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The evolving field of kinase inhibitors in thyroid cancer

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Contents

Abstract

Most of the genetic events implicated in the pathogenesis of thyroid cancer (TC) involve genes with kinase activity. Thus, kinase inhibitors (KIs) are very relevant in this field. KIs are considered the most suitable treatment for patients with iodine-refractory differentiated TC; these patients comprise the subgroup with the poorer prognosis. To date, only sorafenib has been approved for this indication, but promising results have been reported with several other KIs. In particular, lenvatinib has demonstrated excellent efficacy, with both progression-free survival and objective tumour response being better than with sorafenib. Despite being considered to be well tolerated, both sorafenib and lenvatinib have shown a remarkable toxicity, which has led to dose reductions in the majority of patients and to treatment discontinuation in a significant proportion of cases. The role of KIs in differentiated TC may be revolutionised by the finding that selumetinib may restore a clinical response to radioactive iodine (RAI). Vandetanib and cabozantinib have been approved for the treatment of advanced, progressive medullary TC (MTC). Nevertheless, the toxicity of both compounds suggests their selective use in those patients with strong disease progression. Treatment with the mTOR-inhibitor everolimus, alone or in combination with somatostatin analogues, should be studied in metastatic MTC patients with slow progression of disease, these representing the vast majority of patients. KIs did not significantly impact on the clinical features of anaplastic TC (ATC).

Keywords: Thyroid cancer; Cancer therapy; Protein kinases; Kinase inhibitors; Anti-angiogenetic therapy

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1. Introduction

Thyroid cancer is a malignancy with a rapidly growing public health relevance. Apart from being the most common endocrine tumour, its incidence in Western countries has progressively increased in the last decades [1,2]. Typically, endocrine cancers are poorly responsive to DNA-damaging treatments [3]. Particularly, cytotoxic systemic chemotherapies have demonstrated limited efficacy in advanced thyroid carcinomas, with response rates of 25% or less [4]. Thus, treatment of aggressive forms of thyroid tumours is challenging, and the validation of innovative therapies is mandatory in this field. Thyroid cancer involves neoplasms arising from epithelial follicular cells, including papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), poorly differentiated thyroid carcinoma (PDTC), and anaplastic thyroid cancer (ATC), whereas medullary thyroid carcinoma (MTC) derives from parafollicular calcitonin-secreting C cells. PTC and FTC are classified as differentiated thyroid cancers (DTCs) and represent the vast majority of thyroid carcinomas (80–90%) [5]. Conventional treatment of DTC is based on a combined approach consisting in total thyroidectomy and, in selected cases, radioactive iodine (RAI) followed by suppression of thyroid-stimulating hormone (TSH) [5,6]. This approach is highly effective, as DTC usually has an excellent prognosis with a 10-year disease-related survival of 85% [7]. Nevertheless, about 5% of DTC patients develop an aggressive disease with distant metastases and loss of I-131 avidity. Patients with RAI-resistant DTC are generally not responsive to conventional chemotherapy and have a long-term overall survival of 10% [8]. MTC accounts for approximately 5% of thyroid cancers [1]. Given its neuroendocrine origin, MTC is not responsive to either RAI or TSH suppression. Thus, surgery is the only curative approach in such cases. Nevertheless, 60–80% of MTC patients have metastatic disease at the time of diagnosis, and only half of these subjects become disease-free after surgery [9]. Progressive forms of metastatic MTC are generally poorly responsive to chemotherapy and exhibit a 5-year survival rate of less than 50% [10]. ATC accounts for less than 2% of thyroid malignancies, but it is the most aggressive subtype of thyroid cancer, being responsible for 14–39% of deaths related to thyroid tumours [11]. Treatment of ATC is not yet standardised and is mainly empirical and multimodal, including surgery, chemotherapy and radiotherapy [12]. Nevertheless, prognosis of ATC patients is poor, with a mean survival of less than 6 months after diagnosis [13]. PDTC is a controversial entity showing features intermediate between those of DTC and ATC at both the histological and clinical levels [14]. Thus, PDTC patients have a worse prognosis than subjects with classical DTC [15].

In recent years treatment of aggressive forms of endocrine cancer has been revolutionised by the use of kinase inhibitors (KIs). These are small organic molecules that interfere with the interaction between the kinase domain and adenosine triphosphate (ATP) or other mechanisms such as allosteric inhibitors, thereby inhibiting phosphorylation of the kinase and activation of downstream signalling pathways [16] (see Table 1 for KIs referred to in this paper and their molecular targets). The majority of KIs available in clinical practice are non-selective, being active against several molecular targets [17]. This implies that these compounds have a multimodal action. Indeed, anticancer activity of KIs is based on a double mechanism: a direct anti-proliferative function achieved by blocking molecules involved in intracellular pathways of survival, proliferation and growth, and an anti-angiogenic function performed by halting the activation of specific receptors of angiogenic factors, thus inhibiting intracellular pathways that stimulate angiogenesis [18].

2. Rationale for the use of KIs in thyroid cancer

The concept of targeted therapy is a perfect fit for thyroid cancer. Indeed, genetic alterations having a demonstrated oncogenic role have been detected in a significant proportion of thyroid malignancies [19]. Typically, these genetic abnormalities are mutually exclusive, so they can be considered as crucial pathogenetic events [20]. Most of these genetic events involve genes with kinase activity and are implicated in the MAP kinases and/or the PI3K/Akt/mTOR signalling cascades [21]. Activation of these pathways leads to neoplastic transformation and progression [22]. Hence, thyroid cancer represents an ideal model for testing anti-cancer activity of KIs. The T1799A transverse point mutation of BRAF, which is a serine–threonine kinase, is the most common genetic alteration in PTC, being detected in approximately 45% of these neoplasms [23,24]. The mutation results in the V600E amino-acidic substitution leading to the constitutive induction of the kinase activity with aberrant activation of the MAP kinases pathway [25–27]. Furthermore, $BRAF^{V600E}$ has been detected in 20–40% of PDTCs and 30–40% of ATCs [28–31]. The presence of BRAF mutation in both PTCs and less differentiated forms of thyroid cancer of follicular origin (PDTC, ATC) suggests the hypothesis of a critical role of this mutation in PTC progression. To date, the crucial role of mutated BRAF in promoting the biological and clinical evolution of PTC has been widely ascertained. From the molecular point of view, BRAF mutation is associated with decreased expression of mRNAs for proteins that induce differentiation of follicular cells, such as the sodium iodide symporter and the TSH receptor [32], so it promotes tumour dedifferentiation. Clinically, mutated BRAF is associated with clinico-pathological features having a negative prognostic impact, RAI unresponsiveness and increased rates of disease recurrence and mortality [33,34]. A recent study by Guerra et al. [35] demonstrated that the percentage of mutated alleles within the tumour mass correlates with a poorer outcome among BRAF-positive PTC cases. Chromosomal rearrangements of RET, which encodes a tyrosine-kinase receptor, have been detected in a significant proportion of PTCs [36,37]. These genetic events lead to the constitution