Editorial

Emerging multikinase inhibitors for the treatment of differentiated thyroid cancer: whom to treat?

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Thyroid cancer (TC) is the most common endocrine malignancy, showing a rapid growth in its incidence during recent years. In 2013 the predicted number of all people with TC living in the USA was nearly 637,000, whereas estimated number of new cases diagnosed in 2016 is about 64,300. TC accounts for ~3.8% of all new cancer cases, but—due to a generally good prognosis—in 2016 this disease will count for no more than 2000 deaths (0.3% of all cancer mortality) (1).

Differentiated thyroid cancer (DTC) arising from the follicular cell represents the vast majority (>90%) of all TCs. Its most common type, papillary thyroid cancer (PTC) is diagnosed in more than 80% of DTC patients (2).

Is it justified to address clinical trials to DTC population instead of PTC patients? The term DTC is used in common by clinicians since the clinical course of PTC and follicular thyroid carcinoma (FTC) is similar; similar are also the treatment modalities. However, we have to be aware that PTC and FTC differ significantly, considering their molecular biology. BRAF mutation is present exclusively in PTC while being absent in FTC. Thus, selecting the patients based on the presence of $BRAF^{V600E}$ mutation as an indication for the therapy creates a unique cohort of patients, restricted solely to PTC. With some exceptions this approach definitely differs from the trials previously run in DTC, and the selection of patients by the potentially predictive factor—BRAF mutation—might be a reason for an increased drug efficacy in PTC population.

Management of DTC. DTC, particularly PTC is characterized by a very good prognosis with a 10-year survival rate of 93% (2). However, approximately 3–15% of DTC patients demonstrate disseminated disease at its onset or—in up to 30% of cases—DTC recurrence during the further follow-up (3).

Surgery and/or radioiodine (RAI) therapy are considered as the first-line approach for locally advanced and metastatic DTC (4) because in the majority of patients the ability of RAI uptake in cancer foci is preserved (5). Nevertheless, one-third of patients show RAI refractoriness, which is defined by the presence of one of the following conditions: (I) no RAI uptake in cancer foci at the time of initial treatment; (II) loss of the ability of RAI uptake by the tumor previously RAI-avid; (III) the presence of RAI uptake in some DTC lesions but not in all; (IV) progression of DTC RAI-avid lesions. The other commonly used criterion based on the administered cumulative RAI activity (usually 600 mCi, which does not result in DTC cure) is questionable (6). RAI refractoriness is related to much worse disease outcomes with the overall survival rates about 10% at 10 years and 6% at 15 years (5).

Until recently, systemic therapeutic options in DTC were confined to ineffective chemotherapy and local modalities. New treatment options have come along the discovery of a key role of tyrosine kinases in TC pathogenesis. Multikinase inhibitors (MKIs) block distinct growth factor receptors on cellular surface what results in the inhibition of tumor cells growth and divisions. To date two MKIs have proved their activity against RAI-refractory DTC in randomized, placebo-controlled phase III studies: sorafenib and lenvatinib. These drugs inhibit different

vascular endothelial growth factor receptors (VEGFR). Additionally, sorafenib acts against *V-raf murine sarcoma viral oncogene homolog B1* (*BRAF*), both wild type and mutant $BRAF^{V600E}$ and against RET proto-oncogene, whereas lenvatinib targets fibroblast growth factor receptors (FGFR) type 1-4 and platelet-derived growth factor receptor β (PDGFR-β) (7,8). Recently vemurafenib, a mutated BRAF-kinase specific inhibitor has been introduced as a potential drug in BRAF-positive PTCs (9). Vemurafenib (previously known as PLX4032 or RG7204) is a potent kinase inhibitor that selectively blocks mutated $BRAF^{V600E}$ and V-raf-1 murine leucemia viral oncogene homolog 1 (CRAF), whereas its potency against wild type BRAF kinase is substantially lower.

The clinical application of this molecule was initiated by melanoma trials, and taking into account its beneficial effect of progression free survival (PFS) and overall survival (OS) the drug has been approved into a routine clinical use. Vemurafenib in comparison to chemotherapy (dacarbazine) significantly reduced the risk of death and disease progression in patients with $BRAF^{V600E}$-positive melanoma (10). At the extended analysis the median OS and PFS achieved in vemurafenib and dacarbazine arms were 13.6 *vs*. 9.7 months and 6.9 *vs*. 1.6 months, respectively. In contrary to melanoma population, vemurafenib showed a very limited effect in $BRAF^{V600E}$-positive metastatic colorectal cancer patients with a response rate of 5% (11).

