

Tyrosine kinase inhibitors for the treatment of thyroid cancer: present and future

Abstract

Thyroid cancer (TC) is the most common endocrine malignancy. In the majority of cases TC is curable by means of surgery followed when indicated by radioiodine therapy. However, in about 10% of cases the disease is no longer curable with conventional treatments. Until recently, no effective therapeutic options were available for advanced cases. The advances in the field of molecular biology and the discovery of the oncogenes involved in TC pathogenesis and pathways implicated in disease progression led to the development and testing of a new family of promising drugs, tyrosine kinase inhibitors (TKIs). These drugs generally bind multiple membrane tyrosine kinase receptors (TKRs) and arrest tumoral cell proliferation and disease progression. Although up to now the benefits in terms of prolongation of overall survival remains to be established, robust data about an improvement in the progression free survival (PFS) in TC (particularly papillary/follicular TC treated with lenvatinib) with disease progression were provided and demonstrated to outweigh the risks. An update of approved and promising drugs for progressive TC is reported.

Keywords: differentiated thyroid cancer, papillary, follicular, medullary and anaplastic thyroid cancer, tyrosine kinase inhibitors, *BRAFV600E*, *RET* mutation

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Abbreviations: TKIs, tyrosine kinase inhibitors; TKRs, tyrosine kinase receptors; TC, thyroid cancer; PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; MTC, medullary thyroid cancer; PDTC/ATC, poorly differentiated/anaplastic thyroid cancer; VEGFR, vascular endothelial growth factor receptor; RAI-R, radioiodine refractory; PFS, progression free survival; AEs, adverse events; SAEs, serious adverse events

Introduction

Thyroid cancer (TC) is the ninth most common cancer in United States and the most common endocrine malignancy. Moreover, it is the fastest growing neoplasm in the United States with an estimated number of new cases of 62,450 in 2015. This tumor represents 3.8% of all new cancer cases with 1,950 estimated deaths that correspond to 0.3% of all cancer deaths per year. Despite its increasing incidence, it seems that thyroid cancer mortality, that is about 3% at 5 years, remained stable over the last two decades.¹ This led some authors to the conclusion that probably we are facing the diagnosis of indolent tumors that in some cases do not need treatment.²

In fact, in the majority of cases, TC is one of the most curable cancers by means of surgery followed when indicated by radioiodine therapy. However, in about 10% of cases the disease is not curable with conventional treatments and until the introduction of tyrosine kinase inhibitors (TKIs) no effective therapeutic options were available for advanced cases. An update on approved and promising drugs is reported.

Thyroid cancer histotypes

TC is classified in differentiated: papillary (PTC) (80%) and follicular (FTC) (10-15%) thyroid cancer that originates from follicular cells, medullary thyroid cancer (MTC) (2-3%) that originates from parafollicular C cells and poorly differentiated and anaplastic thyroid cancer (PDTC and ATC) (5-10%) that have lost in part or completely

the features of the cell of origin.³

Genetic alterations

Several genetic alterations have been described in TC (e.g. *BRAFV600E*, *RAS*, *RET*, etc). The most common mutations in TC are: *BRAFV600E*, which is most frequent in PTC, *RAS* mutation in FTC, *BRAFV600E* and *RAS* equally expressed in ATC, and *RET* mutation which is the most frequent mutation in MTC. Gene copy gain and the over expression of tyrosine kinase receptors (TKRs) are other molecular features that can contribute to TC development and/or disease progression (e. g. VEGFR, MET/HGFR, etc.).³

Tyrosine kinase inhibitors

Until recently, no therapeutic options were available for patients not achieving disease cure by surgery and patients who were not or no longer responsive to radioiodine treatment; the so called radioiodine refractory (RAI-R) disease. In fact external beam radiotherapy (EBRT) and classical chemotherapy have low efficacy in terms of tumor burden control and only transient response despite significant toxicity. Novel insights into the molecular mechanism responsible for thyroid carcinogenesis, cell proliferation and disease progression lead to the development of new drugs able to inhibit the catalytic activity of TKR to obtain an antiproliferative effect, which is now known as the era of targeted TC therapies.

