The safety and efficacy of vandetanib

in the treatment of

progressive medullary thyroid cancer.

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Summary

Introduction: Traditional therapies for advanced or metastatic progressive medullary thyroid cancer (pMTC) are poor effective. Several TKIs have been tested in clinical trials in pMTC patients.

Areas covered: This paper reviews efficacy and safety of vandetanib in the treatment of pMTC.

Expert Commentary: Vandetanib has been shown to improve progression-free survival (30.5 vs 19.3 months in controls) in pMTC patients. Vandetanib is approved by FDA and EMA for metastatic MTC in adults; in adolescents and children with metastatic or locally advanced MTC, vandetanib seems to be effective. The most common adverse events in vandetanib-treated patients are: diarrhea, rash, folliculitis, nausea, QTc prolongation, hypertension and fatigue. In patients with aggressive differentiated thyroid cancer, vandetanib has shown promising results. Further research is needed to determine the ideal targeted therapy, based on tumor molecular characterization and host factors, to obtain the best response in terms of survival and quality of life.

1. Introduction

The most frequent endocrine tumor is thyroid cancer (TC). The main histologic types of TC are: a) differentiated TC of follicular origin (DTC): papillary (PTC, 80%), follicular (FTC, 11%) and Hürthle cells TC; b) medullary TC (MTC) (developed from C cells); c) anaplastic TC (ATC) (2% of all TCs).

MTC originates from the C cells of the thyroid [that produce calcitonin (CT)]. Most cases of MTC are sporadic, and about 25% are hereditary [1].

MTC is present in 2 forms of multiple endocrine neoplasia MEN2A and MEN2B. MEN2A is the most common (50%) type of hereditary MTC, characterized by multicentric, bilateral MTC in > 90% of index patients, pheochromocytomas in 50% and primary hyperparathyroidism in about 15%. There are three types of MEN2A: a) the first is associated with Hirschsprung disease [2]; b) the second is associated with cutaneous lichen amyloidosis [3]; c) the third is familial MTC (FMTC) without other manifestations.

MEN2B is about 20% of cases of MEN: MTC is present in 100% of carriers, mucosal ganglioneuromas in about 90%, pheochromocytomas in 50%, and a marphanoid habitus almost in all. Early identification of MTC in MEN2B is important because metastases have been described during the first year of life.

Activating mutations of the tyrosine kinase (TK) receptor (TKR) *RET* have been described in nearly all hereditary MTC cases and in about 40% of sporadic tumours [4].

RET is a proto-oncogene (mapped to chromosome 10q11.2) encoding for a trans-membrane TKR, expressed on thyroid C cells [5].

RET/PTC rearrangements (derived from the fusion of the 3' portion of the gene to the

5' of various genes) induce uncontrolled proliferation by the activation of the transcription of RET TK domain [5,6]. RET/PTC rearrangements have been evidenced in about 20-40% of sporadic PTC [7], in thyroid adenomas and benign lesions [8]. RET/PTC1 derive from the fusion with the CCDC6, and RET/PTC3 from the fusion with the NCOA4; these ones are the most frequent among the 13 reported RET/PTC rearrangements [9].

Ninety-eight% of hereditary MTC and approximately 50% of sporadic MTC show activating mutations of RET. Germline gain of function RET mutations have been demonstrated in 98% MEN2A families, 85% FMTC and more than 98% MEN2B [10].

Cys-634 mutations are more frequent in MEN2A [4], while M918T and A883F in MEN2B [4]. In sporadic MTC, M918T is the most frequent and is linked to a more aggressive disease and poorer prognosis [11].

In sporadic MTC without RET mutations, other mutations can be responsible for the development of MTC, such as somatic H-RAS mutations, which are present in 56% of cases, but also KRAS, or rarely NRAS [12].

Furthermore in MTC, an increased expression of VEGF-A, VEGF-C, VEGFR-1, -2, -3 are found [13], and particularly, an overexpression of VEGFR-2 correlating with metastasis [11]. Several antiangiogenic molecules which block VEGF are studied, but often antiangiogenic therapy alone does not induce durable remission [14].

MET (Mesenchymal-epithelial transition) is a protoncogene coding for hepatocyte growth factor (HGF) receptor (HGFR or c-MET), having TK activity [15]. Mutations in c-MET or its overexpression are in several tumors, including MTC. Activated c-MET stimulates cell reproduction, migration and angiogenesis, while inhibits apoptosis; in this way, it leads to tumor progression and metastatic ability [16]. Also,

mutations in MET pathways have been correlated with poor clinical outcomes and drug resistance in patients with cancer [17]. An elevated coexpression of MET and HGF has been shown in a subgroup of MTCs [18]. MET has been recently investigated as a potential target in the treatment of TC and preliminary clinical benefits have been reported [17].

