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Critical Reviews in Oncology/Hematology 93 (2015) 60–73

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

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The evolving field of kinase inhibitors in thyroid cancer

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Accepted 19 August 2014

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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http://dx.doi.org/10.1016/j.critrevonc.2014.08.007
1040-8428/

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

Table 1
Molecular targets of the kinase-inhibitors mentioned in the text.

Compound	RET	BRAF	RAF-1	mTOR	c-MET	c-Kit	VEGFR1	VEGFR2	VEGFR3	PDGFRα	PDGFRβ	EGFR	FGFR1	MEK
Motesanib	X					X	X	X	X	X				
Axitinib							X	X	X					
Imatinib	X					X				X	X			
Sorafenib		X	X					X	X		X			
Sunitinib	X					X	X	X		X	X			
Vandetanib	X							X	X			X		
Lenvatinib						X	X	X	X		X		X	
Pazopanib						X	X	X	X	X	X			
Cabozantinib	X				X		X	X						
Vemurafenib		X*												
Dabrafenib		X*												
Everolimus				X										
Selumetinib														X

* Mutant $BRAF^{V600E}$.

of chimeric genes, namely RET/PTC, which are ectopically expressed in thyroid follicular cells and promote neoplastic transformation through the activation of both MAP kinases and PI3K/Akt/mTOR pathways [38,39]. Besides, RET has a prominent role in the molecular pathogenesis of MTC. Indeed, germline RET point mutations are responsible for hereditary forms of MTC [40], while approximately 50% of sporadic MTCs harbour activating RET mutations [41]. The crucial pathogenetic role of RET in this field has been widely supported by studies on transgenic mice [42,43]. More importantly, there is a clear correlation between genotype and tumour behaviour. A codon 918 somatic RET mutation, which affects the catalytic domain of the receptor, predicts a high rate of metastasis and death in sporadic forms of MTC [44]. The mutation can also be inherited, thus inducing multiple endocrine neoplasia 2B syndrome which is characterised by precocious and aggressive MTC, even treated with prophylactic surgery in the first year of life [45]. Besides single point mutations and chromosomal rearrangements, genetic amplification or copy number gain of genes with kinase activity has been reported in thyroid cancer [21]. A recent study performed by Liu et al. [46], focusing on FTC and ATC, identified copy number gains of several tyrosine-kinase receptors (EGFR, PDGFRα and β, VEGFR1 and 2, c-MET, and c-KIT) and other intracellular kinases (PDK1, Akt-1, Akt-2, PIK3CA, and PIK3CB). The pathogenetic role of these genetic alterations was demonstrated in the same paper, where the activation of the downstream signalling pathways was observed, as attested by the increased phosphorylation of AKT and ERK. Interestingly, copy-number gains of these genes were more frequent in ATC than in FTC, thus suggesting a role of these genetic events in the progression and aggressiveness of thyroid cancer. Furthermore, over-expression of receptors with tyrosine kinase activity (EGFR, c-Met, and FGFR4) has been found also in MTC [47–49]. Pre-clinical data providing crucial support for the use of KIs in thyroid cancer have been published by Xing and his research group. Indeed, these workers have assessed activity of several KIs in thyroid cancer cell lines carrying or not carrying mutations in those molecular pathways specifically targeted by the tested agents. The authors clearly showed that the anti-proliferative effect of the compounds studied was mostly dependent on the presence of genetic alterations involving their own targeted intracellular cascades [50–52]. This genetic dependency has been interpreted by the authors as being related to the driving role of genetic alterations involving the MAP kinases and the PI3K/Akt/mTOR pathways, which induce addiction in those cells harbouring the mutation. As aforementioned, the anti-cancer activity of KIs is related not only to the anti-proliferative function but also to the anti-angiogenetic activity. The pathogenetic role of neo-angiogenesis has been demonstrated in several types of endocrine tumours, including thyroid cancer [53–57]. In particular, elevated expression of angiogenic factors – including VEGF, EGF, and their receptors – has been detected in cell lines, tumour tissues and serum of patients affected with thyroid cancer of follicular origin and was found to be strongly correlated with tumour behaviour [58–61]. Furthermore, a single nucleotide polymorphism of the VEGFA gene, the so-called rs699947, has been found to be associated with the development and aggressiveness of thyroid cancer in men [62]. In PTC, the intensity of VEGF expression correlates with a higher risk of metastasis and recurrence, a shorter disease-free survival, and BRAF mutation status (which is considered an independent negative prognostic factor) [63–65]. These observations strongly suggest that striking angiogenetic pathways by the use of KIs represents a feasible approach for the treatment of thyroid cancer.

3. Clinical trials of KIs in thyroid cancer

3.1. Differentiated thyroid cancer

3.1.1. Current status

Among DTC patients the need for innovative therapies is limited mainly to those who are refractory to RAI. Since 2008, several studies of KIs in RAI-refractory DTC have been published (results reported in Table 2). Although few data are available so far, guidelines from the American

Table 2
Efficacy of kinase-inhibitors for the treatment of iodine-refractory DTC in available trials.

