Application of molecular targeted therapy for refractory metastatic thyroid cancers

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Abstract
Thyroid cancer is one of the leading causes of death worldwide. There have been several risks factors linked with thyroid cancer such as genetics, exposure to radiation, body weight and insulin resistance. Poorly differentiated and recurrent metastatic thyroid cancer cell carcinoma remains a therapeutic challenge because of its strong resistance to both chemotherapy and radiation therapy. Immunotherapy might play a role in the treatment of patients with metastatic thyroid cancer. In this paper, we discuss the potential causes of thyroid cancer, pathophysiology, and currently available molecular targeted therapy for refractory metastatic thyroid cancers and common side effects of treatment.


Introduction/Epidemiology
Thyroid cancer arises in the follicular or para-follicular cells of the thyroid glands. Thyroid cancer is one of the leading causes of death worldwide. The Surveillance, Epidemiology, and End Results (SEER) estimated 62,980 (47,790 in females, and 15,190 in males) new cases and 1,890 (1,060 females and 830 males) cases of death in the United States in 2014. Based on the prevalence of thyroid cancer, it was estimated that there were 566,708 people alive with thyroid cancer in the United States in 2011. Thyroid cancer represents 3.8% of all the cancer cases in the United States. The five year survival rate of thyroid cancer was 97.8% from the year 2004 to 2010 in the United States [1]. The overall worldwide estimated age-standardized incidence and mortality rates were 2.1% and 0.5% respectively [2]. It includes different type of histopathologic and genetic characterististics. The male to female ratio of the incidence of thyroid cancer is 3:1 [3].

Etiology/Predisposing factors
Thyroid cancer is due to the abnormal growth of cells in the thyroid gland secondary to switching on or off of the tumor suppressor or promoter genes.

Risk factors for thyroid cancer include:

Gender and age: Thyroid cancer occurs more often in females as compared to males. Thyroid cancer typically occurs between 40 to 50 years in females and 60-70 years in males.

A diet low in iodine: Follicular thyroid cancer and papillary thyroid cancer are more common in people, with low dietary iodine intake.

Exposure of radiation: Radiation (nuclear weapons, radioactive plants, radiation therapy.) is a proven risk factor the thyroid cancer.

Other risk factors: Thyroid nodules, certain inherited genetic syndromes [4], TSH levels, body weight and insulin resistance [5].

Types of thyroid cancer
Thyroid cancer has four subtypes which include [6]:

- Follicular thyroid carcinomas (FTC): Invasion into vascular structures is common and therefore metastasis to other tissues
- Papillary thyroid carcinomas (PTC): Papillary thyroid carcinoma is the most common type of thyroid cancer. The growth rate of PTC is very slow and often develop in only one lobe of the thyroid. This cancer often spreads to the lymph nodes in the neck
- Medullary thyroid carcinomas (MTC): Medullary thyroid carcinoma develops from the thyroid gland C cells, which produces calcitonin hormone. This hormone controls the level of calcium in the blood. This cancer accounts for only 4% of all the thyroid cancers.
- Anaplastic thyroid carcinomas (ATC): which accounts for 2% of all the thyroid cancers. ATC is an undifferentiated carcinoma, which is very aggressive and difficult to treat.

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Anaplastic thyroid carcinoma occurs due to the changes in CTNNB1 oncogenes and TP53 tumor suppressor gene. Follicular thyroid carcinoma occurs due to the changes in RAS oncogenes. Papillary thyroid carcinoma occurs due to the changes in BRAF tumor suppressor genes and RET/PTC oncogenes. Medullary thyroid carcinoma occurs due to the inherited mutation of RET.

Most thyroid cancers present as asymptomatic thyroid nodules identified on physical exam or as incidental findings during diagnostic imaging. The most common signs and symptoms of thyroid cancer are: a lump in the neck, increasing hoarseness, difficulty in swallowing and breathing, swollen lymph nodes, and pain in the neck and throat.

Pathophysiology and molecular basis

There are several pathways involved in the molecular pathophysiology of thyroid cancer. The RAS mutation, BRAF mutation, MAP kinase signaling pathway, PI3K/Akt signaling pathway, PAX8-PPARγ rearrangement, p53 inactivation and epigenetic regulation are the basic pathways in thyroid cancer. 

RAS mutations: The most important pathway in thyroid cancer is the RAS pathway, which is vital for the growth of papillary thyroid carcinomas (PTC) and also plays a role in follicular thyroid carcinomas (FTC) [7]. There are three types of RAS genes: N-RAS, K-RAS, and H-RAS, and these genes produce 21-kDa proteins [8]. The activation of RAS oncogene due to the point mutation also affects the GTPase domain (codon 61) in exon 2 or the G-to-T binding domain (codons 12 or 13) in exon 1, which keeps the protein in the activated form [9]. Some studies demonstrated that RAS mutations, occurs specifically at codon 61 of N-RAS [10,11].