Although many TKI are under evaluation for the treatment of TC, at the moment the most interesting drugs are vandetanib and cabozantinib for MTC and sorafenib and lenvatinib for PTC/FTC. All these drugs inhibit multiple TKRs with different potency and have in common the inhibition of vascular endothelial growth factor receptor (VEGFR). A novel drug that acts with a completely different mechanism is selumetinib. Unlike other TKIs which are multikinase inhibitors, selumetinib is a selective MEK 1/2 inhibitor (Table 1).

Clinical trials

In 2011 the good results of ZETA trial in terms of progression free survival (PFS) compared with placebo led to FDA approval of vandetanib for the treatment of MTC.⁴ The following year another TKI, cabozantinib, was shown to prolong PFS compared with placebo in a cohort of progressive MTC that in some cases were previously treated with other TKIs (EXAM trial).⁵ In 2013, sorafenib, which was already approved for the treatment of clear renal cell carcinoma and hepatocarcinoma, was demonstrated to be effective also for RAI-R PTC/FTC and with disease progression and approved for its treatment (DECISION trial).⁶ More recently, lenvatinib was demonstrated to prolong PFS of more than 14 months in a large cohort of PTC/FTC and in poorly differentiated TC despite prior treatment with other TKIs (SELECT trial).⁷ All these studies except ZETA trial enrolled only patients with progressive disease demonstrated radiologically in two consecutive CT scans performed within 12-14 months. The

results obtained in these trials are summarized in Table 2.

Safety and tolerability

The treatment with TKI is safe but adverse events (AEs) are frequent. All drugs share the same spectrum of toxicities. The most common AEs for these drugs are hypertension, diarrhoea, fatigue, anorexia and weight loss but with a different prevalence (Table 3). These drugs are quite well tolerated but the dose that was used in the different trials led in many cases to drug interruption or dose decrease due to severe AEs or intolerable such as toxicities (e.g. hand and foot syndrome for sorafenib, prolonged QT interval for vandetanib). However, if known and prevented side effects are quite well tolerated and drug withdrawal is rare. Serious AEs (SAEs) are less common and generally reversible after drug discontinuation (e.g. hypertension for lenvatinib, proteinuria for cabozantinib and lenvatinib).

Table 1 Half maximal inhibitory concentration (IC_{50}) of the approved and most promising TKIs for Thyroid Cancer

IC_{50} (nM)									
Drug	VEGFR1	VEGFR2	VEGFR3	RET	MET	KIT	BRAF	MEK1/2	Other
Vandetanib	1,600	40	108	130	-	-	-	-	EGFR (500)
Cabozantinib	-	0.035	-	4.5	1.8	-	-	-	-
Sorafenib	-	90	20	5.9	-	68	22	-	CRAF (6)
Lenvatinib	22	4	-	35	-	-	-	-	FGFR1 (25)
Selumetinib	-	-	-	-	-	-	-	14	-

Table 2 Results of the approved and most promising TKIs for thyroid cancer.

Drug	No. of Patients	Disease Progression	Histotype	Trial Name	Phase	RR (%)
Vandetanib	331	Not Required	MTC	ZETA	III	-
Cabozantinib	330	14 months	MTC	EXAM	III	28 vs 0
Sorafenib	417	14 months	PTC/FTC/PDTC*	DECISION	III	12.2 vs 0.5
Lenvatinib	392	12 months	PTC/FTC/PDTC*	SELECT	III	64.8 vs 1.5
Selumetinib [#]				ASTRA	III	

RR, response rate; PFS, progression free survival

*Forty and 47 PDTC patients were enrolled in DECISION and SELECT trial respectively

[#]This trial is recruiting participants and no results are unavailable at the moment

Table 3 The most common AEs for these drugs are hypertension, diarrhoea, fatigue, anorexia and weight loss but with a different prevalence.

Adverse Event	Drug			
	Vandetanib	Cabozantinib	Sorafenib	Lenvatinib
Hypertension	33%	33%	9%	73%
Diarrhea	57%	63%	55%	67%
Fatigue	24%	41%	46%	67%
Anorexia	21%	46%	29%	54%
Weight Loss	-	48%	30%	51%

Future directions

All TKIs developed so far are only able to block cell proliferation and disease progression until tumoral cells develop an “escape” mechanism that leads again to uncontrolled proliferation and to disease progression. Future clinical research should address which sequence of drugs or combination would guarantee a better result in terms of PFS and survival.