Furthermore, overexpression of EGFR in some MTC and activation of the mammalian target of rapamycin (mTOR) intracellular signaling pathway in hereditary MTC have been shown [19].

However in general it is difficult to evaluate whether a certain protein is overexpressed or overactive in MTC since the normal control is lacking.

The EGFR contributed to activation of RET kinase, growth stimulation and signalling [20]. This reinforces the concept that RET may collaborate with diverse transduction pathways to promote MTC tumourigenesis and may contribute to activation of other as yet unknown cellular signalling cascades [21].

Recently, the genomic profiles of two MTCs have been described and the presence of a putative oncogenic BRAF fusion has been reported in one of them [22].

2. MTC therapy

MTC prognosis depends on tumor size and RET mutations. In fact, it is good for patients with MTC confined to the thyroid; however, in 50% of cases, at diagnosis, MTC are already metastatic or locally advanced. In these patients there is a worse prognosis (10-year survival rate 40%) [23].

The serum CT (MTC marker) measurement has an important role for an early MTC diagnosis, because it has high diagnostic sensitivity and specificity [24].

In most cases, patients with sporadic MTC have a poorer prognosis because the diagnosis is made late; while MEN2A and FMTC are detected early. Three risk levels related RET mutations have been reported [25].

ATA Guidelines recommend in MTC without neck lymph node or distant metastases, a total thyroidectomy and dissection of the lymph nodes in the central compartment, considering whether to perform the dissection of lymph nodes in the lateral compartments according to serum CT levels; while in patients with MTC confined to the neck and in cervical lymph nodes, a total thyroidectomy, plus dissection of the central lymph node compartment and of the involved lateral neck compartments should be performed [26]. C cells do not concentrate iodine, then radioactive iodine has no effect on MTC.

For locally advanced or metastatic progressive MTC, external beam radiotherapy, systemic chemotherapy (doxorubicin alone or in association with other agent such as 5FU and dacarbazine), and other nonsurgical therapies should be evaluated to reach tumor control. Chemotherapy treatment in MTC is poor effective. For these reasons, the development of new therapies was necessary.

For recurrent or persistent aggressive MTC, tyrosine kinase inhibitors (TKIs) are actually recommended. Recently, several TKIs have been tested in phase I, II, and III clinical trials in patients with aggressive MTC but only vandetanib (2011) and cabozantinib (2012) have been approved by FDA and EMA [26].

3. TKIs

TKIs are molecules that compete with ATP on TKRs, blocking TK activation and the oncogenic pathways [27], like RAF, VEGFR, EGFR, MET, platelet-derived growth factor receptor (PDGFR), c-KIT, RET kinases. A TKI can block only one TK or

several TKs (multikinase inhibitor), in fact TKIs have been tested on different cancers including TC [27].

In the last decade, a possible application of axitinib, motesanib, lenvatinib, pazopanib, sorafenib, cabozantinib, sunitinib and vandetanib alone or in association have been studied in aggressive DTC or MTC, but only a few have been approved [28,29].

4. Vandetanib

4.1 Vandetanib synthesis and chemistry, pharmacokinetics and pharmacodynamics

Vandetanib [IUPAC name: N-(4-Bromo-2-fluorophenyl)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-amine)] (trade name CAPRELSA® [Vandetanib]) was synthesized through sulfonation, condensation, N-methylation, nitrification, reduction, cyclization, chlorination and amination, and it is an oral once-daily TKI (developed by AstraZeneca), able to block RET, VEGFR-2, VEGFR-3 and EGFR and slightly VEGFR-1, that are determinant in TC [28]. Vandetanib selectively inhibits VEGFR-2 and VEGFR-3, blocking VEGF-stimulated endothelial cell proliferation and migration, and in this way it reduces tumor vessel permeability. Moreover, it blocks the activity of EGFR, a receptor TK able to mediate tumor cell proliferation, migration and angiogenesis [30]. IC_{50} values of VEGFR-2, VEGFR-3, and EGFR are 40, 110, and 500 nM, respectively [31]. A chlorine analogue of vandetanib [chloro-vandetanib, N-(4-chloro-2-fluorophenyl)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-amine] has similar or superior biological activities than vandetanib [32,33].

Vandetanib is able to block the enzymatic activity of RET-derived oncoproteins, the *in vivo* phosphorylation and signaling of RET/PTC3 and RET/MEN2B oncoproteins,

and an EGF-activated EGF-receptor/RET chimeric receptor. It has been shown also that vandetanib can inhibit the proliferation of 2 different human PTC cell lines with spontaneous RET/PTC1 rearrangements. Moreover, it blocks the formation of tumors *in vivo* upon RET/PTC3-transformed NIH3T3 fibroblasts injection into nude mice [34].

