Thyroid Cancer

Subjects: Pathology
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Thyroid cancer represents a heterogenous disease whose incidence has increased in the last decades. Although three main different subtypes have been described, molecular characterization is progressively being included in the diagnostic and therapeutic algorithm of these patients. In fact, thyroid cancer is a landmark in the oncological approach to solid tumors as it harbors key genetic alterations driving tumor progression that have been demonstrated to be potential actionable targets. Within this promising and rapid changing scenario, current efforts are directed to improve tumor characterization for an accurate guidance in the therapeutic management. In this sense, it is strongly recommended to perform tissue genotyping to patients that are going to be considered for systemic therapy in order to select the adequate treatment, according to recent clinical trials data.

Keywords: thyroid cancer ; tyrosine kinase inhibitors ; immunotherapy ; RET ; NTRK

1. Introduction

The incidence of thyroid cancer has been steadily increasing over the past decades, mainly due to the evolution of diagnostic techniques and clinical surveillance. However, mortality from thyroid cancer has remained relatively stable over time [1]. Nowadays, one of the main challenges faced by clinicians is how to balance the therapeutic approach to avoid overtreatment in patients with an indolent tumors, while providing adequate care to patients with a more advanced or aggressive disease.

Thyroid cancer represents a heterogeneous neoplasm, with distinct histologic subtypes, resulting in different molecular pathways, clinical presentation, therapeutic approaches and prognosis. However, all thyroid cancer subtypes share common features related to the activation of particular molecular pathways that involve different tyrosine kinases. These molecules have been studied as therapeutic targets with successful results in randomized clinical trials.

2. Histological Subtypes

Thyroid cancer can be histologically classified into three main subtypes: differentiated thyroid cancer (DTC; including papillary, follicular, Hürthle and poorly differentiated thyroid cancer), anaplastic thyroid cancer (ATC) and medullary thyroid cancer (MTC) [2]. Recently, the WHO has published an updated classification of thyroid neoplasms with several histological nuances according to the advancement in the knowledge of novel genetic and molecular particularities[3].

2.1. Follicular-Derived Thyroid Cancers

Differentiated Thyroid Cancer (DTC) accounts for over 97% of all cases of thyroid cancer [1]. In general, they have an excellent prognosis with a 5-year overall survival (OS) rate above 95%. However, patients diagnosed in stages III-IV have a worse outcome, with a 10-year survival rate < 50–60% [2].

Papillary thyroid cancer (PTC) is the most prevalent subtype, representing 80% of all thyroid cancers. PTC has the best prognosis with a 5-year survival rate of 97.7%. In terms of histopathology, PTC includes classic forms (cPTC) and variant forms, which comprises follicular variant, tall cell variant and several other variant types, which are all rarely found [2].

Follicular thyroid cancer (FTC) constitutes 10–20% of all DTC, with a higher prevalence in iodine-deficient geographical areas. It is important to underline that, even though they also have a good prognosis, up to 5–15% of patients will die because of their disease, since minimally invasive tumors tend to have microscopically foci of capsular invasion, which leads to a slightly worse prognosis [2].

Hürthle cell carcinoma accounts for 2–8% of DTC and is composed by eosinophilic thyroid cells with a large number of abnormal mitochondria. The prognosis worsens when there is a lower iodine uptake and the capsular and/or vascular invasion [2].

Recently, the poorly differentiated thyroid cancer (PDTC) has been characterized as a new form of DTC, being the most aggressive subtype, with a mean survival of 3.2 years. The diagnostic criteria for this tumor is based on the Turin proposal: invasive tumors with a solid/trabecular/insular growth and presence of a mitotic index > 3 per 10 high-power fields, necrosis or convoluted nuclei [2].

Anaplastic Thyroid Cancer represents approximately 0.8% of all thyroid cancers diagnosis [2], either arising from a previously developed DTC or appearing de novo. Despite having a very poor prognosis, with a 5-year overall survival rate of 12%, promising preliminary results from ongoing clinical trials may shed light on this aggressive subtype. Three histological subtypes of anaplastic thyroid cancer (ATC) have been described: sarcomatoid (composed of malignant spindle cells), giant cell (abundant in pleomporphic cells) and epithelial (harboring squamoid or squamous tumor nests). Other relevant histological findings comprise a high proliferative rate, marked pleomorphism and extensive vascular invasion [3].

2.2. Neuroendocrine C-Cell-Derived Thyroid Cancers

Medullary thyroid cancer (MTC) accounts for up to 1.6% of thyroid cancers [1]. MTC is a very heterogeneous neoplasm which arises from the parafollicular cells (C cells), that produce calcitonin. In 25% of patients, MTC is part of an inherited syndrome: familial MTC or the multiple endocrine neoplasia syndromes type 2A and 2B (MEN2A and MEN2B). In the remaining 75% of cases, it arises sporadically (sMTC). Somewhere in between 20 and 40% of patients with MTC will, unfortunately, develop metastasis leading to a 10-year survival rate of 40%.

3. Conclusions

Thyroid cancer is a heterogenous disease, but recent advances in understanding its genomic landscape related to the different histology patterns have helped in the development of novel drugs. The first hit has been the approval of MKI that are able to inhibit different tyrosine kinases involved in the activation of key intracellular signalling pathways for thyroid cancer progression. Those drugs have reached phase III clinical trials, from the preclinical findings, with an increase in survival based on the results of phase III studies directed to patients suffering from RAI-DTC and MTC. The second hit has been the identification of selective targeted drugs with considerable antitumor activity and less toxicity, such as *RET* or *TRK* inhibitors. In light on the upcoming trials and approved drugs, it is required to perform tissue genotyping to patients needing systemic therapy for the identification of driver alterations and the selection of the adequate treatment. Also, germline testing is strongly recommended in case genetic counselling is required.

Additionally, new targets are now being explored in the field of thyroid cancer, such as MEK, ERBB2/HER2, ALK or SSTR in order to increase the therapeutic possibilities and offer the adequate directed treatment to the patients. Immunotherapy is also under research, but the efficacy of PD-1/PDL-1 or CTLA-4 inhibitors in all thyroid cancer subtypes is different and novel strategies in the immune cell cycle are needed to achieve better responses.

With these advances coming in, treatment options have significantly increased, but the optimal treatment sequence is still unknown. Though the first decision will be probably determined according to the genetic findings, phase III trials are currently analysing the best treatment option upfront. However, unfortunately, patients will eventually progress to these new drugs, so the identification of acquired resistance mechanisms is mandatory. In this setting, not only research based on tumor tissue, but also on liquid biopsy to identify driver mutations or resistance mechanisms in ctDNA, could be of great interest in order to direct the optimal sequence therapeutic algorithm with a more accessible sample.

In conclusion, thyroid cancer is a landmark in the development of new drugs based on genetic driver alterations. However, even though new drugs keep arising in the field, not all patients experiment antitumor response and most of them will eventually progress, many times showing an adequate performance status to continue receiving more therapeutic options. Thus, translational research focused on novel actionable targets and biomarkers selection is constantly needed.

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