Commentary

Targeting B-Raf kinase for thyroid cancer treatment: promise and challenge

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Thyroid cancer is the most common endocrine malignancy (1). The incidence of thyroid cancer has been steadily increasing in the past four decades, primarily due to the use of more sensitive diagnostic tools. Other factors such as increased obesity rates may play a role (2-4). Approximately 64,300 patients were newly diagnosed with thyroid cancer in the United States of America in 2015 but only 1,980 deaths were reported. Thyroid cancers are divided into several pathological categories, including well differentiated papillary thyroid carcinomas (PTC), follicular thyroid carcinomas (FTC), medullary thyroid carcinomas (MTC), Hürthle cell carcinomas (HTC), and poorly differentiated or anaplastic thyroid carcinomas (ATC). PTC accounts for 80% to 90% of all thyroid cancers (1). *BRAF V600E* mutation occurs approximately in 40% to 60% of PTC, up to 80% of recurrent PTC, and 25% of ATC (5). *BRAF* mutation is associated with more aggressive clinicopathologic characteristics, including increased rate of local invasion and distal metastasis, advanced stage at diagnosis, decreased radioiodine uptake, and increased mortality (5). While most PTC patients can be cured by surgery, suppression of thyroid stimulating hormone, and radioiodine, 15–20% of patients develop recurrent and metastatic disease. Recurrent thyroid cancer tends to be refractory to radioactive iodine therapy. Patients with a recurrent disease have an overall 10-year survival of approximately 10% to 20% (6).

Doxorubicin, the only chemotherapy approved by the Food and Drug Administration (FDA) for treating metastatic and refractory differentiated thyroid cancer, has a low efficacy largely due to its low response rate (1). Sorafenib, a non-specific vascular endothelial growth factor (VEGF) receptor (VEGFR) and Raf multikinase inhibitor, yields a median progression-free survival duration of 10.8 months in advanced disease versus placebo group (5.8 months) (6). The partial response rate in the sorafenib and placebo-treated groups are 12.2% and 0.5%, respectively, but 42% of patients have stable disease for at least 6 months (6). Sorafenib exerts its antitumor effect largely by inhibiting VEGFR tyrosine kinase activity since thyroid cancers with or without *BRAF* mutations respond almost equally well to sorafenib. In addition, sorafenib lacks efficacy in treating *BRAF*-mutated melanomas (6).

Vemurafenib and dabrafenib, two US FDA-approved mutant B-Raf kinase-specific inhibitors, exhibited superior efficacy in treating *BRAF*-mutated melanoma but have marginal or no effect in *BRAF*-mutated colorectal cancer (7). Unfortunately, melanomas develop drug resistance approximately after 6-month of treatment (8), due to *NRAS* and *MEK* mutations, activation of upstream growth receptor tyrosine kinases, splicing variants of *BRAF V600E* gene etc. (6,9). Studies by Montero-Conde and colleagues (10) revealed that thyroid cancer cell lines develop drug resistance to vemurafenib by up-regulating HER3 expression and by increasing the secretion of its ligand, neuregulin-1 (NRG1). Vemurafenib in combination with trametinib, a MEK inhibitor, overcomes drug resistance to vemurafenib and achieves a better therapeutic outcome (10). Numerous phase 1 clinical trials targeting B-Raf kinase for treating *BRAF*-mutated thyroid cancer are under the way (6). Its efficacy, adverse effects, and drug resistance *in vivo* remain to be fully investigated (6,11,12).

Brose and colleagues (13) recently reported the outcome of an open-label, non-randomized, phase 2 clinical trial of vemurafenib in 51 patients with *BRAF*-mutated differentiated thyroid cancer. All patients had recurrent or metastatic papillary thyroid cancers that were refractory to radioiodine therapy. Among them, 26 patients had never received sorafenib (cohort 1), whereas 25 had previously received it (cohort 2). The dose of vemurafenib was 960 mg, twice a day, orally. The median duration of treatment in cohort 1 was 63.6 weeks. Ten of 26 patients (38.5%) achieved a partial response, 9 of 26 patients achieved stable disease for at least 6 months. After a median follow-up of 18.8 months, 13 of 26 patients had a progression-free event. The median progression-free survival in cohort 1 was 18.2 months, whereas the median duration of response was 16.5 months. In cohort 2, the median duration of treatment was much shorter (27.6 weeks) than that in cohort 1. Six of 22 patients (27.3%) (3 patients were excluded from the study for various reasons), achieved a partial response, and 6 other patients had stable disease for at least 6 months. After a median follow-up of 12 months, 12 of 22 patients had died. The median progression-free survival in cohort 2 was 7.4 months, whereas the median duration of response was 14.4 months.