Vandetanib is also effective on the majority of the mutant oncoproteins (RET/E768D, RET/Y791F, RET/S891A, RET/L790F, and RET/A883F), while mutations occurring sometimes in MEN2A, substituting valine 804, to leucine or to methionine are resistant [35].

Moreover, vandetanib could inhibit the growth of a transplantable MTC (derived from a sporadic human MTC with the C634R mutation) in nude mice [36].

Vandetanib shows an important "indirect" effect on angiogenesis *in vivo*, as it interferes with EGFR-induced production of angiogenic growth factors [31].

The vandetanib pharmacokinetics (after a single oral dose) to healthy subjects were studied [37].

Its $t_{1/2}$ is of about 10 days after a single oral dose. Food does not significantly interfere with the extent of absorption. Over 21 days about two thirds (of the dose) was recovered in feces (44%) and in urine (25%). N-desmethyl and N-oxide metabolites or unchanged vandetanib were observed in plasma, urine, and feces [37].

The efficacy and tolerability of vandetanib in TC patients have been investigated in many clinical trials (**Table 1**).

4.2 Overview of the market

Vandetanib was the first drug approved by FDA (April 2011) for the treatment of metastatic MTC in adult patients, ineligible for surgery [38]. Also

cabozantinib, a small molecule inhibitor of the TKs c-Met and VEGFR-2, able to reduce tumor growth and angiogenesis, has been approved by the U.S. FDA for MTC [39] and advanced renal cell [40]. Other clinical trials are going on with cabozantinib for the treatment of prostate, brain, bladder, ovarian, non-small cell lung, melanoma, breast, pancreatic, and hepatocellular carcinomas.

Vandetanib was evaluated in different clinical trials as a potential treatment for non-small-cell lung cancer and promising results were obtained from a phase III trial with docetaxel [41]. Another trial with docetaxel was recruiting by July 2009 [42].

4.3 Vandetanib clinical trials in adults with MTC

Two initial studies explored vandetanib in MTC. In the first study, vandetanib (300 mg/day) was administered to 30 patients with unresectable, locally advanced, or metastatic hereditary MTC [43], 70% of whom with MEN2A. The mutated codons were: 634 (in 33% of cases), 618 (27%), 620 (13%), 918 (13%), 791 (7%), 768 (3%) and 891 (3%). An objective partial response (PR) was obtained in 20% of cases, and stable disease (SD) in 53%, for a median of 24 weeks with a practical adverse event (AE) profile. RET germline mutation and response to vandetanib seemed not to have any association [43].

In the second study, vandetanib had been also administered (100 mg/day or up to 300 mg/day if disease progressed) to 19 patients with advanced hereditary MTC, obtaining also the same data as the preceding study (16% PR, 53% SD, for 24 weeks) [44].

Phase III studies

The ZETA trial (randomized, double-blind, placebo-controlled multicentre phase III trial) was carried out in patients with advanced (5%) or metastatic (95%) MTC [45], offered to receive vandetanib [300 mg daily administered until progressive disease (PD)] in an open-label phase. Among patients: 10% had hereditary MTC; 90% sporadic or unknown origin MTC; 56% had RET mutations; 2% were RET mutation negative; and 41% unknown. Patients belonging to the vandetanib group had a superior progression-free survival (PFS) vs placebo (30.5 vs 19.3 months; p<0.001), while overall survival (OS) was not significantly different (there was a crossover for patients with an objective disease progression), CT (69% vs 3%) and carcinoembryonic antigen (CEA) (52% vs 2%) response rate were higher (p<0.001). Vandetanib was effective in patients with sporadic RET-positive-MTC, and also in those with M918T-negative tumors or RET unknown status [45].

Considering the efficacy of vandetanib in stabilizing symptomatic and/or PD, it was approved in April (FDA) and in November (EU) 2011, to treat unresectable, locally advanced or metastatic MTC in patients with symptomatic or PD [46].

The efficacy of vandetanib was demonstrated by a retrospective study for the treatment of 11 progressive metastatic MTC patients with 36% PR [47].

