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Anti-Tumour Treatment

Targeted therapies in advanced differentiated thyroid cancer

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ABSTRACT

Differentiated thyroid cancer is the most common endocrine malignancy, and its incidence has been rising rapidly over the past 10 years. Although most patients with this disease have an excellent prognosis, a subset develops a more aggressive disease phenotype refractory to conventional therapies. Until recently, there was no effective therapy for these patients. With increasing knowledge of the molecular pathogenesis of thyroid cancer, novel targeted therapies are being developed for this group of patients. Sorafenib and lenvatinib, small-molecule multikinase inhibitors, were approved for the treatment of progressive, symptomatic, radioactive iodine refractory, advanced differentiated thyroid cancer in 2013 and 2015, respectively. This represents a major innovation in the therapy of patients with advanced thyroid cancer. However, these therapies still have many limitations and further research needs to be pursued with the ultimate goal of providing safe and effective personalized therapy for patients with advanced thyroid cancer.

Introduction

Thyroid cancer is the most common endocrine malignancy with incidence rates increasing rapidly over the past 10 years [1]. According to the Surveillance Epidemiology and End Results (SEER) database, rates for new thyroid cancer cases have risen on average 5% per year [2]. While this rapid increase has been attributed to increased detection of early microcarcinomas (<1 cm in size) in times of more accessible high-resolution imaging techniques, the increase in the incidence of tumor of all sizes suggests other potential causes [3]. Nevertheless, the incidence of advanced thyroid cancer has also increased, and death rates from thyroid cancer have been rising on average 0.9% each year [2].

Thyroid cancer is a heterogeneous disease arising from two different epithelial cell types. Most thyroid cancers are derived from the follicular cells, including papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), Hürthle cell carcinoma, and anaplastic thyroid carcinoma (ATC). Medullary thyroid carcinoma (MTC) is derived from the parafollicular calcitonin-producing cells. PTC and FTC are pooled together into the denomination of differentiated thyroid cancer (DTC). Those are by far the most common subtypes of thyroid cancer, accounting for 90–95% of all cases. They are generally slow-growing tumors, and have an excellent overall prognosis with overall 20-year survival rates greater than 90% with conventional therapy [4]. However, a subset of patients with DTC presents a more aggressive disease course and develops recurrent or metastatic disease that is refractory to radioactive iodine therapy. Among these patients, 10-year survival rates decline to approximately 15–20% [5].

Conventional therapies for DTC vary depending on staging of initial diagnosis, but they include surgical resection with or without thyroid remnant ablation with radioactive iodine and thyroid hormone suppression therapy [6]. While this approach has been effective in most patients with DTC, there is a clear unmet need for efficacious therapeutic options for the growing subset of

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patients with advanced disease refractory to radioiodine therapy [2].

Exciting new discoveries in the pathogenesis of thyroid cancer, specifically the molecular genetic pathways involved in thyroid tumorigenesis, have led to the development of novel targeted therapies for patients with advanced thyroid cancer. The tyrosine kinase inhibitors (TKIs) vandetanib and cabozantinib were approved for the treatment of medullary thyroid cancer in 2011 and 2012, respectively. More recently, the FDA approved the TKIs sorafenib and lenvatinib for the treatment of advanced iodine-refractory DTC in 2013 and 2015. These advances represent groundbreaking progress in the management of patients with advanced thyroid cancer and have fostered the development of other targeted therapies with the ultimate goal of improving the outcomes for this disease based on a personalized approach to treatment of patients with thyroid cancer. Gaps of knowledge are yet to be filled regarding efficacy, safety, and specific roles of these new therapies. This review will focus on recent molecular discoveries and promising targeted therapies currently being developed.

Conventional treatment approach for DTC

Thyroid cancer is commonly diagnosed during routine physical examination. Patients are usually asymptomatic at presentation and will have either a palpable thyroid nodule or a nodule incidentally found on imaging exam. Most patients with differentiated thyroid cancer will be cured with surgery alone or a combination of surgery, radioactive iodine therapy, and suppression therapy with thyroid hormone.

The goal of surgery is to remove the tumor and any disease extending beyond the thyroid gland, typically through a total thyroidectomy and, if indicated, central and lateral neck dissection. Post-operatively, radioiodine (I-131) may be administered for ablation of normal remnant thyroid tissue, adjuvant therapy of micrometastases, or treatment of apparent residual or metastatic thyroid cancer. Upon uptake by follicular thyroid cells, I-131 induces cell-death by emission of short path-length beta rays. Patients with iodine-avid disease may continue to receive repeated courses of I-131. The ability of the thyroid follicular cell to concentrate iodine may eventually become impaired in advanced dedifferentiated thyroid cancer, which may render radioiodine treatment ineffective. Finally, as part of conventional therapy, thyroid hormone suppression therapy is recommended for patients with intermediate and high-risk thyroid cancer, since thyroid simulating hormone (TSH) may contribute to growth of residual or metastatic thyroid cancer [6].

