Review Article

# Target-based therapies in thyroid cancer

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**Poor prognosis of thyroid cancer and advanced disease together with the absence of effective therapeutic measures has induced recent intensified basic and clinical research in this area. Complete total thyroidectomy is the treatment of choice for PTC, FTC, and MTC. Radioiodine is routinely recommended in high-risk patients and considered in intermediate risk DTC patients. Patients with unresectable or metastatic thyroid cancer are candidates for systemic treatment with targeted therapeutics. Several genetic alterations in different molecular pathways in TC have been shown in the past few decades, associated with TC development and progression. Rearranged during transfection (RET)/ PTC gene rearrangements, RET mutations, BRAF mutations, RAS mutations, and vascular endothelial growth factor receptor 2 angiogenesis pathways are some of the known pathways determinants in the development of TC. Tyrosine kinase inhibitors (TKIs) are emerging as new therapies of aggressive TC, including DTC, MTC, and anaplastic thyroid cancer, is capable of inducing clinical responses and stabilization of disease. These drugs prolong median progression-free survival, but until now no significant increase has been observed on overall survival; side effects are common. New efforts are made to find new more effective and safe compounds and to personalize the therapy in each TC patient. Targeted novel compounds have been demonstrated to induce clinical responses and stabilization of disease.**

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Thyroid cancer is the most common endocrine malignancy with increasing incidence in females than males[1]. More than 90% of differentiated thyroid carcinomas (DTC) arise from follicular cells. According to their histopathological criteria, DTC is classified as papillary (PTC), follicular (FTC) and medullary (MTC)[2]. In the last decades, PTC has shown an increasing spike in all thyroid cancers (TC).

Ultrasonography and fine needle aspiration (FNA) of thyroid nodules remain the main diagnostic criteria for the diagnosis of small thyroid cancers (TCs). The main stimulus for thyroid cancer includes ionizing radiations, exposure to nuclear explosions, low doses of radiation exposure and the exposure to iodine-deficient areas. Furthermore, autoimmune thyroiditis has been implicated to be a risk factor for PTC[3-10].

Complete total thyroidectomy is the first choice for management of PTC and FTC[11]. Radioactive iodine (I131) should be routinely used in intermediate and high-risk patients[12]. After surgery, and eventually RAI, patients should be scanned for neck ultrasonography and also measure thyroid-stimulating hormone (TSH)-stimulated thyroglobulin (Tg) for further management of the patients[13].

- **The newer targeted medical therapies addressed the issue of resistance and mutations beyond the conventional treatment for advanced thyroid cancer.**
- **Modern targeted therapies (eg, TKIs) evolved from an understanding of cellular signalling pathways, angiogenesis, cellular division, and epigenetic events in thyroid cancer.**
- **Further research is needed for ideal targeted therapy owing to better survival and quality of life.**

As the tumour progresses, the thyroid cells find difficulty to maintain the functional integrity of the cells like loss of iodide uptake ability hence cancer becomes resistant to the present pharmacotherapeutic strategies, and thus prognosis looks grim[4]. In a cancer cell, certain molecular rearrangement happens which leads to resistant to traditional drugs. Thus these changes are supposed to be the new targets for thyroid cancer. The most probable targets are RET/PTC rearrangements, RAS and BRAF mutations and ß-catenin mutations which leads to loss of iodide uptake ability[15].

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## Pathways and its targets in Thyroid Cancer

### Rearranged during Transfection (RET) Pathway

RET gets activated during rearrangements during transfection and mutations in various cancers[16]. Nearly half of adult PTC, RET/PTC rearrangements are present; most commonly RET/PTC1 and RET/PTC3[17]. It has been hypothesized that RET/PTC are determinant for tumor initiation[18]. CLM3, [(R)-1-phenethyl-N-(1-phenylethyl)-1H pyrazolo[3,4-d]pyrimidin-4-amine] and CLM29 (pyrazolo[3,4-d]pyrimidine) are the two molecules which has potential to inhibit RET pathway. It also has inhibiting effects on BRAF, VEGFR-2 and EGFR thus exert antiangiogenic activity. CLM3 showed antiproliferative, proapoptotic and inhibition of migration and the neoplastic neovascularization[19,20]. Other pyrazolo[3,4-d]pyrimidines] such as PP1, PP2, and Si34, have been studied in TC and showed important inhibitory effect on RET kinase and thus reduce RET/PTC mediated MAPK signaling and thus inhibit the proliferation of thyroid carcinoma cells[21].

### Raf Kinase Pathway :

RAS mutations are present in more in FTCs than PTCs. Its mutations represent more aggressive thyroid cancer[22]. BRAF mutation is associated loss of differentiation and decreased metabolizing capacity of iodide and NIS genes[23]. NIS expression repression is due to TGF-Beta secretion by BRAF V600E oncogene that may further increase malignancy in TC[24]. Sorafenib is multi-targeted tyrosine kinase inhibitors (TKI), that also has inhibitory activity against VEGFR-2 and 3, c-Kit, PDGFR, RET/ PTC, Raf kinases and the Raf/Mek/Erk pathway (MAPK pathway). A multicenter (DECISION trial), double-blind randomized phase III study, showed that sorafenib showed significantly improved in the patients administered with sorafenib (10.8 months) with median progression-free survival (PFS) as compared with placebo (5.8 months), and it got better in all prespecified clinical and genetic biomarker subgroups[25,26].

