

Thyroid Cancer and Current Therapeutic Approaches

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Thyroid cancer is the most common endocrine malignancy. Most thyroid cancers originate from thyroid follicular cells [1]. There are four histological types of thyroid cancer papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), poorly differentiated thyroid cancer and anaplastic thyroid carcinoma (ATC). Papillary thyroid cancer (PTC) accounts for more than 85% to 90% of all thyroid malignancies. In particular, PTC and FTC are considered as differentiated thyroid cancer (DTC) and the current treatment for DTC remains surgical intervention, with in some cases adjuvant radioactive iodine therapy (RAI). Importantly, recurrent and RAI refractory DTC, poorly differentiated thyroid carcinoma and ATC are very aggressive [2,3]. The recent advances in the understanding of molecular pathogenesis of thyroid cancer have significantly improved the treatment strategies and the clinical management of patients with aggressive thyroid cancer.

Primarily, constitutive activation of mitogen activated protein kinase (MAPK) pathway has been shown to be involved in thyroid cancer initiation. This can be due to the alteration in the expression or activity of the receptors tyrosine kinases, Ras or Raf [4-6]. About 40-80% of PTC and 40% of ATC harbor BRAFV600E mutations that leads to a constitutive activation of BRAF, dysregulation of the MAPK pathways, thus inducing cell growth and promoting survival of cancer cells [7]. Therefore, several tyrosine kinase inhibitors (TKI) including sorafenib, vemurafenib and selumetinib targeting the MAPK pathway are currently under clinical trials in the past decades.

Sorafenib, a kinase inhibitor of VEGFR, PDGFR, RET and RAF has shown significantly improved progression free survival in a phase III clinical trial in a cohort of patients with RAI refractory locally advanced or metastatic differentiated thyroid cancer in both RAS and BRAFV600E groups. [8]. Another tyrosine kinase inhibitor, Lenvatinib targeting VEGFR, FGFR, PDGFR- β , RET and KIT demonstrated anti-tumor activity primarily mediated by inhibition of angiogenesis in preclinical studies of thyroid cancer models [9,10]. The encouraging preclinical and Phase II clinical data has led to a randomized phase III clinical trial in a large cohort of patients with progressive and RAI refractory thyroid cancer that were randomly assigned to receive lenvatinib or placebo. This study showed that lenvatinib treatment was associated with prolonged progression survival (14.7 months longer) compared to placebo arm [11]. Furthermore, lenvatinib treatment was also effective in patients who received one prior treatment of tyrosine kinase inhibitors. Thus, suggesting that lenvatinib is also beneficial for patients with RAI refractory tumors as a second line of treatment. The improvement of PFS observed with lenvatinib was greater than the one observed with other tyrosine kinase inhibitors such as axitinib, sorafenib and sunitinib [8,12,13]. Lenvatinib administration was beneficial in all histological types of differentiated thyroid cancer regardless of their mutation status.

On the other hand, vemurafenib (PLX4032) is a specific BRAFV600E kinase inhibitor. A phase I clinical trial in a very small cohort of patients with advanced PTC harboring BRAFV600E mutation showed partial response in one patient and stable disease in the others [14]. Subsequent phase II clinical trials in patients with BRAFV600E positive metastatic or unresectable radioiodine refractory papillary thyroid cancer showed a partial response in 38.5% of the patients who have never received TKI treatment before, with a median progression

-free survival of 18 months. However, the group of patients who have been previously treated with other TKI, the vemurafenib showed a best overall response of 27% and a median progression-free survival of 8.9 months only. These data highlight the clinical utility of BRAFV600E genetic testing and suggest the vemurafenib as a treatment option for patients with BRAFV600E metastatic and RAI refractory thyroid tumors even in the group of patients who have previously been treated with TKI.

Preclinical studies have demonstrated that inhibition of the downstream targets of BRAF restores I131 uptake in RAI refractory thyroid cancer mouse model [15]. A pilot clinical study performed in a small cohort of patients with RAI refractory thyroid cancer showed that the selumetinib treatment increased the radioiodine uptake in 60% of the cases. In all patients, reduction of the tumor size of the target lesion after RAI treatment was observed. The therapeutic benefit of selumetinib was more pronounced in NRAS mutated tumors compared to BRAF mutated cases [16]. Recent studies suggest that RAF and MEK inhibitors are not effective in BRAFV600E mutated tumors due to a MAPK rebound effect [17,18]. Preclinical data, suggested that combination treatment of Selumetinib with another MEK inhibitor, CKI enhances RAI uptake in BRAFV600E PTC mouse model [19]. Combination of two MAPK inhibitors might improve outcome of patients with BRAFV600E positive tumors.

Neovascularization in cancer is mediated by the VEGFs and their receptors (VEGFRs). Increased expression of VEGF in thyroid cancer has been associated with an increase in tumor size, local and distant metastasis, and poor prognosis [20-22]. Emerging studies suggested high efficacy of VEGF-targeted therapies. The multi-kinase inhibitor Pazopanib that targets VEGFR and PDGFR was investigated in metastatic RAI- refractory thyroid tumors in a phase II clinical trial and showed in 81% a median overall survival at 1 year. Furthermore, and the median of progression free survival was 11.7 months and tumor size decreased in most patients [23].

ATC is often advanced and metastatic at diagnosis with median survival less than a year and no targeted therapy has proven benefit in clinical trials with lack of cytotoxic effect and survival advantage. The genetic complexity of ATC has made the discovery of effective agents very challenging. Several preclinical studies suggest that targeted therapy need to be investigated in combination rather than single agent in ATC. In fact, combination of BRAFV600E specific inhibitor (PLX4720) with dasatinib has shown a significant tumor reduction

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in preclinical mouse model of ATC [24] and the HDAC inhibitor valproic acid significantly increased the anti-proliferative effects of doxorubicin [25]. The proteasome inhibitor Carfilzomib enhances the cytotoxic activity of CUDC 101, a dual inhibitor of EGFR and HDAC [26]. Moreover, HDAC inhibitor and PARP inhibitor in combination inhibits ATC cell proliferation [27]. A pilot clinical study suggests that Pazopanib in combination Paclitaxel is a promising therapeutic strategy in ATC [28].

Although these studies have shown very encouraging results in DTC, several adverse effects (stage III and IV) have been reported with these anti-neoplastic agents, leading to a dose reduction or exclusion of patients from clinical trials. The most common side-effects reported were skin rashes, hypertension and cardiomyopathy. As shown in some preclinical studies and mentioned above, combination therapy of these drugs over monotherapy leads to promising results. Therefore, further studies investigating the side effects of the drugs in combination and the mechanism of resistance developed by the tumors and markers of response to the treatment are highly needed.

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