KI [Ref.]	Type of study	N. of patients	Best TR (%)	mPFS (months)
Motesanib [68]	II	93	CR 0 PR 14 SD 67	10
Axitinib [69]	II	45	CR 0 PR 31 SD 42	–
Axitinib [70]	II	32	CR 0 PR 41 SD 18	–
Sunitinib [72]	II	29	CR 3 PR 24 SD –	–
Sorafenib [73–77]	II, retrospective	122	CR 0 PR 15-30 SD 34-71	9–21
Sorafenib [78]	III, RCT, placebo controlled	207 sorafenib	CR 0 PR 12.2* SD 42	10.8*
		210 placebo	CR 0 PR 0.5 SD 33	5.8
Lenvatinib [81]	II	58	CR 0 PR 54 SD 46	13.3
Lenvatinib [82]	III, RCT, placebo controlled	392 (2:1 to lenvatinib or placebo)	CR 1.5 PR 63.2 SD –	18.3*
			CR 0 PR 1.5 SD –	3.6
Pazopanib [83]	II	37	CR 0 PR 49 SD 46	11.7
Vandetanib [85]	II, RCT, placebo controlled	72 vandetanib	CR 0 PR 8 SD –	11.1*
		73 placebo	CR 0 PR 5 SD -	5.9
Vemurafenib [90]	II	26 Kis-*naive*	CR 0 PR 35 SD 23	15.6
		25 Kis-pretreated	CR 0 PR 26 SD 10	6.8
Everolimus [99]	II	24	CR 0 PR 4.2 SD 95.8	10.75
Everolimus [100]	II	33	CR 0 PR 3 SD 55	16
Everolimus + sorafenib [102]	II	19	CR 0 PR 57.9 SD 36.8	–
Selumetinib [108]	II	39	CR 0 PR 3 SD 54	8

Abbreviations: KI, kinase-inhibitor; Ref., reference; N., number; TR, tumour response; Mpfs, median progression-free survival; CR, complete response; PR, partial response; SD, stable disease; RCT, randomised controlled trials.
* Difference statistically significant.

Thyroid Association [6] have recommended the use of KIs in this clinical setting since 2009. Despite still being a controversial issue, the demonstration of disease progression represents the main indication for referring iodine-refractory DTC patients for medical treatment [66,67]. Thus, trials that selectively enrolled patients with a documented progressive disease should be considered as having a higher clinical relevance, rather than those not requiring disease progression before entry. The first published paper about use of KIs in this field was a phase-II trial with motesanib [68], which targets the tyrosine-kinase receptors RET, c-Kit, PDGFRα and all three types of VEGFRs. Notably, only patients showing disease progression in the previous 6 months were enrolled. A rate of 14% of subjects had a partial response (PR) and 67% had stable disease (SD) with a median PFS (progression-free survival) of 10 months. Axitinib targets mainly VEGFRs, thus exhibiting a predominant anti-angiogenic action. A phase-II clinical trial by Cohen et al. [69], including 45 patients affected with DTC, showed PR in 31% and SD in 42% of these subjects. Nevertheless, the study was limited by the inclusion of patients with heterogeneous disease aggressiveness, as the evidence of radiological progression was not required before entry. By contrast, a recent contribution presented at the American Society of Clinical Oncology (ASCO) 2014 meeting has assessed the activity of axitinib in 32 iodine-refractory DTC patients having documented disease progression [70]. Authors reported objective tumour response in 41% of subjects, thus suggesting a meaningful role for axitinib in this clinical setting. Sunitinib targets RET, c-Kit, VEGFR1 and 2, and PDGFRα and β. It seems to be effective against endocrine cancers as it has been approved for the treatment of advanced pancreatic neuroendocrine tumours [71]. Nevertheless, the efficacy of sunitinib for the treatment of DTC has been studied only in one phase-II clinical trial, where patients were included independently of the demonstration of disease progression [72]. Authors reported a case of complete response to treatment in one out of 29 patients affected with DTC, while seven more subjects (24%) achieved PR. SD was obtained in 48% of the overall study population which included also six patients with MTC. The most studied KI for the treatment of RAI-refractory DTC is sorafenib. Its specificity was suggested by the inhibition of the RAF kinases, which are strikingly involved in the development and progression of thyroid cancer [20]. From 2008 to 2012, several studies with heterogeneous designs and inclusion criteria have assessed the activity of sorafenib in this field [73–77]. A meta-analysis of these papers, including a total of 122 patients, showed PR rates between 15% and 30% and SD rates from 34% to 71% with a median PFS ranging from 9 to 21 months. These findings led to the first phase-III trial of any KI in DTC. The DECISION study (NCT00984282) was a randomised, placebo-controlled, double-blind, multicentre, international study enrolling KIs-*naive* RAI-refractory DTC patients showing disease progression in the previous 14 months. Results from the DECISION trial have been recently published [78]. Overall, 417 patients were enrolled (207 to sorafenib and 210 to placebo). Tumour histology assessed by independent review revealed 57% PTC, 25% FTC, and 10% PDTC. A significant improvement in median PFS was observed in the sorafenib group as compared with placebo (10.8 versus 5.8 months; HR 0.58, 95%CI 0.45–0.75, $P < 0.0001$), and this was the primary endpoint of the study. Median overall survival (OS) was not reached in either group, and, given that 70% of placebo patients crossed over, it is likely that no differences would have been found. PR rate in the sorafenib versus