Another study was carried out to show the efficacy of vandetanib outside any trial [48]. Sixty-eight patients were administered with vandetanib in France from August 2010 to February 2012. Eight patients were excluded and the results obtained in the 60 MTC patients were analyzed; 6 had hereditary MTC. Fifty-six (93%) had metastatic disease in the mediastinum (82%), bones (65%), liver (53%), or lung (53%), and 4 had only locally advanced disease. Median PFS was 16.1 months. Twenty-five patients discontinued treatment for disease progression (range 0.3-29 months). Best tumor response was a complete response in 1 patient, PR in 12 (20%),

SD in 33 (55%), and progression in 7 (12%). The main adverse events (AEs) were skin toxicity, diarrhea, and asthenia; 16 patients (27%) discontinued treatment for toxicity, and 1 patient died from vandetanib-induced cardiac toxicity [48].

Actually, a first phase IV randomized trial is underway to investigate differences in response to vandetanib in MTC patients administered with 300 mg vs 150 mg/day [49].

4.4 Vandetanib in pediatric MTC

In children (5-12 years) and adolescents (13-18 years) with metastatic or locally advanced MTC, a phase I/II trial has been carried out. Vandetanib 100 mg/m(2)/d was administered to 16 patients, and the authors concluded that this dose is well-tolerated, and strongly effective for adolescents and children with locally advanced or metastatic MTC and MEN2B [50].

More recently a child with advanced, metastatic, MTC associated with MEN2B has been described who showed a response to vandetanib with a fall in CT levels and a reduction in size of the thyroid malignancy, lymph nodes, and pulmonary metastases, with a SD for about 4 years [51].

These studies suggest that vandetanib can be used for the treatment of pediatric patients with MTC.

4.5 Vandetanib in ectopic Cushing syndrome by MTC

MTC may rarely presents with paraneoplastic syndrome and ectopic Cushing syndrome (ECS). Bilateral adrenalectomy is often required to manage this situation.

The regression of ECS was first observed in a patient with MTC treated with vandetanib [52].

A subsequent study described a 17-year-old adolescent with metastatic MTC and associated ACTH-dependent ECS (in the context of MEN2B), who showed a rapid decrease in serum cortisol and improvement of clinical symptoms when treated with vandetanib [53].

Recently, a patient with sporadic advanced MTC with lymph node and liver metastases, that after 16 years of follow-up developed an ECS was treated with 300 mg/day vandetanib. After one month a biochemical and clinical response of the ECS was achieved but without a significant reduction of tumor [54]. These studies suggest that vandetanib can be used for the medical treatment of MTC patients with ECS.

4.6 CT, CEA, miRNA for monitoring vandetanib treatment

The first two phase II trials [35,36] of vandetanib in MTC evidenced a high decrease (≥50%) in CEA and CT levels. CT was not associated with tumor growth inhibition, while CEA was hypothesized to be a more accurate marker of tumor response to vandetanib.

However, to evaluate the role of CEA and CT for treatment monitoring and the decision-making process, 21 patients with progressive MTC receiving vandetanib (300 mg orally per day) were studied [55]. Tumor restaging was performed every 3 months by computed tomography. Furthermore, CEA and CT were measured at the day of computed tomography imaging. During long-term follow-up [range, 97-1140 days], CT and CEA initially declined in 71.4% and 61.9% of patients, followed by fluctuations. A rise in CT ≥40% between 2 subsequent measurements was associated

with a PD (71% sensitivity, 83% specificity, and 82% accuracy). Fluctuations in CEA circulating levels were not associated with PD. These data suggest a significant rise in CT ≥40% might be an early indicator of PD [55].

Further studies are needed to elucidate the role of CT and CEA circulating levels determination for treatment monitoring and the decision-making process of MTC patients treated with vandetanib.

More recently, a study evaluated the strongest up-regulated miRNA in MTC samples, miR-375 [56]. It was shown that miR-375 overexpression was associated with decreased cell proliferation and synergistically increased sensitivity to vandetanib. The combination of increased expression of miR-375 and decreased expression of SEC23A points to sensitivity to vandetanib, suggesting the expression levels of miR-375 and SEC23A should be evaluated as an indicator of eligibility for treatment with vandetanib of MTC patients [56].

4.7 Vandetanib in aggressive DTC

Leboullex et al. [57] conducted a double-blind phase II, randomized trial, in 145 patients with metastatic or locally advanced DTC [PTC, FTC, or poorly differentiated (PDTC)] on the efficacy of vandetanib (300 mg/day) vs placebo. In patients belonging to the vandetanib group vs placebo, PFS (primary endpoint) was 11.1 months vs 5.9 months, PR 8% vs 5%, and SD 57% vs 42%. PTC than FTC and PDTC showed better results [57].

Currently, a new randomized, double-blind, placebo-controlled, multi-centre phase III study is underway in aggressive DTC patients [58].

