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Overview

Targeted Therapy in Thyroid Cancer: State of the Art

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Abstract

Thyroid cancer typically has a good outcome following standard treatments, which include surgery, radioactive iodine ablation for differentiated tumours and treatment with thyrotropine hormone-suppressive levothyroxine. Thyroid cancers that persist or recur following these therapies have a poorer prognosis. Cytotoxic chemotherapy or external beam radiotherapy has a low efficacy in these patients. 'Target therapy' with tyrosine kinase inhibitors (TKIs) represent an important therapeutic option for the treatment of advanced cases of radioiodine refractory (RAI-R) differentiated thyroid cancer (DTC), medullary thyroid cancer (MTC) and possibly for cases of poorly differentiated (PDTC) and anaplastic thyroid cancer (ATC). In the last few years, several TKIs have been tested for the treatment of advanced, progressive and RAI-R thyroid cancers and some of them have been recently approved for use in clinical practice: sorafenib and lenvatinib for DTC and PDTC; vandetanib and cabozantinib for MTC. The objective of this overview is to present the current status of the treatment of advanced DTC, MTC, PDTC and ATC with the use of TKIs by describing the benefits and the limits of their use. A comprehensive analysis and description of the molecular basis of these drugs and the new therapeutic perspectives are also reported. Some practical suggestions are also given for the management to the potential side-effects of these drugs.

Key words: Advanced thyroid cancer; adverse events; molecular targets; targeted therapy; tyrosine kinase inhibitors

Statement of Search Strategies Used and Sources of Information

A literature search of PubMed was carried out using the following key words: advanced thyroid cancer; advanced medullary thyroid cancer; tyrosine kinase inhibitors in thyroid cancer; vandetanib in thyroid cancer; cabozantinib in thyroid cancer; sorafenib in thyroid cancer; lenvatinib in thyroid cancer; cancer patient communication.

Introduction

Differentiated thyroid cancers (DTC), both papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC), are generally associated with an indolent disease course and, as they maintain the typical features of thyroid cells, they are usually curable with surgery and radioactive iodine (^{131}I) therapy [1,2]. In about 10% of cases, patients have a locally advanced or metastatic disease at diagnosis, with local invasion and/or distant metastases in the bone (25%), lungs (50%), lungs and bone (20%) and other sites (5%). In one third of advanced DTC the metastatic lesions have a low avidity for iodine and ^{131}I therapy has no effects [3].

Anaplastic thyroid cancer (ATC) is the undifferentiated form, unable to take up ^{131}I and with no chance of cure [4]. Fortunately it is rare (2% of thyroid cancer) but is associated with rapid progression, especially at the local level, with a high risk of suffocation and a high mortality. Poorly differentiated thyroid cancer (PDTC) has a disease course that is in between those of DTC and ATC. The reason for this poor prognosis is related to the fact that in these cases the tumoural cells become rapidly dedifferentiated and are no longer able to take up iodine and secrete thyroglobulin, if they were in the beginning.

Similarly, advanced medullary thyroid cancers (MTCs) are not able to take up ^{131}I, do not produce thyroglobulin

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and are not responsive to the thyrotropine hormone . In fact they derive from malignant transformation of parafollicular C-cells that are neuroendocrine cells located peripherally to thyroid follicles. At variance from DTC, they produce several peptides, among which the most important and specific is calcitonin [5].

Until a few years ago, no effective therapeutic options were available for patients with advanced thyroid cancer resistant to radioiodine (RAI-R). Other conventional therapies were used, such as external beam radiotherapy and chemotherapy, but they had important toxicity and played mainly a palliative role as efficacy was low and transient (10–20%) with no prolongation of survival in response to the use of either a single therapeutic agent or a combination [6,7].

In recent years, a variety of molecular-targeted agents have been developed that are able to inhibit tyrosine kinases receptors (TK-R), which are responsible for tumour growth and angiogenesis [8]. In the last 12 years, several of these tyrosine kinase inhibitors (TKIs) have been evaluated in advanced thyroid cancers for their ability to block TK-R and/or other kinases involved in cell proliferation and tumoural transformation of thyroid cells (Table 1). Four of them have now been approved by the Food and Drug Administration (FDA) and the European Medical Agency (EMA) for the treatment of advanced RAI-R (i.e. sorafenib and lenvatinib) and MTC (i.e. vandetanib and cabozantinib).