placebo arm was 12.2% and 0.5% ($P < 0.0001$), while the SD rate lasting more than 6 months was 42% and 33%, respectively. Based on these efficacy results, sorafenib has become the first KI approved by the US Food and Drug Administration (FDA) for the treatment of progressive RAI-refractory DTC. The most frequent treatment-related adverse events reported in the DECISION trial were hand–foot skin reaction (76.3%), diarrhoea (68.6%), alopecia (67.1%), rash or desquamation (50.2%), fatigue (49.8%), weight loss (46.9%), and hypertension (40.6%). It should be noted that, despite being mostly of grade 1 or 2, these toxicities led to dose interruptions, reductions, or withdrawals in 66.2%, 64.3%, and 18.8% of patients, respectively. This represents a crucial issue for the clinical use of sorafenib, as many patients with iodine-refractory DTC are asymptomatic, even if disease progression is documented. Lenvatinib targets RET, c-Kit, VEGFRs, FGFR1 and PDGFRβ. Inhibition of human xenograft tumour growth by lenvanitib was observed at doses as low as 1.0 and 10.0 mg/kg, suggesting greater efficacy than the majority of pre-tested KIs [79]. Recently, an inhibitory effect of lenvatinib on both oncogenic signal and cell growth has been demonstrated in thyroid cancer cell lines harbouring RET fusion genes [80]. Exciting results for lenvatinib in DTC were first obtained in a phase-II trial of 58 RAI-refractory patients [81] with progressive disease, where authors reported 54% of PR and 46% of SD. These data led to a randomised, placebo-controlled, double-blind, multicentre, international phase-III study enrolling RAI-refractory DTC patients with documented disease progression in the previous 13 months (SELECT trial, NCT01321554). Results from the SELECT trial have recently been presented at the ASCO 2014 meeting [82]. Overall, 392 patients were enrolled and randomised with a 2:1 ratio to lenvatinib or placebo. A significant improvement in median PFS was observed in the lenvatinib group as compared with placebo (18.3 versus 3.6 months; HR 0.21, 95%CI 0.14–0.31, $P < 0.0001$), thus achieving the primary endpoint of the study. Given that cross-over was allowed for patients receiving placebo upon progression, median OS was not reached. Notably, lenvatinib obtained an objective tumour response in 64.7% of patients, including four subjects (1.5%) who achieved complete responses. According to these results, lenvatinib seems to be more effective in both improving PFS (18.3 versus 10.8 months) and obtaining an objective tumour response (64.7% versus 12.2%) as compared with sorafenib. These data are even more meaningful if it is considered that the SELECT trial enrolled patients with more advanced disease who had been already treated with KIs, whereas the DECISION trial did not allow previous KI treatment. The most frequent treatment-related adverse events reported in the SELECT trial were hypertension (68%), diarrhoea (59%), appetite decrease (50%), weight loss (46%), and nausea (41%). As with sorafenib, the reported toxicities were mainly grade 1 or 2, but led frequently to dose reductions or withdrawals (78.5% and 14.2%, respectively). Pazopanib is a KI targeting c-Kit, VEGFRs and PDGFRs. Like axitinib, its activity is expected to be primarily anti-angiogenetic. In 2010, a multicentre phase-II trial headed by the Mayo Clinic [83] tested activity of pazopanib in 37 RAI-refractory DTC patients. Distinctive features of the study were that up to two previous systemic treatments (including KIs) were allowed, and radiographic progression of disease was requested in the 6 months preceding the enrolment. These criteria led to the selection of a population of highly aggressive RAI-refractory DTC cases. Notably, authors found a PR rate of 49%, while 46% of patients experienced SD. Furthermore the likelihood of a response lasting more than 1 year was calculated to be 66%. Notably, PRs were higher in FTC than in PTC (73% versus 33%). Vandetanib is a KI that targets RET, VEGFR2, VEGFR3, and EGFR. As discussed below, it has been already approved by the FDA for the treatment of adults with symptomatic or progressive MTC [84]. In 2012, Leboulleux et al. [85] have performed a randomised, multicentre, placebo-controlled, phase-II trial of vandetanib in RAI-refractory DTC, with no requirement of disease progression for enrolment. Although no significant difference was found in radiological response between groups, authors demonstrated a significant improvement of PFS in the treatment group compared with placebo (11.1 versus 5.9 months; HR 0.63, 60%CI 0.54–0.74, one-sided $P = 0.008$; 95%CI 0.43–0.92, two-sided $P = 0.017$), thus achieving the primary endpoint of the study. This discrepancy could be related to at least two issues: (a) the inclusion of patients with heterogeneous disease aggressiveness, and (b) the use of RECIST criteria, which are based solely on the dimensional assessment, thus excluding the evaluation of tumour necrosis, a recognised marker of response to targeted therapies [86]. Another relevant finding of the study was that the positive effect of vandetanib on PFS was stronger for the PTC histotype. It was concluded that vandetanib may be a useful tool for the long-term control of patients with iodine-refractory DTC (especially PTC). Nevertheless, toxicity of vandetanib was worse than that of other KIs. Indeed, adverse events leading to discontinuation were detected in 33% of the vandetanib group, QTc prolongation and diarrhoea being the most frequent. Furthermore, two drug-related fatal events (haemorrhage from skin metastases and pneumonia) were reported. Thus, the toxicity profile hampers the long-term administration of vandetanib in this clinical setting.