### Vascular Endothelial Growth Factor (VEGF) Pathway :

Aggressive TC behaviour correlates more with increased angiogenesis, and the expression of angiogenesis inhibitors or stimulators [like VEGF/VEGF receptor (VEGFR), epidermal growth factor (EGF)/EGFR, platelet-derived growth factor (PDGF)/ PDGFR, etc][27]. VEGF is an expression in DTC is associated with neoplastic progression and aggressiveness. Its increased aggressiveness, growth and distant spread is due to its characteristics features that mediate endothelial cell adhesion and migration on extracellular matrix[28]. Vandetanib (an orally active TKI) is a good inhibitory activity of VEGFR-2, but can also target VEGFR-3, EGFR, and RET kinases[29]. Vandetanib prolonged PFS as compared to placebo. It was approved in April 2011 by FDA, being the first TKI able to treat adult patients with aggressive MTC[30]. Another molecule is Motesanib diphosphate, an ATP-competitive inhibitor of VEGFR-1, -2, and -3, PDGFR, and Kit, administered orally 125 mg/day in patients with metastatic or advanced TC which is currently in various phases of clinical trials with promising results[31].

The second-generation inhibitor is axitinib (AG-013736) which inhibit PDGFR and Kit in cell-based assays better than more than other VEGF-TKIs[32,33]. It is also in phase II trial showing promising results in metastatic or locally advanced MTC or DTC[34]. Another multitargeted TKI sunitinib (SU011248) is a selective inhibitor of VEGFR-1, -2, and -3, PDGFR, c-KIT, and RET/PTC subtypes 1 and 3[35]. It inhibits the growth of TPC1 cells that have a RET/PTC rearrangement.45 It is currently in phase 2 clinical trials[36].

Cabozantinib (XL184) is an oral multiple receptor kinase inhibitor that inhibits VEGFR-1 and -2, C-MET, RET, c-Kit, FLT3, and Tie-2.37 FDA approved cabozantinib for MTC treatment[37].

Paclitaxel (a microtubule inhibitor) is tried in combination with pazopanib due to their synergistic antitumor activity in ATC cells. The combination of pazopanib/ paclitaxel showed a lasting effect in a patient with metastatic ATC[38]. Lenvatinib (E7080) is another oral, multitargeted TKI[39]. It is currently in phase III clinical trial[40,41].

### Vascular Disrupting Drug :

Combretastatin A4 phosphate (a microtubule depolymerizing agent) has the property of disrupting tumoral blood flow and causing necrosis to the tumoral mass[42]. In phase II clinical study, it shows promising results in advanced stage of the disease[43].

### Epidermal Growth Factor Receptor (EGFR) Pathway :

The EGFR cell-surface protein is a belongs to a subfamily of four related receptor TKs (the ErbB-1, -2, -3, and -4). The upregulation or the overactivity of EGFR, due to mutations, has been correlated with different cancers[44-46]. It participates in the tumor progression and invasion in TC, and it is overexpressed in ATC[47]. Its mutations contribute to RET activation in TC while RET/PTC1 and RET/PTC3 upregulate EGFR expression[48,49]. Gefitinib (ZD1839) is an EGFR inhibitor was shown to inhibit the

ATC proliferation and inducing apoptosis in vitro[50]. Gefitinib and doxorubicin have synergistic effects as inactivation of EGFR increases due to the cytotoxic activity of doxorubicin that leads to decreases extrusion of gefitinib. The combination have been proposed to treat metastatic FTC and ATC[51]. It has been recently shown that there was a PFS of >11 months in a man with metastatic PDTC.

## Histone Deacetylase (HDAC) Inhibitors :

Acetylation of NH2-terminal lysine residues on histones controls the cellular differentiation and biological behaviour of tumoral cells. The activity of histone acetyltransferase or histone deacetylase (HDAC) may be dysregulated in some cancer cells[52]. Vorinostat (suberoylanilide hydroxamic acid) is an oral HDAC inhibitor that is approved by the US FDA due to its ability to block TC cell growth as it induces apoptosis in vitro.

## Peroxisome Proliferator-activated Receptor-gamma (PPAR-γ)

PPAR-? belongs to a superfamily of nuclear hormone receptors whose activation causes antineoplastic and anti-inflammatory effects[53,54]. PPARγ activation was shown to induce apoptosis, block the proliferation of PTC cells, to stop distant metastasis and induce the process of redifferentiation[55,56]. Its ligands downregulated the invasive potential of ATC cell lines[57]. Ciglitazone and rosiglitazone (RGZ) are the two PPAR-γ agonists used in ATC cell lines[58].

Another molecule with high-affinity for the PPAR-γ receptor, RS5444, inhibit the proliferation of ATC cells and also can reactivate RhoB enzyme by inducing the cyclin-dependent kinase inhibitor p21[59,60]. Combination of paclitaxel and efatutazone (an oral PPAR-γ agonist) at different doses resulted in safety and tolerability with high biologic activity is in phase I study is being evaluated for thyroid cancer[61,62].

## Conclusion :

Advanced thyroid cancer or surgically unresectable recurrences or symptomatic or progressive disease have more options than ever before. The newer targeted medical therapies have addressed the issue of resistance and mutations beyond the conventional treatment with RAI, TSH suppression, and palliative cytotoxic chemotherapy for patients with advanced thyroid cancer. Modern targeted therapies evolved from an understanding of cellular signalling pathways, angiogenesis, cellular mechanisms of division, and epigenetic events in thyroid cancer. The main pathways involved as targets for these drugs include the MAPK pathway, the PET pathway, and angiogenesis via VEGFR, RAS, and EGFR receptors. Current medical therapies are classified by their mechanism of action or inhibition related to these and other cellular pathways. Although tumour responses to these medical therapies vary by type of thyroid cancer and type of therapy selected, they remain encouraging and provide therapeutic options for selected patients while new drugs are in development. Further research is needed to determine the ideal targeted therapy, based on molecular characterization of the tumour and of the host factors, to obtain the best response in terms of survival and quality of life.

## Conflict of Interest :

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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