5. Safety and tolerability

Vandetanib treatment may cause different AEs but it is generally tolerable as AEs are usually mild. The most common AEs are diarrhea, hypertension, QTc prolongation and fatigue (of at least grade 3), but also nausea, headache, rash and folliculitis, reduced appetite and acne [43-45, 50, 57].

The half-life of vandetanib is 19 days, and this is to be noticed in the management of AEs [59,60]. AEs grade 1 or 2 may improve if the dose is reduced, while in case of AEs grade 3 or 4, it is recommendable to stop the treatment with vandetanib until AEs resolve, then the drug might be taken up again but at a lower dose [44].

5.1 Dermatological AEs

The ZETA trial showed that dermatological AEs were present in 45% of patients [45].

Among EGFR inhibitors, vandetanib often causes a papulopustular eruption, owing to EGFR inhibition, as EGFRs are highly expressed in epidermis and its appendages [61], leading to hyperkeratosis, follicle obstruction and inflammation of the pilo-sebaceous follicle [61].

The reported incidence of all-grade and high-grade rash was 46.1% and 3.5% in 2961 MTC patients administered with vandetanib [62].

Photosensitivity (always present), xerosis, finger clefts, paronychia, genital skin reactions, hair changes, subungual splinter hermorrhages and blue-dots are other vandetanib-associated dermatological AEs [61].

Photoallergic dermatitis has been described in patients treated with vandetanib, that could be treated by discontinuation of the drug, and supportive care including topical and oral steroid administration [63].

Mucositis, erythrodysesthesia, pruritus are AEs less frequent, and 1 case of Stevens-Johnson syndrome has been reported [64].

Dermatological AEs in children administered with target anticancer drugs (as vandetanib) are quite the same as in adults [65].

Dermatological AEs are simply treatable, but owing to their high incidence, their prevention and early management are determinant to decrease the risk to reduce the dosage or interrupt it.

5.2 Gastrointestinal AEs

A recent meta-analysis has evaluated the relative risk and incidence of gastrointestinal AEs during vandetanib in patients with cancer. Twenty-two trials with 6382 patients were evaluated, summarizing incidences of all-grade gastrointestinal AEs in patients with cancer were anorexia 24%, constipation 17%, diarrhea 46%, nausea 29%, and vomiting 17% [66].

In the ZETA trial, the most common gastrointestinal AE is diarrhea (56% of patients), then nausea (33%), reduced appetite (21%), vomiting (14%) and abdominal pain (14%) [45]. These AEs (particularly diarrhea) often lead to poor patient compliance and interruption of the therapy. Patient education with dietary measures is determinant.

The increased hormone production by MTC may accelerate intestinal transit, causing diarrhea; for this reason, it improves with vandetanib. Diarrhea often depends on the treatment with vandetanib and its therapy is based on correct hydration and possibly loperamide.

To treat nausea it is not recommended the use of 5-HT3 antagonists (ondansetron) for the risk of prolongation QTc interval [67], and it is also necessary to administer metoclopramide prudently. In the antiemetic therapy, another option is palonosetron [68].

In the case of severe gastrointestinal AEs, vandetanib shoud be interrupted upon the improvement of the symptoms.

5.3 Cardiovascular AEs

Cardiovascular AEs are associated with vandetanib, as hypertension, bleeding, ventricular dysfunction, arterial thrombosis, fatal cardiac failure and QTc interval prolongation [69,70].

The incidences of all-grade and high-grade hypertension have been evaluated in 3154 patients, showing to be 24.2% [95% confidence interval (CI), 18.1-30.2%] and 6.4% (95% CI, 3.3-9.5%) [71]. All-grade hypertension had a more significant incidence in MTC patients than in the others [71]. For this reason, an appropriate blood pressure monitoring and treatment with ACE inhibitors (if needed) are recommendable in vandetanib-treated subjects. Calcium antagonist and beta blockers can be administered if blood pressure is uncontrolled.

The case of a patient with metastatic MTC who presented a favorable response to vandetanib therapy, who developed after 14 months of therapy a fatal cardiac failure has been described. Postmortem examination of the heart marked myocyte degeneration in the subendocardial zones and papillary muscles of the myocardium suggestive of drug-induced cardiotoxicity [69].

Also in the study by Chougnet et al. 1 patient died from vandetanib-induced cardiac toxicity [48].

QTc prolongation is a determinant cardiological AE associated wth vandetanib (and TKIs therapy). In the ZETA trial, QTc >500 ms was reported in 14% of patients administered with vandetanib; 2 cases of death in patients with QTc >550 ms have been shown (1 caused by sepsis and 1 to heart failure) [60].