3.1.2. Future perspectives

In recent years a new class of pyridoimidazolone-containing molecules, including vemurafenib and dabrafenib, has been introduced into clinical trials. These drugs act as potent and selective inhibitors of the BRAFV600E oncogene, and this provides the rationale for testing their efficacy in tumours harbouring the BRAF mutation. The responsivity to vemurafenib and dabrafenib in melanoma patients harbouring mutated BRAF suggests that these agents may be effective also in advanced thyroid cancer harbouring BRAF mutation [87,88]. Recently, an anecdotal

experience about use of vemurafenib in three patients affected with RAI-refractory PTC, who were positive for the BRAF mutation, has been published [89]. A radiological response was demonstrated in all subjects. In particular, one patient achieved PR with a time to progression of 11.7 months, whereas SD was observed in the remaining two subjects, with a time to progression of 13.2 and 11.4 months, respectively. This led to an open-label, multicentre, phase-II trial (NCT01286753) about vemurafenib in RAI-refractory PTC patients harbouring the BRAFV600E mutation; this trial is still ongoing, but has recently terminated recruitment. Preliminary results have been presented at the European Cancer Congress (ECC) 2013 meeting [90]. Among the 51 patients enrolled, two cohorts were individualised, on the basis of the previous assumption of KIs (naive or pre-treated). PR was observed in 35% of the KIs-naive patients and in 26% of the pre-treated patients, whereas clinical benefit (PR + SD) was observed in 58% and 36%, respectively. Furthermore, PFS was higher in the naive group, as compared with the patients pre-treated with KIs (15.6 and 6.8 months, respectively). Treatment was almost well-tolerated – rash, fatigue, weight loss, and increased bilirubin being the most common adverse events. Hence, authors concluded that vemurafenib has a relevant anti-tumour activity in PTC patients harbouring BRAFV600E, especially in the subgroup without previous KI treatment. This could be related – at least in part – to the positive selection of neoplastic clones without the BRAF mutation that could occur in patients pre-treated with KIs, where alternative intracellular pathways are activated in order to circumvent the molecular blockade, thus promoting the failure of the targeted therapy [91]. Nevertheless, the trial did not require demonstration of disease progression before entry, and this reduces its clinical relevance. Everolimus is a selective inhibitor of mTOR, a serine/threonine kinase that plays an important role in cellular growth and homeostasis [92]. Recent studies have found that the mTOR pathway is involved in the pathogenesis of several endocrine cancers such as neuroendocrine tumours and adrenocortical carcinoma [93–98]. Everolimus has been approved recently for the treatment of advanced pancreatic neuroendocrine tumours [84]. In December 2013, Lim et al. [99] published the first clinical trial of the activity of everolimus in aggressive forms of thyroid cancer in cases where RAI was ineffective or inappropriate. Thus, thyroid malignancies of any histology were included. Importantly, only patients having progressive disease were enrolled. Despite the fact that data about specific histotypes were not precisely reported, disease control was obtained in the vast majority of DTC patients, with a median PFS of 10.75 months. Nevertheless, PR was reported in only one DTC subject. Another phase-II trial about everolimus in RAI-refractory thyroid cancer (including MTC and ATC) had already been presented at the ASCO meeting in 2013 [100]. Thirty-three DTC patients with documented disease progression in the previous 6 months were enrolled. PFS, which was the primary endpoint, was 16 months. Consistently with reports by Lim et al., only one patient experienced PR, whereas 18 (55%) and ten (30%) achieved SD lasting 6 and 12 months, respectively. Activation of autophagy without markers of apoptosis was detected in three patients subjected to sequential biopsies, and this is consistent with the increasing trend to achieve disease stability rather than an objective tumour shrinkage. Carracedo et al. [101] has demonstrated that mTOR inhibition can activate MAPK through a PI3K-dependent feedback loop in human cancer, thus inducing therapeutic escape. Hence, a combination of everolimus with KIs targeting alternative signalling pathways may yield both an improved efficacy and a longer response. A phase-II trial (presented at the ASCO meeting 2013) has assessed the combination of sorafenib (400 mg twice a day) and everolimus (10 mg daily) in progressive RAI-refractory thyroid cancer, excluding the anaplastic histotype [102]. Among DTC patients, PR rates were higher than those reported for sorafenib as a single agent, the Hurtle cell FTC variant being the most responsive histotype (PR = 67%). Nevertheless, authors reported the occurrence of several grade-4 adverse events, which were likely related to the combined study treatment. In past years, several medical treatments – including lithium [103] and retinoids [104] – have been tested in order to restore RAI avidity in patients with iodine-refractory DTC, but no relevant results were obtained. Selumetinib is a selective inhibitor of MEK, which is a dual-specificity kinase having both serine–threonine and tyrosine kinase activity. Importantly, MEK represents the primary downstream target of B-RAF [105]. In 2007, Liu et al. demonstrated that targeting the MAP kinases cascade through a specific MEK inhibitor could restore expression of thyroid iodide-metabolising enzymes in rat cells harbouring the BRAFV600E mutation [106]. This insight was further empowered by Chakravarty et al., who published pre-clinical data from mouse models in which switching off downstream signalling from BRAF has led to the regain of the tumour's RAI avidity [107]. These findings led to a growing interest in selumetinib as a feasible therapeutic tool for thyroid cancer. To date, anti-tumour activity of selumetinib in progressive iodine-refractory DTC has been assessed by Hayes et al. [108], with unsatisfactory results. Indeed, the authors found a higher rate of disease progression (28%) and a shorter PFS (8.25 and 2.75 months in patients with and without BRAF mutation, respectively), as compared with the majority of other KIs. Nevertheless, Ho et al. [109] have recently published a trial assessing the possible role of selumetinib in resensitising DTC to RAI. Patients were treated with selumetinib 75 mg twice daily for 4 weeks and were than re-evaluated with an iodine-124 positron-emission tomography (PET) scan. Restoration of RAI uptake was observed in eight out of 24 subjects (40%). These patients were subjected to RAI treatment and all of them achieved clinical benefit with confirmed PR in five and SD in three patients. Notably, these responses lasted more than 6 months in the majority of subjects (seven patients). Hence, selumetinib may restore RAI avidity in a relevant proportion of RAI-refractory DTC patients, thus retrieving