All TKIs investigated for TC treatment are cytostatic. New lines of research should move to the development of novel and less toxic drugs or to a combination of drugs that could lead to tumoral cell death. Hypothetically this objective can be achieved by combining different TKIs with classical cytotoxic chemotherapeutic agents or EBRT but this remains to be established. Another option that could play a significant role in the near future for TC patients could be the use of a drug that was recently demonstrated to restore and/or potentiate radioiodine uptake (e.g. selumetinib).⁸ Another promising new area of research will be the development of drugs that could modulate the human immune system against the tumor as recently demonstrated for the treatment of metastatic melanoma with ipilimumab, a novel monoclonal antibody.⁹

Discussion

The description of the genetic alterations involved in the pathogenesis and progression of solid tumors led to development of a novel family of drugs called TKIs. Since the approval of the first TKI for the treatment of chronic myelogenous leukaemia. 2001 several drugs were investigated for the treatment of TC patients. Until 2011 the only drug that was approved for TC treatment was doxorubicin. However, this chemotherapeutic agent had a significant toxicity and the tumoral response was not durable. In the last 4 years four new drugs that belong to the family of TKIs were approved for the treatment of advanced TC patients. These drugs block with different potencies multiple TKRs, but interestingly, all of them have in common the inhibition of VEGFR. Angiogenesis is considered one of the main players in the progression of solid tumors. The inhibition of angiogenesis in addition to the inhibition of other TKRs that are over expressed in TC is the reason of the effectiveness of TKI treatment.

Until now two alternative treatments are available for the treatment of the two most frequent TC histotypes. Vandetanib and cabozantinib for MTC and sorafenib and lenvatinib for RAI-R PTC/FTC. In particular the latter drug was demonstrated to be effective also for the treatment of poorly differentiated TC. All these drugs were demonstrated to prolong significantly the PFS of the cohort of patients treated with the drug compared to those treated with placebo (Table 2).

Despite the good results in terms of partial remission and PFS compared with placebo, after a variable period of time (about 7 months MTC and 5-14 months for PTC/FTC) the disease no longer responded to TKI treatment. Moreover, there is no scientific evidence that patients receiving TKI had an advantage over untreated patients in terms of overall survival, rather than PFS. This could be attributed to various reasons, in fact, the patients that experience disease progression while treated with placebo has the possibility to be treated with the drug (“cross over”). Other reasons could be the possibility to be treated with other TKIs when disease progression is demonstrated, the rarity of the disease and the relative small sample sizes of all studies.

Although the first line treatment and the superiority of one drug compared with another are not established yet, the population enrolled

in the EXAM (MTC patients) and SELECT (PTC/FTCPDTC) studies demonstrated that cabozantinib and lenvatinib were effective also in the cohort of patients previously treated with other TKIs suggesting that these treatments could be reserved for the patients that experience disease progression while on treatment with vandetanib or sorafenib, respectively. Even if severe AEs and SAEs are rare and could be prevented in the majority of cases, all patients experience at least an AE that impairs their quality of life. Considering that these drugs are not free of side effects and that TC remains stable for a long period of time, in the presence of stable or slowly progressive and asymptomatic disease, TKI treatment is not indicated and should not be administered until disease progression in 12-14 months according to RECIST criteria is demonstrated.

Conclusion

In the last decade many TKIs were evaluated for TC treatment. Even if some drugs are still under evaluation, so far only 4 drugs were approved for TC treatment by the Food and Drug Administration (FDA) and the European Medicine Agency (EMA). Considering that in many cases TC is stable or slowly progressing for a long period of time and that TKI treatment is the cause of several AEs that impair the patient’s quality of life, only those with progressive disease (increase of 30% or more in the size of the target lesion) should be treated with these drugs. When the patients experience disease progression while on treatment, before interrupting the drug, alternative therapies with other TKIs should be considered and administered to avoid serious consequences.

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Conflicts of interest

The author declares there is no conflicts of interest.

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