colorectal cancer screening in the general population. Its utility in staging and treatment planning, post-surgery follow-up, and the monitoring of therapy, however, has proven to be effective.

Slide 7: CEA Utilities – Screening and Staging

According to the 2006 American Society of Clinical Oncology (ASCO) updated guidelines for gastrointestinal cancers, CEA is not recommended for general screening purposes due to its low sensitivity and specificity. For instance, one study used 2.5 ng/mL as the cutoff and reported 36% sensitivity and 87% specificity in screening during the early stages of colorectal cancer. These levels of diagnostic power, in combination with the low prevalence of colorectal cancer, were not sufficient enough for screening the general population.

CEA can be used to help in the staging and planning of treatment before surgery takes place. For instance, CEA levels of > 5ng/mL may indicate a worse prognosis, although there isn't enough evidence to use this cutoff to determine whether the patients should receive additional treatment. Some studies have shown that a CEA level of less than 30 ng/mL is associated with longer survival times of 34.8 months, while higher CEA levels are associated with a median survival of 22 months. One caveat is that poorly-differentiated colorectal cells may produce less CEA than well-differentiated cells either based on per gram of total protein or per volume (mL) of serum.

Slide 8: CEA Utilities – Post Surgery & Monitoring

Post-surgery follow-up:
The goal of measuring CEA after surgery is to assess the success of the surgery and to detect metastasis. This function is usually combined with radiology and the patient's clinical history. CEA levels typically return to a normal range four to six weeks after a successful surgery. ASCO 2006 guidelines suggest retesting CEA levels every three months in patients with stage II and stage III disease for a minimum of three years. Elevated CEA levels, if confirmed by retesting, suggest further evaluation for potential metastasis. However, an elevated CEA level alone is not sufficient to justify therapy. The guideline was based on at least three meta-analyses that have shown a reduction in mortality, early detection of recurrence, and/or more detection of asymptomatic recurrence from combined intensive follow-up programs after a colorectal cancer operation. The data also suggest that CEA and liver imaging can have a significant impact on overall survival.

Bear in mind that chemotherapy can increase CEA levels. Therefore, the initial surveillance should start after chemotherapy is finished.

Therapy monitoring:
Longitudinal CEA measurements have been widely used to monitor therapy and are usually combined with radiology and a patient's clinical history. Such measurements help monitor metastatic colorectal cancer during systemic therapy. Measurements should be done at the beginning of the therapy and repeated every 1-3 months during treatment. A persistent rise in CEA level should prompt restaging of the disease and consideration of alternative treatment strategies.

When interpreting the results, it's important to remember that new therapies such as oxaliplatin may cause elevation of CEA during the first 4-6 weeks of treatment.

Slide 9: Surveillance Using Serial CEA

Although CEA has been in clinical use for over 30 years, controversy remains in terms of surveillance using serial CEA levels. The arguments in favor of CEA include that it provides a lead time of 1.5 to 6 months for early detection of recurrence, and some data has indicated a significant increase in survival using serial CEA as part of the follow-up.

However, CEA isn't perfect for the job, and there are arguments against its usage in surveillance. For example, there is a 30-40% recurrence rate which is not associated with elevated CEA levels. The test only benefits a small group of patients, and there is no data to show an improvement in quality of life due to CEA-based follow-up strategy.

While not perfect, CEA has been one of the most widely used tumor markers. It is the most frequent indicator of cancer recurrence in asymptomatic patients. CEA is also the most useful indicator in the early detection of liver metastasis in patients with colorectal cancer. More studies and research are taking place to provide better markers for colorectal cancer.

Slide 10: CA19-9 Utilities for Pancreatic Cancer

Although CA19-9 was first identified in a colorectal cancer cell line, its most significant use has been in the management of pancreatic cancer.

Screening:
Quantitative measurements of serum CA19-9 has been approved by the FDA for monitoring patients with pancreatic cancer. It is not recommended, however, to use CA19-9 for general screening. The upper limit of CA19-9's reference range is 37 U/mL, which is determined based on the 99th percentile of normal subjects.

One recent systematic review reported the diagnostic power of CA19-9 for pancreatic cancer. The report was based on 2283 patients from 26 manuscripts published between January 1990 and December 2005. Case reports, review articles, and reports not providing data on serum markers in pancreatic cancer were excluded. The median sensitivity, specificity, positive predictive value, and negative predictive value were 79%, 82%, 72%, and 81% respectively.

Operability:
CA19-9 is not recommended to be used alone to determine surgical resectability, although preoperative CA19-9 can predict patient outcome. In previous studies, when CA19-9 values were greater than 1000 U/mL, 96% of tumors were found to be unresectable. Pancreatic cancer typically has a very unfavorable prognosis, with surgery being the only treatment with curative options. For late-stage pancreatic cancer patients, the goal is to avoid unnecessary treatments if the patients have unresectable tumors, while not missing potential curative treatments with surgery. CA19-9 has demonstrated usage in assessing a patient's resectability, although there is no agreement on the specific cutoffs to use for this purpose.

Post-surgery recurrence:
Some studies have shown a correlation between CA19-9 decline and an increase in survival times in patients after surgery. A persistent elevation of CA19-9 may indicate recurrence. However, CA19-9 alone can't be used as definitive evidence for recurrence; it should be determined in combination with imaging studies and biopsy.

Slide 11: CA19-9 Utilities: Pancreatic Cancer

Although no sufficient data exists to recommend routine usage, CA19-9 has been shown to be a useful tool in monitoring a patient's response during therapy. In this case, the serum level of CA19-9 should be measured at the beginning of the treatment and every 1-3 months during treatment. A decline in CA19-9 levels could confirm the effectiveness of the treatment, while serial elevations of CA19-9 indicate disease progression. However, the disease progress should be confirmed by other approaches before taking any actions or making any therapy adjustments.

One caveat regarding CA19-9 is that it is not expressed in Lewis null blood type (le a-b-) patients, representing about 5% of the population or 10% of Caucasians. This is believed to be due to the lack of fucosyltransferase on Lewis null blood type populations.

Slide 12: Summary

This slide summarizes this pearl of laboratory medicine on CEA and CA19-9.

CEA is one of the most widely used tumor markers, particularly for the management of colorectal cancer patients. Although first discovered from a colorectal cancer cell line, CA19-9 has shown its greatest utilities in the management of pancreatic cancer patients. Neither marker has accumulated sufficient data to demonstrate usage as a screening test, while both have shown applications in detecting post-surgery recurrence and therapy monitoring. In addition, CEA is the most useful marker for early detection of liver metastasis, while CA19-9 can aid in assessing a patient's resectability.

Slide 13: References

Slide 14: Disclosures

Slide 15: Thank You from www.TraineeCouncil.org

Thank you for joining me on this Pearl of Laboratory Medicine on "Carcinoembryonic Antigen and Cancer Antigen 19-9 for Gastrointestinal Cancers." I am Yan Zhang.