the efficacy of RAI. The possible role of selumetinib in enhancing tumour responsiveness to RAI led to a phase-II study comparing the efficacy of the combination selumetinib (administered in a 5-week course, 75 mg twice daily) with adjuvant RAI versus placebo with single-adjuvant RAI in determining remission of DTC with a high risk of treatment failure (primary tumour >4 cm, or gross extra-thyroid extension, or one lymph node >1 cm, or five or fewer lymph nodes of any size) (NCT01843062). Currently, this trial is actively recruiting.3.2 Medullary thyroid cancer.

3.2. Medullary thyroid cancer

3.2.1. Current status

Results from available clinical trials on the use of KIs in advanced MTC are reported in Table 3. Given its ability to inhibit RET at low concentrations [110], imatinib was the first KI assessed in this field. Nevertheless, results from two small-sized studies showed no reduction in tumour size, although several subjects had SD [111,112]. Axitinib blocks VEGFRs but not RET. This may explain why, in the Cohen's trial [69], results achieved in the 11 patients with medullary histology were poorer than those in DTC subjects. In particular, disease control rate (PR and SD) of the MTC cohort was less than 50%. In a phase-II study performed by Schlumberger et al., which enrolled MTC patients showing either disease progression or symptomatic disease, [113] motesanib achieved PR in only 2% of subjects, while 81% achieved SD. Nevertheless, only 47% of patients experienced SD lasting more than 6 months. Sorafenib efficacy in MTC was evaluated in two small phase-II studies performed by Ahmed et al. [114] and Lam et al. [115], where objective tumour shrinkage was obtained in 25% and 7%, respectively. Notably, only in Ahmed's trial was disease progression required before entry. In the aforementioned phase-II trial of sunitinib in thyroid cancer, PR was achieved in 43% of patients with MTC, but the sample size was extremely small [72]. Vandetanib is a KI that targets RET, VEGFR2, VEGFR3 and EGFR. In April 2011 and in February 2012, it was approved for the treatment of adults with symptomatic or progressive MTC by the US FDA and the European Medicines Agency (EMA), respectively. Activity of vandetanib on RET activation in cell lines harbouring RET/MEN2B mutation was first reported by Carlomagno et al. in 2002 [116]. Later on two phase-II studies were performed to assess the activity of vandetanib in patients with hereditary advanced MTC. Wells et al. [117] achieved PR in six out of 30 patients (20%), while 73% of subjects achieved SD. Nevertheless, only 53% of subjects achieved SD lasting at least 6 months. Robinson et al. [118] reported similar results administering vandetanib at a lower dose (100 mg/day versus 300 mg/day). Therapeutic efficacy of vandetanib was definitely demonstrated in a randomised, double-bind phase-III clinical trial enrolling 331 patients with advanced MTC (ZETA trial, NCT01876784) [119]. Patients were randomised in a 2:1 ratio to vandetanib 300 mg daily versus placebo. Authors clearly showed significant improvements in objective response rate (45% versus 13%; $P<0.001$), disease control rate (87 versus 71; $P=0.001$), calcitonin response (69% versus 3%; $P<0.001$), and CEA response (52% versus 2%; $P<0.001$) in patients treated with vandetanib compared with the placebo group. Despite not reaching the median in the vandetanib group, a significant prolongation of PFS, which was the primary endpoint of the study, was demonstrated in patients who received vandetanib compared with those on placebo, with an estimated 11-month increase (30.5% versus 19.3%; $P<0.001$). Interestingly, a post hoc analysis of RET mutational status found that vandetanib achieved a higher PR rate in sporadic

