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The BRAF V600E Mutation Increases Mortality in Papillary Thyroid Cancer

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Xing M, Alzaharani AS, Carson KA, Viola D, Elisei R, Bendlova B, Yip L, Mian C, Vioanello F, Tuttle RM, et al. Association between BRAF V600E mutation and mortality in patients with papillary thyroid cancer. JAMA 2013;309:1493-1501

SUMMARY

Background

Papillary thyroid cancer (PTC) has a very low 5-year mortality, usually in the range of 3 to 5%. The BRAF V600E oncogenic mutation results in a valine to glutamic acid change in codon 600 of the BRAF protein, resulting in constitutive activation of the mitogen-activated protein kinase signaling pathway. This mutation occurs in about 45% of PTC and is more common in conventional PTC than in the follicular variant. The BRAF V600E mutation is associated with more aggressive tumors based on conventional staging and with higher recurrence of PTC as compared with PTC without the mutation (1). The purpose of the present multicenter study was to define the association between the BRAF V600E mutation and PTC-related mortality.

Methods

The retrospective study was conducted at 13 medical centers in 7 countries and included data on 1849 patients. The United States and Italy contributed about two thirds of the patients. Genomic DNA was isolated from the primary tumor and used to analyze the sequence of exon 15 of the BRAF gene for the V600E mutation. This was done after surgical and medical therapy to ensure that mutation status did not influence decisions about therapy. PTC-specific death was defined as death occurring from incurable advanced cancer that compromised vital organs.

Statistical analysis included Kaplan–Meier survival curves and Cox proportional-hazards regression analyses to compare survival in patients based on mutation status. Interactions of mutation status with various clinicopathological factors was calculated. There was no adjustment for multiple comparisons in doing subgroup analyses.

Results

The overall median follow-up time was 33 months after the initial treatment. The prevalence of the mutation was 45.7%. There were 56 PTC-related deaths among the 1849 patients, representing an overall mortality of 3.0%. Eighty percent of those who died had the BR AF mutation, and 5.3% of those with the BRAF mutation died, as compared with only 1.1% of those without the mutation (P<0.001). Rates of deaths per 1000 patient-years in mutation-positive versus mutation-negative patients were 12.9 (95% CI, 9.6 to 17.2) versus 2.5 (95% CI, 1.4 to 4.5).

The age-adjusted hazard ratio (HR) for those with the mutation was 2.66 (95% CI, 1.30 to 5.43). However, when aggressive tumor features of lymph-node metastases, extrathyroidal invasion, and distant metastases were included in the model, the association of the mutation with mortality was no longer statistically significant.

There was a significant positive interaction between the mutation and lymph-node metastases, distant metastases, stage IV disease, or patient age at diagnosis. The increased mortality with age was very evident in those with the mutation as compared without it. However, the association of the mutation

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with mortality was not statistically significant in patients with disease stages I, II, or III. In patients with distant metastases, the presence of the BRAF mutation increased mortality from 1.4% (without mutation) to 51.5% (with mutation).

Conclusions

This retrospective multicenter study shows that the presence of the BRAF V600E mutation was significantly associated with increased cancer-related mortality in patients with PTC.

ANALYSIS AND COMMENTARY

This important study with contributions from many countries provides convincing data to show that the BRAF V600E mutation causes PTC to be so aggressive that it results in mortality. The results also provide confidence in the staging system that uses conventional clinicopathological criteria to predict outcome. This does not detract from the conclusion that having the BRAF mutation makes PTC more aggressive. With time for the disease to develop, those with the mutation are more likely to progress to a worse outcome, previously recognized as recurrence and now shown to result in increased mortality.

Why does this occur? Tumors with the BRAF mutation are more likely to be dedifferentiated and to have lost the expression of the sodium–iodide symporter (NIS) so they do not concentrate radioiodine (1,2). The paper by Ho et al (reviewed in the April 2013 issue of Clinical Thyroidology, p. 76) shows that therapy that can induce reexpression of NIS usually fails in patients with this mutation (3). In addition, the BRAF mutation up-regulates various tumor-promoting molecules (1).

Should BRAF mutation status be included in assessing the risk of recurrence and mortality of thyroid cancer? The present study argues in favor of including this mutation as a predictor of mortality in high-risk patients based on conventional staging, but not in low-risk patients. In regard to recurrence, BRAF mutation status had an additional effect in predicting recurrence when added to conventional staging systems, including TNM, Ames, and Macis (4). The current study relating the BRAF V600E mutation to mortality as well as data showing that these tumors are more likely to recur provide a basis for using more aggressive treatment and surveillance in patients with this mutation.

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