BRAF Mutation Predicts Thyroid Ca Recurrence

BY KERRI WACHTER

FROM A MEETING SPONSORED BY THE AMERICAN THYROID ASSOCIATION

MINNEAPOLIS — BRAF mutations may offer one answer to the growing need for biomarkers that can accurately predict the risk of thyroid cancer recurrence, said Dr. Stefan K.G. Grebe.

Thyroid cancer, with its rising incidence and low mortality rate, will be the third most common diagnosis in living cancer patients in the next 5-10 years, behind breast and prostate cancers, according to Dr. Grebe. For a newly diagnosed thyroid cancer patient, the lifetime risk of dying from the disease in 10 years—across all ages and stages—is less than 3%.

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"We have to bear this in mind when we talk about prognostic markers. … Predictive markers may be more important because hardly anyone ever dies of thyroid cancer," Dr. Grebe said at the meeting. Depending on the cancer morphotype, 15%-50% of patients will suffer a recurrence in their lifetime. "There really is a need for prolonged—over decades—follow-up of these patients," which will require sensitive and specific means of detecting recurrences, he stressed.

The BRAF T1799A (V600E) mutation accounts for more than 90% of BRAF mutations in melanoma and papillary thyroid cancer (PTC). Importantly, this mutation is not found in normal tissue. While this mutation occurs in 40%-80% of melanomas and papillary thyroid cancers, it is present in fewer than 10% of other cancers, making it a good candidate biomarker for PTC recurrence, said Dr. Grebe, chair of clinical biochemistry and immunology in the department of laboratory medicine and pathology, Mayo Clinic, Rochester, Minn.

A good candidate marker also needs a good test. In the case of BRAF V600E this means developing an assay that can detect nucleic acids with this mutation in human blood, plasma, or serum with high sensitivity and specificity. "For residual disease follow-up …you have to have a low sensitivity to detect a low number of mutant copies," said Dr. Grebe, who has been working on the development of such an assay with his colleagues. They started by evaluating a number of assay techniques to detect BRAF V600E mutations. "Finally we settled on real-time PCR [polymerase chain reaction]," he said.

Once they achieved success with a proof-of-principle study, they prospectively collected blood from all thyroid cancer patients attending a follow-up visit between May 2004 and December 2006 (J. Clin. Endocrinol. Metab. 2009;94:5001-9).

They enrolled 193 patients, of whom 173 had papillary thyroid cancer. Circulating BRAF V600E was detected in 20 of the 173 patients with PTC. It was not detected in the 20 patients with other types of thyroid cancer. Tissue BRAF status correlated with blood BRAF status.

"Overall we found that the BRAF mutation in blood conveyed about a two-and-a-half-fold relative risk of having active or recurrent disease," said Dr. Grebe. "Potentially this will be an assay of increased value in the future."

For now, clinicians have to rely on thyroglobulin, which has proved to be a good, but not perfect, tumor marker. Thyroglobulin is highly organ specific but cannot distinguish between benign and cancerous tumor tissue. Its reliability is compromised by residual thyroid tissue.

Perhaps more importantly, thyroglobulin is subject to analytical interferences with uninterpretable results in up to a quarter of patients and measurements. This is largely due to false negatives. "These limitations of thyroglobulin will get worse in the future," said Dr. Grebe, who predicted that increasing numbers of thyroid cancer patients with even lower mortality will lead to less extensive treatment.

"I don't think in this day and age that you could convince a woman to have a radical mastectomy plus an extensive dissection for a 0.4-cm microcancer of the breast. The same will happen sooner or later with thyroid cancer," he said. As a result, more patients will have remnant thyroid tissue producing greater background levels of thyroglobulin with greater TSH-related fluctuations. ■

Disclosures: *Dr. Grebe reported that he has no relevant financial relationships.*

CLINICAL GUIDELINES FOR FAMILY PHYSICIANS

Cancer Screening Guidelines

BY NEIL S. SKOLNIK, M.D., AND VALERIE A. BONICA, D.O.