Table 3
Clinical trials in patients with advanced sporadic and hereditary medullary thyroid carcinoma.

KI [Ref.]	Type of study	N. of patients	Best TR (%)	mPFS (months)
Imatinib [111]	II	9	CR 0 PR 0 SD 40	–
Imatinib [112]	II	15	CR 0 PR 0 SD 78	–
Axitinib [69]	II	11	CR 0 PR 18 SD 27	–
Motesanib [113]	II	91	CR 0 PR 2 SD 81	12
Sorafenib [114]	II	15	CR 0 PR 25 SD 75	–
Sorafenib [115]	II	15	CR 0 PR 7 SD 93	17.9
Sunitinib [72]	II	7	CR 0 PR 43 SD 29	–
Vandetanib [117]	II	30	CR 0 PR 20 SD 73	27.9
Vandetanib [118]	II	19	CR 0 PR 16 SD 64	–
Vandetanib [119]	III, RCT, placebo controlled	231 vandetanib	CR + PR + SD 87*	30.5*
		100 placebo	CR + PR + SD 71	19.3
Vandetanib** [120]	I-II	15	CR – PR 47 SD –	–
Cabozantinib [122]	I	37	CR 0 PR 35 SD 49	–
Cabozantinib [123]	III, RCT, placebo controlled	220 cabozantinib	–	11.2*
		110 placebo		4
Everolimus [99]	II	9	CR 0 PR 0 SD 100	–

Abbreviations: KI, kinase-inhibitor; Ref., reference; N., number; TR, tumour response; mPFS, median progression-free survival; CR, complete response; PR, partial response; SD, stable disease; RCT, randomised controlled trials.

* Difference statistically significant.

** Only children (5–12 years) and adolescents (13–18 years) affected with MEN-2B included.

MTC harbouring the somatic M918T RET mutation than in M918T-negative cases (55% versus 31%). Nevertheless, severe and sometimes fatal adverse events were reported in a relevant portion of patients. The most frequent grade-3 or higher adverse events included diarrhoea (11%), hypertension (9%), QTc prolongation (8%), fatigue (6%), decreased appetite (4%), and rash (4%). The potential toxicity associated with long-term administration of vandetanib highlights the importance of appropriate selection of patients for treatment with this agent. The relatively indolent behaviour of disease in some patients with MTC who were enrolled onto the Wells trial, which did not require demonstration of progression before entry, is evident from the time to progression of 19.3 months in patients who received the placebo. For these reasons, the risk/benefit ratio of vandetanib is likely to be unfavourable in asymptomatic patients or in patients with a low disease burden who experience slow progression. Importantly, a recent phase-I/II trial by Fox et al. [120] has demonstrated that vandetanib (100 mg/m^2 administered once daily for 28 days treatment cycles) was effective in obtaining objective tumour response in a relevant proportion (PR = 47%) of children and adolescents with MEN2B-related MTC (carrying the germline M918 T mutation). Notably, the authors reported a more favourable toxicity profile compared with that in adults. The KI cabozantinib has been approved by the US FDA (November 2012) for the treatment of progressive, metastatic MTC. Similarly to vandetanib, cabozantinib targets both RET and VEGFRs. In addition, it is active against the receptor of the hepatocyte growth factor c-MET. It is noteworthy that increased co-expression of c-MET and its ligand has been demonstrated in a subset of MTC [48] and could be considered a direct result of RET signalling activity [121]. A preliminary phase-I study of cabozantinib was designed to identify the maximum tolerated dose in patients with a variety of solid tumours, including 37 subjects with MTC [122]. An early analysis reported an increased activity of cabozantinib in these patients, noting a reduction in serum calcitonin in all cases. This prompted the addition of an expansion cohort of patients with MTC within the trial. Among 35 patients with MTC having measurable disease, 25 (68%) had PR or SD for at least 6 months. Importantly, a response was observed in three patients who had been pre-treated with vandetanib or sorafenib, thus supporting the hypothesis of c-MET being an escape pathway from RET and VEFGR inhibition. These findings led directly to a multicentre, randomised, phase-III trial named EXAM (Efficacy of XL184 in Advanced Medullary Thyroid Cancer, NCT00704730) [123]. This study compared cabozantinib (administered daily at the dose of 140 mg) with placebo in 330 patients with locally advanced or metastatic MTC. Importantly, only patients with progressive disease were enrolled, and this represents a crucial difference from the vandetanib trial. Median PFS was 11.2 months in the treatment arm versus 4.0 months in the placebo arm, with a statistically significant difference of 7.2 months ($P < 0.001$). Interestingly, PFS was increased independently from prior systemic treatment, prior TKI use, and RET mutational status. In the light of these results cabozantinib can be considered an effective tool for MTC patients who experience disease progression despite chemotherapy and treatment with other KIs. Nevertheless, an interim analysis of OS (with 44% of 217 required events) showed no difference between the treatment and the placebo group. Given that this trial did not allow cross-over between groups, this failure in the improvement of OS represents a significant result. The toxicity profile of cabozantinib was generally similar to that of vandetanib, the most frequent grade 3 or higher adverse events being diarrhoea (15.9%), hand–foot syndrome (12.6%), fatigue (9.3%), hypertension (8.4%), and asthenia (5.6%). A dedicated analysis of RET and RAS mutations in the phase-III cohort was presented at the ASCO meeting in 2013 [124]. Despite obtaining clinical benefit in all subgroups, cabozantinib achieved a higher median PFS in RET-mutated tumours, as compared with RET wild-type counterparts (60 versus 25 weeks; $P < 0.0001$). Furthermore, patients with the poor prognosis M918T mutation showed a longer PFS as compared with other RET mutations (15 versus 9 months; $P = 0.009$). Finally, patients with RAS mutations achieved similar clinical benefit, as compared with subjects harbouring RET mutations.