The role of BRAF mutation in PTC. The RAF proteins are cytoplasmic serine/threonine protein kinases. They represent downstream effector molecules of RAS in the mitogen-activated protein kinase (MAPK) signaling pathway. BRAF plays an important role in the development of different neoplasms, including TC, melanoma and colorectal cancer (12). Kinase activating point mutation in the *BRAF* proto-oncogene, leading to its RAS-independent activation, is the most common molecular event in PTC, as it occurs in 35% to 70% of PTCs (12). In the recurrent or metastatic form of PTC the frequency of BRAF mutation rises even up to 80% (13). A single amino acid substitution at codon 600 from valine to glutamic acid (V600E) constitutes ~90% of all BRAF mutations in PTC (14). Some studies showed the association between the $BRAF^{V600E}$ mutation and aggressive pathological features, RAI refractoriness or poor outcomes. Xing *et al*. proved a significant negative impact of mutated BRAF on PTC mortality. The overall mortality in BRAF-positive and BRAF-negative patients was 5.3% and 1.1%, respectively (15). However, although considerably different, these rates were rather low. Similarly, the risk of PTC recurrence was significantly higher in BRAF-positive subjects than in BRAF-negative group, even after adjustment for patient age, sex, tumor size, extrathyroidal invasion, lymph node metastasis, multifocality and PTC subtype (16). Noteworthy, the presence of BRAF mutation was also reported in poorly differentiated thyroid carcinoma (PDTC) and anaplastic thyroid cancer, with significant clinical implications (17). Additionally, $BRAF^{V600E}$ mutation was also linked to VEGF overexpression, with potentially important role in aggravating of the tumor invasiveness (18). Lankenau *et al*. showed BRAF mutations in PTC and melanoma drove an increase in expression of microRNA-3151 (miR-3151). The authors demonstrated that miR-3151 directly targeted TP53 and other members of TP53 pathway. A reduction in miR3151 expression led to an increase in TP53's RNA and protein expression. Thus, knockdown of miR3151 also resulted in caspase-3-dependent apoptosis. Simultaneous inhibition of activated, mutated BRAF and knockdown miR3151 increased the effect of sole BRAF inhibition with vemurafenib, what indicated a novel therapeutic possibility in PTC patients (19).

Recent TCGA study reported the differences in genomic, epigenomic, and proteomic profile between *BRAF*-like (consisted mostly of $BRAF^{V600E}$- positive cases) and *RAS*-like PTCs, what suggested the need to reclassify TCs into molecular subtypes. The authors indicated also that the heterogeneous nature of the BRAF-like PTC set may be reflected in the clinical course of these tumors, problems with treatment and strengthened the need of searching co-morbid molecular events (20). This heterogeneity was confirmed in analysis of miRs expression as well, which gave six molecular PTC subtypes. The authors focused on two oncomiRs (miR-21 and miR-146b) and one suppressor miR (miR-204), since these were epigenetically regulated and correlated with the BRAF-like/Ras-like score (BRS) and thyroid differentiation score (TDS). However, in this study there was no mention about the miR3151, originally identified in melanoma samples, probably due to the fact that in the TCGA study only PTCs with good prognosis were analyzed.

The use of selective BRAF inhibitor in BRAF positive PTC. The encouraging experiences with vemurafenib in TC came from first-in-human phase one study, which involved among others 3 patients with metastatic, $BRAF^{V600E}$-positive PTC. Two of them achieved PTC stabilization as the best response and one—partial response (21). Another paper reported an extended antitumor response in 73-year old

female with RAI-refractory PTC harboring the $BRAF^{V600E}$ mutation in a metastatic lymph node (22). The outcomes of the off-label use of vemurafenib in 17 patients with advanced, $BRAF^{V600E}$-positive PTC patients were published in 2015. The durable response rate was obtained in 67% of patients. Noteworthy, four patients who progressed on prior MKI, responded to vemurafenib. Surprisingly, there was no information if these patients were RAI-refractory or not. Furthermore, there is no data whether these patients received any therapeutic RAI activity at any time (23). There was also an attempt with the first-line vemurafenib to enable thyroidectomy and RAI treatment in a patient with bulky metastatic PTC. The administration of the drug led to a 42% reduction in the volume of pulmonary metastases and made thyroidectomy possible.

Recently, Brose *et al*. have presented the results of the first prospective, phase 2, multicenter, non-randomized, open-label study evaluating the efficacy and safety of vemurafenib in RAI-refractory, $BRAF^{V600E}$-positive PTC (9). The study enrolled 51 patients stratified into two cohorts: cohort 1 involved 26 patients without previous administration of any VEGFR-inhibitor and cohort 2 comprised of 25 patients who received before at least one VEGFR inhibitor. Patients, who were previously given specific BRAF or MEK inhibitor, were excluded from the study. Interestingly, the use of non-specific BRAF inhibitors (sorafenib) was allowed.