BRAF mutation and MAP kinase signaling pathway: BRAF mutation plays a key role in the activation of mitogen-activated protein kinase (MAPK) signaling pathway in cancer [12]. There are three types of RAF kinases: A-Raf, B-Raf (BRAF), and C-Raf. Among these RAF kinases, BRAF is the most effective activator of MAPK pathway [13]. This is the outcome of the addition of 18 nucleotides at nucleotide T1799 [14-16]. Thus, the BRAF mutation is a molecular marker for thyroid cancer. The BRAF pathway, which appears to be essential for the growth of (PTC) also plays an additional role in (FTC) [17].

PI3K/Akt signaling pathway: The genetic modification of proteins inside the phosphatidylinositol-3-kinase (PI3K)/AKT signaling pathway have been reported in sporadic thyroid carcinomas, (FTC) and (ATC) [18]. The phosphatidylinositol-3 kinase (PI3K)/Akt signaling pathway (PI3K pathway) also plays an essential role in the survival, cell growth and proliferation and formation of tumors, similar to that of the MAP kinase pathway [19,20]. The class I of PI3Ks is made up of heterodimers of a regulatory subunit, mainly p85 and p110 catalytic subunits. The α-type (PIK3CA) and β-type (PIK3CB) p110 subunits are found in all tissues, while other p110 subunits are found in the limited tissues. There are three main types of Akts: Akt-1, Akt-2, and Akt-3 [21]. These Akt isoforms are present in abundance in thyroid cancer cells. The amplification of PIK3CA is found mainly in ATC and FTC [22,23].

PAX8-PPARγ rearrangement: The PAX8-PPARγ rearrangement is a chromosomal translocation t(2;13)(q13;p25), which promotes the growth of thyroid cancers [24]. Paired-box gene 8 (PAX-8) encodes a transcription factor, which is necessary for the growth of thyroid follicular cell lineage and thyroid-specific gene expression in thyroid cancer [25]. The PAX8-PPARγ rearrangement hints to the in-frame syntheses of exon 7, 8, or 9 of PAX8 on 2q13 through exon 1 of PPARγ on 3p25 [26]. The PAX8-PPARγ rearrangement is also involved in the growth of thyroid cancer through RAS mutation [27].

p53 inactivation: The tumor suppressor gene (TP53) is located on chromosome 17 and is frequent in ATC and PDTC. It may be responsible for the loss of differentiation in these tumors [7]. Alterations in the p53 tumor suppressor gene by inactivating point mutations, usually involving exons 5–8, or by deletion result in additional mutations, progressive genome destabilization and propagation of malignant clones. It represents the most common genetic abnormality in cancer, which occurs typically as late tumorigenic events [28-30].

Epigenetic regulation: The epigenetic changes, such as the altered DNA methylation in the CpG islands of the gene promoters, are vital in the usual thyrocyte function, such as the TSH receptor and the sodium-iodide symporter [31,32]. The elementary structural part of chromatin contains 147 bp of DNA that enfolds about an octamer of four essential histone proteins such as H2A, H2B, H3, and H4 [33]. The different histone modification comprises ubiquitination, phosphorylation, acetylation, and methylation that acts with DNA promoter methylation to regulate gene silencing [34] (Figure 1).

Immunotherapy overview

Targeted therapy might offer therapeutic options for patients with medullary thyroid cancers, advanced cases that don’t respond to radioactive iodine therapy and anaplastic thyroid carcinomas. These therapies are not curative, but may slow the progression of the tumor. The cost effectiveness of targeted agents in advanced thyroid cancer has not been established, because the drugs are so new. Targeted therapies are generally better tolerated than traditional chemotherapy with the most common side effects of biological therapies are Diarrhea fatigue, rash, cardiac dysfunction, thrombosis and hypertension Clinical studies are needed to identify patients most likely to benefit from these therapies.

Current immunotherapy options for thyroid cancer are discussed in following categories: kinase inhibitors, monoclonal antibodies, mTOR inhibitors, proteasome inhibitors, vaccine therapy and cancer cell stemness inhibitors.

Kinase inhibitors

FDA approved kinase inhibitors

Sorafenib: It is a kinase inhibitor that blocks the enzyme RAF kinase, a critical component of the RAF/MEK/ERK signaling pathway that controls cell division and proliferation. In addition, Sorafenib inhibits the VEGFR-2/PDGFR-beta signaling cascade, thereby blocking tumor angiogenesis. Sorafenib is indicated for the treatment of metastatic or recurrent, progressive, differentiated thyroid carcinoma (DTC), refractory to ablative radioactive iodine treatment. It is contraindicated in combination with taxane and platinum chemotherapy [35].