3.2.2. *Future perspectives*

Based on the finding that the mTOR pathway is over-expressed in neuroendocrine tumours [93–95], some anecdotal experiences of the activity of everolimus in MTC have been published in recent years. Faggiano et al. [125] reported two cases of patients with advanced MTC under treatment with octreotide – long-acting and repeatable – who were subjected to treatment with everolimus. In both cases a tumour response was observed and a significant reduction in calcitonin levels was obtained. Furthermore, this study demonstrated anti-proliferative activity of everolimus in two different MTC cell lines. Druce et al. [126] described the case of a MEN2A patient with a pluri-metastatic progressive MTC where treatment with everolimus induced a transient radiological stabilisation of disease and a dramatic increase in the calcitonin doubling time. These reports have been confirmed mainly by Lim's trial [99], in which all MTC patients achieved SD. Furthermore, a decrease of >50% of calcitonin and CEA levels was observed in 30% and 44% of subjects, respectively. Interestingly, data about everolimus in pancreatic neuroendocrine tumours show a higher PFS in patients concomitantly treated with somatostatin analogues [127]. Somatostatin receptors are expressed in 85% of MTC [48], but previous studies failed to demonstrate any efficacy of somatostatin analogues in this field [128]. Recently, several authors have raised the hypothesis that combining a somatostatin analogue with a KI would have therapeutic value because there are links between somatostatin receptor activation and KI-sensitive signalling pathways. Given that somatostatin receptors 5, 1, 3, and 2 are simultaneously expressed in 40–60% of MTC cases, the multi-somatostatin receptors ligand pasireotide is considered the best indication in this field. To date, a trial assessing the combination of

pasireotide and everolimus for the treatment of progressive MTC is still recruiting (NCT01625520). Recently, a potent RET inhibitor, ponatinib, is being explored in a phase-II trial, which is also actively recruiting (NCT01838642).

3.3. Anaplastic thyroid cancer

To date, anecdotal experiences and small-sample studies have been published on the effects of KIs in ATC. In the paper by Cohen et al. [69], treatment with axitinib led to PR in one out of two ATC patients. In a phase-II study presented at the ASCO meeting in 2009 [129] imatinib led to disease control in six out of eight patients (75%). By contrast, Savvides et al. [130] reported PR in only two out of 15 subjects (13%) from a cohort of ATC patients treated with sorafenib, with poor PFS and OS (1.9 and 3.9 months, respectively). Furthermore, a phase-II multicentre trial assessing pazopanib in ATC revealed no responses [83]. Recently, Grande et al. [131] reported an anecdotal experience of sunitinib in ATC, where the treatment induced an almost complete regression of the neck tumour mass despite having no impact on distant metastases. In the aforementioned Lim trial [99], everolimus achieved SD in five out of six ATC patients, and a marked tumour shrinkage was observed in one of them. Ultimately, current data about the activity of KIs in ATC are still partial and contradictory. Thus, larger and dedicated trials are needed to better define the possible role of KIs in this clinical setting. In recent years, several pre-clinical studies demonstrated that a combination of chemotherapeutic agents and KIs showed anti-neoplastic activity in cell lines and xenograft models of ATC [132–135]. Thus, ongoing clinical trials of combined KIs and cytotoxic chemotherapy may give more promising results.