To identify the $BRAF^{V600E}$ mutation the most recent tumor sample obtained from the patient was tested. However, the authors did not provide any information regarding the number of patients in whom the $BRAF^{V600E}$ mutation was confirmed in primary or metastatic tumor. Furthermore, we do not have any information whether the analyzed PTCs were multifocal or not, what, as reported in several studies, may have impact on the presence or absence of BRAF mutation in metastases since particular foci may represent multiple synchronous primary tumors (MSPTs) and display heterogeneous molecular background. This fact together with the intratumoral heterogeneity does not justify an assumption of the lack of mutation in the primary foci, when it was not found in metastatic tumor. On the other hand, it was observed that $BRAF^{V600E}$ mutation may arise *de novo* in lymph node-metastasized PTC and in recurrent metastasis, while it was absent in a primary tumor (22,23). It suggests that BRAF status should be reassessed in the metastasis before the application of appropriate therapy.

Partial response was achieved in 38.5% and in 27.3% of patients from cohort 1 and 2, respectively. Disease stabilization for at least 6 month was obtained in 35% of patients from cohort 1 and 27.3 % of patients from cohort 2. Thus, the administration of vemurafenib resulted in PTC control in 73.5% and 54.6% from cohort 1 and, 2 respectively. While, progressive disease was noted in 3.8% of patients from cohort 1 and in 4.5% of patients from cohort 2. In cohort 1 the median treatment duration was 63.6 weeks, median duration of response—16.5 months, median progression free survival—18.2 months, whereas median OS was not yet reached. In cohort 2, these values were respectively 27.6 weeks, 7.4, 8.9 and 14.4 months. At the time of analysis 8% of patients from cohort 1 and 32% of patients from cohort 2 died due to PTC progression. According to the authors, although a direct comparison was not possible due to different patient populations, the treatment outcomes noticed in patients from cohort 1 were similar to these obtained in clinical trials with other MKIs.

The authors did not analyze the reasons leading to differences in the response to vemurafenib. There was also no information whether they were statistically significant or not. The starting dose of vemurafenib was 960 mg twice a day in all but one patient from the whole study group, whereas the median cumulative dose was 619.3 g in cohort 1 and 293.8 g in cohort 2. This disparity could result from distinct treatment duration in both cohorts and finally could result in worse outcomes in cohort 2 in comparison to cohort 1. It is however unclear, why median treatment duration in cohort 2 was shorter, especially when the number of dose reductions and interruptions seemed to be similar in both cohorts. It was probably related to statistical assumptions, because cohort 2 used a two-stage design: first 15 patients were involved. Next, after confirming the drug activity in at least 13% of subjects, the study group was extended up to 25 patients (9).

Interestingly, considering sorafenib—a non-selective BRAF inhibitor, there were no significant differences in treatment outcomes regarding BRAF status (BRAF positive versus BRAF wild type) in DTC patients treated under DECISION trial (7). It is surprising that the authors of vemurafenib clinical trial, discussing their findings, did not address this issue.

Frequently observed vemurafenib-related adverse effects (AE) included rash, fatigue, alopecia, weight loss, dysgeusia, arthralgia, decreased appetite, nausea, diarrhea and skin papilloma. Most of them were manageable by concomitant medications or dose modifications (9). This toxicity profile was concordant with that reported by other studies carried

out in PTC and melanoma (10,21-24). The most common vemurafenib-related side effects were dermatologic AE, among them non-neoplastic events (keratosis piliaris-like eruptions, hair follicle changes, hand-foot skin reaction, neutrophilic dermatoses, neutrophilic panniculitis, photosensitivity, radiation recall dermatitis, vitiligo or sarcoidosis) and neoplastic diseases [actinic keratosis, verrucous keratosis or skin squamous cell carcinoma (SCC) or even new primary melanoma]. Another common AEs comprised gastrointestinal disturbances (nausea, dysgeusia, anorexia, diarrhea) and constitutional disturbances (arthralgia, headache, fatigue). The development of secondary non-cutaneous SCC or leukemia may constitute a rare vemurafenib-related complication (24).

There are other important questions related to this paper that should be answered:

Does BRAF really constitute an appropriate molecular target in DTC considering:

- The lack of BRAF mutation in FTC—an important component of DTC;
- PTC heterogeneity;
- The results of Brose study (9) with no impact of the presence of BRAF mutation on treatment outcomes in patients, who were given sorafenib—a non-selective BRAF inhibitor?
- We do not understand why vemurafenib is ineffective in BRAF-positive colorectal cancer.

Conclusions

The results of a phase 2 study with vemurafenib, published by Brose *et al*., demonstrated its efficacy and acceptable toxicity profile in patients with RAI-refractory, $BRAF^{V600E}$ positive, unresectable or metastatic PTC. The drug may constitute an additional therapeutic option, both first and second line in this group of patients. However its impact on PFS and OS needs to be confirmed in a randomized, placebo-controlled phase 3 trial.

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Footnote

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