In its 2010 report, the American Cancer Society (ACS) provides a summary of its guidelines for cancer screening and reports on recent updates made by other organizations (CA Cancer J. Clin. 2010;60:99-119). Here are some highlights:

Breast Cancer

Women at average risk for breast cancer should receive annual mammography beginning at age 40 years, a clinical breast exam every 3 years from ages 20 to 39 and annually after age 40, and counseling on breast cancer symptoms beginning at age 20. Self examination is no longer advised.

Starting at age 30, annual screening mammography and MRI are recommended for women with a known *BRCA* mutation, women who are untested but who have a first-degree relative with a *BRCA* mutation, and women with a 20%-25% or greater lifetime breast cancer risk as estimated by a specialized breast cancer pedigree analysis model.

The ACS report addresses the U.S. Preventive Services Task Force's 2009 breast cancer screening guidelines, which advised that screening should start at age 50 years, as opposed to 40. The ACS questioned the methodology by which the USPSTF came to this conclusion and argued that the number of years gained in preventing death among women in their 40s makes the higher number needed to screen to save one life acceptable.

Also addressed is the USPSTF's recommendation in favor of biennial versus annual mammography. ACS points out that the shorter detectable preclinical period in younger women makes biennial screening less efficient and references data showing that advantages from annual screening persist among women aged 50 and over.

Cervical Cancer

Cervical cancer screening should be initiated about 3 years after the onset of vaginal intercourse but no later than 21 years of age.

Among women of average risk, those aged 30 and younger should receive an annual conventional Pap test or a biennial liquid-based Pap test. Women over age 30 with three consecutive negative Pap tests may choose to be screened every 2-3 years using conventional or liquid-based Pap tests, or every 3 years with human papillomavirus testing and a Pap test. After age 70, women with no abnormal Pap tests in the previous 10 years and three consecutive normal Pap tests may choose to stop screening.

Among women who have undergone total hysterectomy for benign disease, cervical cancer screening is not indicated. Women at average risk who have had supracervical hysterectomy should continue screening.

HPV vaccination is recommended for girls 11-12 years old, with "catch up" vaccination recommended for girls aged 13-18 years.

These guidelines differ from those recently issued by the American College of Obstetricians and Gynecologists, which recommend initiation of cervical cancer screening at age 21, screening biennially among women younger than age 30, screening every 3 years in women over age 30 with a history of three consecutive normal Pap tests, and stopping screening among women aged 65-70 with a history of three negative Pap tests in the past 10 years.

Colon Cancer

Colon cancer screening should be initiated at age 50 for individuals at average risk, using annual fecal occult blood testing (FOBT) or fecal immunochemical testing (FIT), stool DNA testing (interval not yet established), flexible sigmoidoscopy every 5 years (with or without FOBT or FIT), colonoscopy every 10 years, or CT colonoscopy every 5 years. More intensive surveillance is recommended for individuals at increased risk.

Endometrial Cancer

Endometrial cancer screening is not recommended in women at average or increased risk. At the onset of menopause, women should be informed about the risks and symptoms of endometrial cancer and encouraged to report symptoms to their physician. Women at very high risk for endometrial cancer should consider annual testing beginning at age 35 years.

Prostate Cancer

Asymptomatic men with a life expectancy of 10 or more years should be educated about the benefits, limitations, and risks of prostate cancer screening. For men at average risk, this discussion should occur at age 50. Those at increased risk, such African American men and men with a first-degree relative diagnosed with prostate cancer before age 65, should be educated about screening at age 45. Men with multiple family members diagnosed with prostate cancer before age 65 should consider screening at age 40.

For men choosing to be screened, the ACS recommends prostate-specific antigen testing with or without a digital rectal exam. For men with a PSA less than 2.5 ng/mL, screening intervals may be lengthened to every 2 years. For men with a PSA of 2.5 to less than 4.0 ng/mL, screening should be conducted annually. Men with a PSA over 4.0 ng/mL should be referred for further evaluation and potential biopsy.

DR. SKOLNIK *is an associate director of the family medicine residency program at Abington (Pa.) Memorial Hospital.* DR. BONICA *is a third-year resident in the program. A handheld computer version of this guideline is available at www.redi-reference.com.*