This is the first prospective phase 2 trial aimed at using vemurafenib to target mutant B-Raf kinase for thyroid cancer treatment. Compared to several phase 1 trials reported earlier (6,11,12), this phase 2 trial enrolled a relatively large number of patients, 51. The trial has several important findings. First, cohort 1 patients treated with vemurafenib achieved the best overall response (38.5%) and progression-free survival (18.2 months). This efficacy is comparable to that of other kinase inhibitors (vandetanib, sorafenib, motesanib, axitinib, pazopanib, cabozantinib, and lenvatinib) whose response rates range from 8–65% and progression-free survival (9.2–18.7 months) in phase 2 and phase 3 trials (6). Since patients' characteristics and enrollment cross studies are different, the direct comparisons cannot be made. However, considering that thyroid cancer with *BRAF* gene mutations tends to be more aggressive, and that patients with *BRAF*-mutated thyroid cancer are older and generally have a poorer prognosis than those without *BRAF* mutations, the response rate and progression-free survival achieved by vemurafenib are remarkable. It will be interesting to know if the overall survival in patients treated with vemurafenib will be comparable or superior to those treated with clinically approved multikinase inhibitors. The second highlight from this clinical trial is that in cohort 2 patients, vemurafenib achieved a response rate of 27.3 [95 confidence interval (CI), 10.7–50.2] and median progression-free survival of 8.9 months (95% CI, 5.5–NE), which are comparable to other kinase inhibitors previously studied in phase 2 and phase 3 trials. It should be noted that patients in cohort 2 had been heavily treated with other agents before being treated with a multikinase VEGFR inhibitor, and that these patients had exhausted all treatment options.

Brose *et al*. (13) note a couple of limitations in their trial. The number of participants enrolled in their study is relatively small. There is no direct historical comparison of overall survival for patients treated with vemurafenib. Regardless, this clinical trial has important clinical implications: (I) the therapeutic outcome in this phase 2 trial is very promising. Unlike BRAF-mutated colorectal cancer which has a dismal response rate to vemurafenib, BRAF-mutated thyroid cancer responded modestly to vemurafenib; (II) if the therapeutic outcome in this phase 2 trial can be confirmed in future phase 3 trials, vemurafenib will offer a new therapeutic option for patients with refractory thyroid cancer, in particular for those who have exhausted all treatment options including the multikinase VEGFR inhibitor; (III) *BRAF*-mutated thyroid cancer can be potentially treated with a B-Raf inhibitor plus a MEK kinase inhibitor to achieve a better therapeutic outcome. An ongoing clinical trial is testing the efficacy of dabrafenib in combination with trametinib for treating patients with recurrent thyroid cancer (6); (IV) a recent *in vitro* study revealed that insensitivity of BRAF-mutated thyroid cancer cell lines to vemurafenib is largely due to the relief of suppression of HER3 expression and increased secretion of the ligand, NRG (10). Vemurafenib in combination with HER3 inhibitors such as lapatinib achieved a synergistic effect in suppressing thyroid tumor growth in a xenograft model (10). An ongoing clinical trial is testing the synergistic effect of dabrafenib in combination with lapatinib for treating refractory thyroid cancer (6); (V) inhibition of B-Raf kinase activity leads to the re-differentiation of thyroid cancer and increased iodine uptake in a *BRAF*-mutated mouse thyroid cancer model (14). Vemurafenib may enhance radioiodine incorporation into *BRAF*-mutated refractory thyroid cancer; (VI) terminal reverse transcriptase (*TERT*) mutation is associated with *BRAF* mutation in PTC (15,16). Thyroid cancer patients with double mutations of *BRAF* and *TERT* have a worse prognosis than those with a single mutation (15,16). Patients with *BRAF*-mutated thyroid cancer can be stratified

into the *TERT* wild-type and mutant groups to determine if *TERT* mutation will confer a poor response to vemurafenib.

While the results from vemurafenib trial are encouraging (13), there are several challenges in applying vemurafenib to successfully treat thyroid cancer: (I) the mechanisms of drug resistance to vemurafenib in patients have not been investigated (13). Whether thyroid cancer confers drug resistance via HER3 up-regulation and increased NRG1 secretion is not known. Whether chronic use of vemurafenib acquires drug resistance by *KRAS G12D* activating mutation (17), HER3 amplification (18) or c-Met reactivation (19) is also not known; (II) ATC represents the most difficulty cancer to be treated. Current trials of Raf kinase inhibitors did not include patients with *BRAF*-mutated ATC (13); (III) thyroid cancer patients treated with vemurafenib develop adverse effects similar to those that occurred in melanoma patients (13). These side effects include dermatologic (keratosis-pilaris-like eruptions, panniculitides, and photosensitization), neoplastic (actinic and verrucous keratoses and squamous cell carcinoma), gastrointestinal (nausea, dysgeusia, anorexia, and diarrhea), constitutional (arthralgias, headache, fatigue, and fever), and hematologic (anemia) effects (13). These adverse effects need to be monitored closely by multidisciplinary expertise.

Overall, data from this first phase 2 clinical trial (13) suggest that targeting mutant B-Raf kinase with vermurafenib to treat refractory thyroid cancer is feasible. Unlike *BRAF*-mutated colorectal cancer (20), *BRAF*-mutated thyroid cancer responds modestly to vemurafenib but is less sensitive than *BRAF*-mutated melanomas (8). Further investigation in double-blinded, randomized clinical trials is warranted to compare the efficacy of B-Raf kinase inhibitors and to evaluate the synergistic effect of a B-Raf kinase inhibitor in combination with a MEK or HER3 inhibitor or with radioactive iodine. Future clinical trials should also include patients with poorly differentiated PTC or ATC. The mechanisms of *in vivo* drug resistance and the loss of sensitivity to vemurafenib should also be studied.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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