Earlier than the beginning of vandetanib, ECG and echocardiogram are highly suggested and the treatment had not be done in the case of QTc >450 ms (US) or >480 ms (EU). During the treatment with vandetanib, drugs prolonging QTc interval should not be administered. Electrolyte and circulating TSH levels should be kept within the normal interval. QTc interval prolongation is quite slight at clinical dosages, not leading to significant morbidity clinically [70], though owing to the potential for QT prolongation, torsades de pointes, and sudden death, vandetanib is limited through a Risk Evaluations and Mitigation Strategy program [46].

5.4 Thyroid dysfunctions

Thyroid dysfuctions are reported in patients treated with vandetanib [72].

Thyroid function was studied in 19 patients treated with vandetanib (100 mg) for locally advanced or metastatic hereditary MTC [44]. All 19 patients receiving vandetanib had undergone prior thyroidectomy and were receiving thyroid hormone replacement before entering the study. Baseline TSH data were available for 17 patients, and in these patients TSH levels increased [5.1-fold (mean) and 7.3-fold (median) increases over baseline]. No patients were reported to have symptomatic hypothyroidism, but thyroid hormone replacement therapy was increased in 2 patients [44].

The pattern of thyroid hormones levels was studied in 13 pediatric patients with MEN 2B and MTC (median age 13.0) [73]. Eleven patients (85%) had undergone prior thyroidectomy and received single-drug therapy with vandetanib for >6 months. While on vandetanib treatment, all 11 athyerotic patients had significantly increased circulating TSH, after a median time to reach the initial peak of elevated TSH of 1.8 months (0.3 - 9.3). An increase of levothyroxine (LT4) dosage was observed from

a baseline of 91 mcg/m(2)/day (±24) to 116 mcg/m(2)/day. For the 2 patients with intact thyroid glands, free T4 and TSH remained normal. It was suggested that an indirect effect of vandetanib on the metabolism of thyroid hormone, or an altered TSH sensitivity at the pituitary could cause elevated TSH levels in athyreotic patients. A correct recognition and management of abnormal thyroid hormone levels is determinant in growing children on TKIs. This study suggests that pediatric athyreotic MTC patients during the first few months of vandetanib therapy necessitate an increase in LT4 dose [73].

5.5 Other AEs

Fatigue, headache, hypocalcemia, hypoglycemia, and increased transaminase levels are other frequent side effects [72].

6. Limits and drug resistance

TKIs therapy is not toxic as chemotherapy, but severe AEs need interrumption of the treatment. Moreover, TKIs stop tumor growth but can not remove it. The reported discordant results by clinical trials about the efficacy of TKIs in aggressive DTC patients perhaps are caused by mechanisms of drug resistance, activating different mitogenic signals [74]. Combining TKIs targeting different pathways is now under evaluation.

Mechanisms of primary and acquired resistance to vandetanib have been evaluated. The presence of RET mutations is not suitable to predict clinically the response to the treatment in MTC [75]. The clinical efficacy of vandetanib has been confirmed by ZETA trial in patients with sporadic MTC with M918T mutation. The rare RET V804M and V804L mutations occurring in sporadic

and hereditary MTC confer resistance to vandetanib [35], as shown in *in vitro* studies, leading clinically to primary or acquired resistance. Sorafenib is effective against the V804 mutant *in vitro* [76].

Further research is necessary to investigate whether Ras mutations, present in 60-80% of RET-negative sporadic MTC [12], may lead to clinical resistance to vandetanib. Anyway, *in vitro* cell lines with acquired resistance to vandetanib have a constant activation of the Ras/Raf/MEK pathway (that sorafenib is able to abolish) [77].

The evaluation of the sensitivity of TC cells to TKIs could improve the response to treatment, as *in vitro* drug screening with human primary tumor cells has a 60% positive predictive and a 90% negative predictive value of clinical response *in vivo* in the same patient. This could permit not to administer inactive drugs to patients [78,79]. Moreover, primary TC cell cultures from anaplastic thyroid cancer (ANA) can be established from fine-needle aspiration giving the possibility to test in these cells the chemosensitivity to different drugs in each patient (avoiding useless surgical biopsies, used till nowadays to establish ANA) [79-83].

7. Combination studies

The synergic activity of various antineoplastic drugs in combination studies have been investigated [84].

A synergic inhibition of tumor growth has been reported combining treatment with bortezomib (proteasome inhibitor), and EGFR inhibitors (gefitinib, vandetanib, cetuximab), in EGFR-expressing human cancer cell lines [85]. A not randomized, phase I/II trial on vandetanib with bortezomib is recruiting patients with solid tumors (as MTC) [86].