4. Discussion

The role of KIs in aggressive forms of thyroid cancer is an evolving field. To date, KIs are considered the most suitable systemic treatment for DTC patients with iodine-refractory disease; these patients comprise the subgroup with the poorer prognosis. Although sorafenib is the only KI approved so far for this specific indication, promising results have been reported regarding several other agents. In particular, the phase-III trial of lenvatinib, results of which were presented at the recent ASCO meeting (2014), has demonstrated excellent efficacy, with both PFS and objective tumour response being even better than with sorafenib. In our opinion, approval of lenvatinib for the treatment of iodine-refractory DTC should be considered by the dedicated agencies. Even if defined as well-tolerated agents, phase-III trials of sorafenib and lenvatinib in DTC have showed a remarkable toxicity, which led to dose reductions in the majority of patients (64.3% and 78.5% for sorafenib and lenvatinib, respectively) and to discontinuation of treatment in a significant proportion of cases (18.8% and 14.2% for sorafenib and lenvatinib, respectively). Given that patients with iodine-refractory DTC can be asymptomatic despite evidence of disease progression, the impact of KIs on patients' quality of life should be taken into consideration by clinicians. Furthermore, KI withdrawal may result in a rebound phenomenon, thus inducing a more rapid disease progression [136]. Thus, if and when to begin treatment with KIs in iodine-refractory DTC are key issues. These decisions should consider several aspects, including overall tumour burden, the evidence of disease progression, symptoms, and the possible occurrence of local complications. Up to now, the majority of authors have agreed that patients with a limited tumour burden (few lesions, and/or lesions less than 1 cm in size) and who are non-progressive should be subjected to active follow-up, without any systemic treatment [67]. To date, chemotherapy is mostly considered an outdated therapeutic approach in DTC. This statement is based mainly on old studies about doxorubicin (which is the only chemotherapeutic agent approved for DTC so far) in which low response rates (25%) and considerable toxicities were reported [137]. Nevertheless, recent data may lead to a reconsideration of the role of chemotherapy in this field. In particular, a small retrospective study by Spano et al., including 14 patients with progressive RAI-refractory DTC, has demonstrated that the GEMOX regimen (gemcitabine and oxaliplatin combination) reached a durable objective tumour response in 57.2% of subjects, whereas SD was reported in 28.6% [138]. Furthermore, treatment was well tolerated as no grade-4 toxicities were reported. Although limited by the retrospective nature and small sample size, these data show that both anti-neoplastic activity and safety profile of the GEMOX regimen are comparable with those reported for KIs. Thus, prospective and larger studies are needed to assess the possible role of the GEMOX as well as other chemotherapy regimens in the therapeutic management of RAI-refractory DTC. A new frontier for the use of KIs in iodine-refractory DTC may be opened up by the recent finding that selumetinib can restore iodine avidity and, therefore, clinical response to RAI. Further studies are needed to confirm this aspect definitively, to analyse the RAI-restoring activity of other KIs, and to set up standardised therapeutic algorithms. Two KIs, vandetanib and cabozantinib, have recently been approved for the treatment of advanced, progressive MTC. It is not clear whether one of them should be preferred over the other, as they have similar efficacies and toxicities. Nevertheless, the efficacy of cabozantinib has been proven to be independent of previous treatments with KIs, so we can consider this treatment for those patients experiencing therapeutic escape from vandetanib. However, the considerable toxicity of both compounds, which determines the occurrence of severe adverse events (grade 3 or higher) in a relevant proportion of patients, suggests a selective use in those subjects having a heavy disease burden and/or a strong disease progression. Nevertheless, MTC usually exhibits an indolent behaviour with just a slow progression of disease, even if metastatic. Therefore, further studies are needed to identify therapeutic approaches which could improve the

risk/benefit ratio in this type of patient. Treatment with the mTOR inhibitor everolimus, alone or in combination with somatostatin analogues, should be considered in this field. Given that benefits of KIs are at best transitory and always followed by a restoration of tumour growth and progression [91], further unsolved questions include how to use KIs sequentially or in combination. Generally, further insights are needed about therapeutic decision-making after the escape from first-line therapy with KIs. Moreover, further studies are needed to correlate the efficacy of each specific compound with genetic factors (e.g. presence of $BRAF^{V600E}$ in DTC and RET mutational status in MTC), histological factors (e.g. papillary and follicular DTC histotypes), and medical history (e.g. previous treatment with KIs). This will allow clinicians to perfectly fit the treatment on the basis of the patient's features. Another open question is the actual impact of KIs on OS. Given the relatively long survival of these patients and the fact that the majority of trials allow crossing over from the placebo to the study group, it is difficult to address this aspect. Importantly, the interim analysis of OS in the EXAM trial (cabozantinib in MTC), which did not allow crossing over between groups, reported no significant differences between the treatment and placebo groups. Trials assessing OS as the primary endpoint should be planned to better identify the actual impact of KIs on the clinical outcome of aggressive thyroid cancer. KIs do not significantly impact on clinical features of ATC. Further molecular characterisation leading to different targeted therapy is mandatory in this field.

Conflict of interest statement

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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