The objective of this overview is to present the current status of the treatment of advanced thyroid cancers using these innovative targeted therapies by describing both the benefits and the limits of their use.

The Rationale of Targeted Therapies in Thyroid Cancer: Molecular Alterations

Aberrant signalling pathways have been implicated in the onset, progression and invasiveness of DTCs. The most common genetic changes in PTC are point mutations in *BRAF* and *RAS* and rearrangement of the *RET* proto-oncogene [9]. Several *RET/PTC* rearrangements have been described, almost exclusively in PTC cells, mainly in radio-induced PTC, but also in a not negligible percentage of sporadic cases [10]. In FTC, point mutations of *RAS* and rearrangements of *PPARγ* and *PAX8* genes, to create the *PPFP* fusion gene, are the most common oncogenic alterations but, to a lesser extent, also *PTEN* deletion/mutation, *PIK3CA* and *IDH1* mutations can be found [11]. At variance from PTC and FTC, in which oncogene mutations are almost mutually exclusive, PDTC and even more ATC are characterised by a higher number of mutations in the same tumoural tissue and the overexpression of these proteins is probably responsible for a more aggressive phenotype. The most prevalent oncogene alterations in ATC are *p53* point mutations, $BRAF^{V600E}$, *PIK3CA*, *PTEN*, *IDH1* and *ALK* mutations,

Table 1
Tyrosine kinase inhibitors tested in phase II, III or IV clinical trials in thyroid cancer: the multitarget activity and the molecular targets are indicated

DRUG	VEGF-R	c-Kit	RET	PDGF-R	FGF-R	EGF-R	Other targets	Study phase	Approved for thyroid cancer treatment
Axitinib	Yes	Yes	No	Yes	No	No		II	No
Bevacizumab	No	No	No	No	No	No	dual PI3K/mTOR	II	No
Cabozantinib	Yes	Yes	Yes	No	No	No	MET, *RET- KIF5B rearrangement*	III*	Yes
Imatinib	No	Yes	No	Yes	No	No	Bcr-Abl	II	No
Lenvatinib	Yes	Yes	Yes	Yes	Yes	No	*RET-KIF5B*, *CCDC6-RET*, *NcoA4-RET rearrangement*	III*	Yes
Motesanib	Yes	Yes	Yes	Yes	No	No		II	No
Nintedanib	Yes	No	No	Yes	Yes	No		II	No
Pazopanib	Yes	Yes	No	Yes	No	No		II	No
Ponatinib	No	No	Yes	Yes	Yes	No	*Bcr-Abl*, FLT3, KIT	II	No
Selumetinib	No	No	No	No	No	No	MEK	III	No
Sorafenib	Yes	Yes	Yes	Yes	No	No	Raf, FLT3	III	Yes
Sunitinib	Yes	Yes	Yes	Yes	No	No	FLT3	II	No
Vandetanib	Yes	Yes	No	No	No	Yes	*RET-KIF5B rearrangement*	III*	Yes
Vemurafenib	No	No	No	No	No	No	$BRAF^{V600E}$, CRAF	II	No
Everolimus	No	No	No	No	No	No	mTOR	II	No
Temsirolimus	Yes	No	No	No	No	No	mTOR	II	No

*These drugs have also been tested in phase IV studies devoted to verifying the activity and the adverse events of different daily dosages of the drug.

Bcr-Abl, Abelson and breakpoint cluster region fusion gene; CSF-1R, colony stimulating factor 1 receptor; EGF-R, epidermal growth factor receptor; FGF-R, fibroblast growth factor receptor; KIT, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene; Raf, v-raf murine sarcoma viral oncogene homolog; $BRAF^{V600E}$, valine to glutamic acid substitution of BRAF gene; CRAF, v-raf murine sarcoma viral oncogene homolog 1; FLT3, Fms-like tyrosine kinase 3; MEK, mitogen activated protein kinase; MET, hepatocyte growth factor [HGF] receptor; PDGF-R, platelet-derived growth factor receptor; RET, REarranged during Transfection receptor; RET gene fusions: KIF5B-RET, CCDC6-RET and NcoA4-RET; VEGF-R, vascular endothelial growth factor receptor.