The synergic activity of vandetanib plus irinotecan has been also investigated. Vandetanib inhibits tumor growth *in vitro*, as shown by preclinical data, in a sequence-dependent manner with chemotherapeutic agents, as irinotecan in colon cancer cell lines [87]. Another paper evaluated the combination with irinotecan in a murine xenograft model of vandetanib-treated human colon cancer, showing an additional synergic activity of these drugs [88].

The response to vandetanib, radiotherapy and irinotecan was investigated in human LoVo colorectal tumoral cells, reporting an increased antineoplastic effects of irinotecan and radiation if administered with vandetanib, leading to a decreased tumor growth [89].

Many papers have reported that the PI3K/Akt/mTOR signaling pathway is involved in the pathogenesis and progression of neuroendocrine tumors and MTC, as it seems that the deregulation of such a pathway contributes to the tumorigenic effect of RET mutations. A possible effective therapeutic option in patients with advanced MTCs could be directed towards this pathway, by specific inhibitors at simple or multiple sites.

8. Conclusions

Vandetanib has been shown to improve PFS (30.5 vs 19.3 months in the placebo group) in patients with MTC. Patients with sporadic RET-positive-MTC took advantages from vandetanib and a good response was also shown in those with M918T-negative tumors or RET unknown status. Vandetanib was approved in 2011 by FDA for metastatic MTC and in 2012 by EMA.

Also in adolescents and children with metastatic or locally advanced MTC, vandetanib is well-tolerated, and seems to be effective. The regression of ECS has been observed in MTC patients treated with vandetanib, too.

Further studies are required to elucidate the role of CT and CEA circulating levels determination for treatment monitoring and the decision-making process of MTC patients treated with vandetanib.

Diarrhea, QTc prolongation, hypertension and fatigue, headache, rash and folliculitis, nausea, reduced appetite and acne are the most common AEs associated to vandetanib treatment. AEs grade 1 or 2 may improve if the dose is reduced, while in case of AEs grade 3 or 4, it is recommendable to stop the treatment with vandetanib until AEs resolve, then it might be taken up again but at a lower dose.

To increase the antineoplastic effect of vandetanib, and to overcome the appearance of drug resistance, combination studies with other anticancer agents are on-going. To personalize the TKIs therapy in each patient with MTC or aggressive DTC, attempts have been made on the basis of the molecular characterization of the tumor. More recently, it has been suggested the possibility to evaluate the sensitivity *in vitro* of primary aggressive DTC or MTC cells from each subject to different TKIs to ameliorate the effectiveness of the treatment, preventing the administration of inactive drugs, potentially dangerous, to these patients.

In conclusion, vandetanib has been shown to exert an important therapeutic effect in patients with MTC improving PFS. In aggressive DTC patients vandetanib has shown promising results, and a phase III trial is on-going.

Further studies are necessary to establish the ideal targeted therapy, considering the molecular characterization of the tumor and host factors, in order to improve survival and quality of life.

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Expert commentary

Vandetanib (trade name CAPRELSA® [Vandetanib]) is an oral once-daily TKI, able to block RET, VEGFR-2, VEGFR-3 and EGFR and slightly VEGFR-1, that are determinant in medullary thyroid cancer (MTC).

It was shown that vandetanib could inhibit the growth of a transplantable MTC (derived from a sporadic human MTC with the C634R mutation) in nude mice. Vandetanib shows an important "indirect" effect on angiogenesis *in vivo*, as it interferes with EGFR-induced production of angiogenic growth factors.

In a phase III clinical study, vandetanib improved progression-free survival (PFS) (30.5 vs 19.3 months in the placebo group) of patients with MTC. Patients with sporadic RET-positive-MTC took advantages from vandetanib and a good response was also shown in those with M918T-negative tumors or RET unknown status.

Recently, a phase I/II trial has been conducted for adolescents and children (5-12 years) with metastatic or locally advanced MTC, showing that treatment with vandetanib 100 mg/m(2)/d, is well-tolerated, and strongly effective.

The regression of ectopic Cushing syndrome was observed in MTC patients treated with vandetanib.

Vandetanib was approved in 2011 by FDA for metastatic MTC and in 2012 by EMA.

The most frequent adverse events (AEs) in vandetanib-treated patients are: diarrhea, rash and folliculitis, nausea, QTc prolongation, hypertension and fatigue, headache, decreased appetite and acne. AEs grade 1 or 2 may improve if the dose is reduced, while in case of AEs grade 3 or 4, it is recommendable to stop the treatment with vandetanib until AEs resolve, then it might be taken up again but at a lower dose.

In a phase II clinical study, vandetanib improved PFS (11.1 months vs 5.9 months months in the placebo group) of patients with aggressive differentiated thyroid cancer (DTC).