Until recently, patients with advanced, radioactive iodine refractory progressive disease had limited and ineffective treatment options. The only systemic therapy approved by the FDA for these patients was doxorubicin [7]. However, this therapy alone or in combination with other cytotoxic agents such as cisplatin has very limited efficacy and is associated with serious adverse events including cardiac and hematologic toxicities [8,9]. Therefore, there has been an enormous unmet need for treatment of this disease.

New discoveries in the pathogenesis of thyroid cancer

Over the past 20 years, new discoveries in the pathogenesis of thyroid cancer have given insight into better diagnostic, prognostic and therapeutic procedures for patients with thyroid cancer. Like for other types of cancer, understanding how cancer initiation and progression occur allows for specific interventions for early diagnosis and targeted therapies.

Thyroid cancer development occurs when genetic and epigenetic alterations affect the mechanisms controlling cell cycle, cellular proliferation and survival signaling networks. Somatic mutations, including point mutations and chromosomal rearrangements have been described as key determinants of early thyroid cancer development [10,11]. Many of these mutations lead to constitutive activation of two major signaling pathways that regulate cell growth, proliferation, and differentiation: mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase/v-akt murine thymoma viral oncogene homolog 1/mammalian target of rapamycin (PI3K/AKT/mTOR). Thyroid cancer progression appears to result from accumulation of these genetic alterations and corresponding abnormal activation of the signaling pathways.

The Cancer Genome Atlas (TCGA) project provided a detailed description of the molecular alterations in 496 cases of papillary thyroid carcinoma with significant impact in the understanding of pathogenesis, and it revealed novel potential therapeutic targets [12]. The study showed that PTC has a lower mutational burden (0.4 mutations/Mb) compared to other epithelial cancers (i.e. melanoma, lung cancer and bladder cancers), but potential driver genetic alterations were identified in approximately 97% of tumors, substantially reducing the previously described "dark matter" from 25% to 3% [13]. The results demonstrated two molecularly driven groups of PTC characterized as BRAF- and RAS-driven tumors with distinct histologic phenotypes and pathway activation patterns. BRAF-driven tumors were frequently undifferentiated with predominant signaling through the MAPK pathway. RAS-driven tumors were well differentiated, associated with follicular histology and displayed activation of both MAPK and PI3K pathways. Additional findings included, among others, novel mutations in the *CHEK2*, *ATM*, *TERT* genes, translocations involving *BRAF*, *ALK* and *FGFR2*, and alterations in DNA repair and chromatin remodeling genes. The landmark nature of these results is reflected by the remarks suggesting a novel classification of thyroid cancers based on the genomic aberrations identified and they provide a solid foundation to advance the treatment of this disease.

Angiogenesis

Vascular endothelial growth factor (VEGF) stimulates endothelial cell proliferation and is key to tumor angiogenesis and growth [14]. VEGF has shown to have an important role in thyroid cancer development [15,16]. Expression of VEGF is increased in thyroid cancer and its expression level correlates with advanced disease [17–19]. Targeting VEGF or its receptor (VEGFR) may limit tumor induced angiogenesis, vascular supply to the tumor and halt tumor growth. The therapeutic benefits of this strategy have been proven in several solid tumors including non-small cell lung cancer, colon cancer, and renal cell carcinoma [20–23]. The VEGF pathway can be inhibited with monoclonal antibodies against VEGF (e.g. bevacizumab) or the extracellular domain of the VEGFR (e.g. ramucirumab), as well as by several small molecule tyrosine kinase inhibitors targeting VEGFR (e.g. sorafenib, lenvatinib, sunitinib, pazopanib, among others) [24]. The success of VEGF blockage in other diseases combined with the important role of VEGF in thyroid cancer pathogenesis have fostered the investigation of some of these compounds for treatment of advanced thyroid cancer. Ongoing studies and results will be discussed below.

Somatic mutations: BRAF and RAS

Point mutations are characterized by single nucleotide substitution within the DNA chain. The first and best characterized point mutation in thyroid cancer occurs in the *BRAF* (v-raf murine sarcoma viral oncogenes homolog B1) gene resulting in a valine to glutamate mutation at residue 600 (V600E) leading to constitutive activation of the BRAF kinase that confers continuous activation of the MAPK signaling pathway with consequent uncontrolled cell