Association between genetic mutation and risk of death for patients with thyroid cancer

April 9 2013

Presence of the genetic mutation BRAF V600E was significantly associated with increased cancer-related death among patients with papillary thyroid cancer (PTC); however, because overall mortality in PTC is low and the association was not independent of tumor characteristics, how to use this information to manage mortality risk in patients with PTC is unclear, according to a study in the April 10 issue of *JAMA*, a Genomics theme issue.

"Papillary thyroid cancer is the most common endocrine malignancy and accounts for 85 percent to 90 percent of all thyroid cancers," according to background information in the article. "The overall 5-year patient survival rate for PTC is 95 percent to 97 percent. A major clinical challenge is how to reliably distinguish patients who need aggressive treatments to reduce mortality from those who do not. This represents a widely controversial issue in thyroid cancer medicine, particularly because of the low overall mortality of this cancer. The issue has become even more challenging given the high annual incidence of PTC." BRAF V600E is a prominent oncogene [a gene, one or more forms of which is associated with cancer] in PTC and "has drawn considerable attention as a potential prognostic factor for PTC. However, the clinical significance of this mutation in PTC-related mortality has not been established."

Mingzhao Xing, M.D., Ph.D., of the Johns Hopkins University School of Medicine, Baltimore, and colleagues conducted a study to examine and define the association between the BRAF V600E mutation and PTC-related mortality. The study included 1,849 patients (1,411 women and

438 men) with a median (midpoint) age of 46 years and an overall median follow-up time of 33 months after initial treatment at 13 centers in 7 countries between 1978 and 2011.

The overall prevalence of BRAF V600E was 45.7 percent (845/1,849). There were 56 PTC-related deaths among the 1,849 patients, representing an overall mortality of 3.0 percent. Among these deaths, 45 cases (80.4 percent) were positive for BRAF V600E. The overall mortality of all PTC cases was 5.3 percent (45/845) in BRAF V600E-positive patients vs. 1.1 percent (11/1,004) in mutation-negative patients.

When the aggressive tumor features of lymph node metastasis, extrathyroidal invasion, and distant metastasis were also included in the model, the association of BRAF V600E with mortality for all PTC was no longer significant, the authors write. "A higher BRAF V600E-associated patient mortality was also observed in several clinicopathological subcategories, but statistical significance was lost with adjustment for patient age, sex, and medical center."

"In summary, in this multicenter study, the presence of the BRAF V600E mutation was significantly associated with increased cancer-related mortality among patients with PTC. However, overall mortality in PTC is low, and the association was not independent of tumor behaviors. Therefore, how to use BRAF V600E for the management of mortality risk among patients with PTC is not clear. These findings support further investigation of the prognostic and therapeutic implications of BRAF V600E status in PTC."

In an accompanying editorial, Anne R. Cappola, M.D., Sc.M., and Susan J. Mandel, M.D., M.P.H., of the University of Pennsylvania, Philadelphia (Dr. Cappola is also Contributing Editor, *JAMA*), write that "these analyses provide 2 important insights."

"First, they suggest that the BRAF V600E mutation mediates features of the clinically aggressive tumors that account for the vast majority of PTC mortality. This provides a strong biological rationale for current trials of targeted tyrosine kinase inhibitor therapy for BRAF V600E-positive PTC patients with advanced disease. At the same time, these study results suggest that BRAF V600E testing does not add predictive value for PTC-related mortality beyond the information collected in the process of PTC tumor staging, including postoperative histopathology reporting and clinical evaluation. This is particularly relevant when considering that 45 percent of all PTC tumors are BRAF V600E-positive, and implies that additional tumor or host genomic factors may influence tumor aggressiveness."

"Although these findings do not support widespread BRAF V600E testing, they do support the need for additional study of how BRAF testing can be used to improve the already excellent prognosis of patients with PTC."

More information: *JAMA*. 2013;309(14):1493-1501
JAMA. 2013;309(14):1529-1530