In conclusion, vandetanib has been shown to exert an important therapeutic effect in patients with MTC improving PFS. In aggressive DTC patients vandetanib has shown promising results, and a phase III trial is on-going.

Five-year view

Patients with familial, or sporadic MTC (with different RET mutations) will be treated with vandetanib, to evaluate a possible predictive role of these mutations to the response to therapy.

Further studies are needed to elucidate the role of calcitonin and CEA circulating levels determination for treatment monitoring and the decision-making process of MTC patients treated with vandetanib.

In aggressive DTC patients, vandetanib has shown promising results, suggesting that in the next future it will be an alternative to sorafenib in these patients.

To increase the antineoplastic effect of vandetanib, and to overcome the appearance of drug resistance, combination studies with other anticancer agents are on-going. To personalize the TKIs therapy in each patient with MTC or aggressive DTC, attempts have been made on the basis of the molecular characterization of the tumor. More recently, it has been suggested the possibility to evaluate the sensitivity *in vitro* of primary aggressive DTC or MTC cells from each subject to different TKIs to ameliorate the effectiveness of the treatment, preventing the administration of inactive drugs, potentially dangerous, to these patients.

Further studies are necessary to establish the ideal targeted therapy, considering the molecular characterization of the tumor and host factors, in order to improve survival and quality of life.

Key issues:

1- Vandetanib (trade name CAPRELSA® [Vandetanib]) is an oral once-daily TKI, able to block RET, VEGFR-2, VEGFR-3 and EGFR and slightly VEGFR-1, that are determinant in MTC.

2- It was shown that vandetanib could inhibit the growth of a transplantable MTC (derived from a sporadic human MTC with the C634R mutation) in nude mice. Vandetanib shows an important "indirect" effect on angiogenesis *in vivo*, as it interferes with EGFR-induced production of angiogenic growth factors.

3- In a phase III clinical study, vandetanib improved progression-free survival (PFS) (30.5 vs 19.3 months in the placebo group) of patients with MTC. Patients with sporadic RET-positive-MTC took advantages from vandetanib and a good response was also shown in patients with M918T-negative tumors or RET unknown status.

4- Recently, a phase I/II trial has been conducted for adolescents and children (5-12 years) with metastatic or locally advanced MTC, showing that treatment with vandetanib 100 mg/m(2)/d is well-tolerated, and strongly effective.

5- Vandetanib was approved in 2011 by FDA for metastatic MTC and in 2012 by EMA.

6- The most frequent AEs in vandetanib-treated patients are: diarrhea, rash and folliculitis, nausea, QTc prolongation, hypertension and fatigue, headache, decreased appetite and acne. AEs grade 1 or 2 may improve if the dose is reduced, while in case of AEs grade 3 or 4, it is recommendable to stop the treatment with vandetanib until AEs resolve, then the therapy might be taken up again but at a lower dose.

7- Further studies are needed to elucidate the role of calcitonin and CEA circulating levels determination for treatment monitoring and the decision-making process of MTC patients treated with vandetanib.

8- In aggressive DTC patients, vandetanib has shown promising results, suggesting that in the next future it will be an alternative to sorafenib in these patients.

9- To increase the antineoplastic effect of vandetanib, and to overcome the appearance of drug resistance, combination studies with other anticancer agents are on-going. To personalize the TKIs therapy in each patient with MTC or aggressive DTC, attempts have been made on the basis of the molecular characterization of the tumor. More recently, it has been suggested the possibility to evaluate the sensitivity *in vitro* of primary aggressive DTC or MTC cells from each subject to different TKIs to ameliorate the effectiveness of the treatment, preventing the administration of inactive drugs, potentially dangerous, to these patients.

10- Further studies are necessary to establish the ideal targeted therapy, considering the molecular characterization of the tumor and host factors, in order to improve survival and quality of life.

Information resources

Most important related websites:

European Thyroid Association (ETA): http://www.eurothyroid.com/

American Thyroid Association (ATA): http://www.thyroid.org/

Table 1: Clinical trials of vandetanib in patients with medullary thyroid cancer.

References	Thyroid cancer	Responses			
		PR	SD	PD	PFS (months)
Wells et al.[43]	30 MTC	20%	53%	3%	27.9
Robinson et al.[44]	19 MTC	16%	53%	16%	5.6
Wells et al.[45]	231 MTC	45%	42%	/	/
Chougnet et al.[48]	60 MTC	20%	55%	12%	16.1
Fox et al.[50]	16 MTC pediatric MEN2B	47%	/	/	/

Medullary thyroid cancer (MTC); partial response (PR); progressive disease (PD); progression-free survival (PFS); stable disease (SD).