Its in vitro binding to human plasma protein is 99.5%. Sorafenib is metabolized by CYP3A4 and steady state plasma is reached within 7 days, with a half-life of 25-48 hours. Sorafenib should not be given to patients with cardiac ischemia. It should be discontinued in case of bleeding. Women of reproductive potential should be advised not to get pregnant as Sorafenib can harm the fetus. Sorafenib should be discontinued for dermatologic toxicities, such as toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS). The most common adverse effects are hemorrhage, hypertension, and gastrointestinal.
Bevacizumab: A recombinant humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF), a pro-angiogenic cytokine. Bevacizumab binds to VEGF and inhibits VEGF receptor binding, thereby preventing the growth and maintenance of tumor blood vessels.

mTOR inhibitors

Few mTOR inhibitors are under clinical trials in phase I-III are listed in Table 3.

Everolimus: It is a derivative of natural macrocyclic lactone sirolimus and has anti-angiogenic and immunosuppressant properties. It binds to FKBP-12 to generate an immunosuppressive complex and inhibits the activation of mTOR. Everolimus is an orally bioavailable inhibitor of the mTOR pathway. The effects of Everolimus in cancer
cells include reduced growth and proliferation as well as inhibition of protein translation and VEGF production.

**MLN0128**: An inhibitor of raptor-mTOR (TOR complex 1 or TORC1) and rictor-mTOR (TOR complex 2 or TORC2) with potential antineoplastic activity. TORC1/2 inhibitor MLN0128 binds to and inhibits both TORC1 and TORC2 complexes of mTOR, which may result in tumor cell apoptosis and a decrease in tumor cell proliferation. TORC1 and 2 are upregulated in some tumors and play an important role in the PI3K/Akt/mTOR signaling pathway, which is frequently dysregulated in human cancers.

**Vaccines**

There are no vaccines that are currently approved by FDA for thyroid cancer. However, the vaccine that is under clinical trials in phase I-III is given in Table 4.

**GI-6207**: A whole, heat-killed, recombinant Saccharomyces cerevisiae yeast-based vaccine genetically altered to express the carcinoembryonic antigen (CEA) peptide 610D with potential immunostimulating and antineoplastic activities. Upon administration, recombinant Saccharomyces cerevisiae-CEA(610D) vaccine GI-6207 may stimulate a host cytotoxic T-lymphocyte (CTL) response against CEA-expressing tumor cells, which may result in tumor cell lysis. CEA, a tumor associated antigen, is overexpressed on a wide variety of human cancer cells including colorectal, gastric, lung, breast and pancreatic cancer cells. CEA 610D encodes for 9 amino acids (605-613), in which aspartate is substituted for asparagine at position 610 (610D) in order to strengthen the induction of the CTL response against CEA-expressing tumor cells.

**Cancer cell stemness inhibitors**

The discovery of therapeutic approaches that counteract relapse and metastasis is, therefore, extremely important for advancing cancer medicine. Hypermalignant cancer cells, termed cancer stem cells or stemness-high cancer cells, have been isolated from patients with a variety of tumor types and found to be highly malignant, tumorigenic, and resistant to chemotherapies. A cancer stemness inhibitor effectively blocks cancer relapse and metastasis in xenografted human cancers, suggest targeting cancer stemness as a novel approach to develop the next generation of cancer therapeutics to suppress cancer relapse and metastasis [54].

**BBI608**: It is a cancer cell stemness inhibitor with potential antineoplastic activity. Even though the exact target has yet to be fully elucidated, BB1608 appears to target and inhibit multiple pathways involved in cancer cell stemness. This may ultimately inhibit cancer stemness cell (CSC) growth, as well as heterogeneous cancer cell growth. CSCs, self-replicating cells that are able to differentiate into heterogeneous cancer cells, appear to be responsible for the malignant growth, recurrence and resistance to conventional chemotherapies (Table 5).

**Conclusion**

The recent discoveries of the pathogenesis of thyroid cancer are very
important for the growth of novel and capable therapies. Several genetic modifications that are recognized so far, concentrate on the PI3K/ AKT, RTK/RAS, and BRAF/MAPK signaling pathways, contributes to a powerful foundation for the growth of novel therapeutic, prognostic, and gene-based strategies. The treatment of thyroid cancer is altered significantly as a result of the development of kinase inhibitors. It is not yet resolved whether the various combinations of targeted therapies with radiotherapy or chemotherapy will improve the response rates of advanced and difficult to treat thyroid cancer.

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