Vandetanib in Children and Adolescents with Multiple Endocrine Neoplasia Type 2B Associated Medullary Thyroid Carcinoma

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Abstract

Purpose: Medullary thyroid carcinoma (MTC) is a manifestation of multiple endocrine neoplasia type 2 (MEN2) syndromes caused by germline, activating mutations in the RET (REarranged during Transfection) proto-oncogene. Vandetanib, a VEGF and EGF receptor inhibitor, blocks RET tyrosine kinase activity and is active in adults with hereditary MTC.

Experimental Design: We conducted a phase I/II trial of vandetanib for children (5–12 years) and adolescents (13–18 years) with MTC to define a recommended dose and assess antitumor activity. The starting dose was 100 mg/m² administered orally, once daily, continuously for 28-day treatment cycles. The dose could be escalated to 150 mg/m²/d after two cycles. Radiographic response to vandetanib was quantified using RECIST (v1.0), biomarker response was measured by comparing posttreatment serum calcitonin and carcinoembryonic antigen (CEA) levels to baseline, and a patient-reported outcome was used to assess clinical benefit.

Results: Sixteen patients with locally advanced or metastatic MTC received vandetanib for a median (range) 27 (2–52) cycles. Eleven patients remain on protocol therapy. Diarrhea was the primary dose-limiting toxicity. In subjects with M918T RET germline mutations (n = 15) the confirmed objective partial response rate was 47% (exact 95% confidence intervals, 21%–75%). Biomarker partial response was confirmed for calcitonin in 12 subjects and for CEA in 8 subjects.

Conclusion: Using an innovative trial design and selecting patients based on target gene expression, we conclude that vandetanib 100 mg/m²/d is a well-tolerated and highly active new treatment for children and adolescents with MEN2B and locally advanced or metastatic MTC. Clin Cancer Res; 19(15); 4239–48.

Introduction

Medullary thyroid carcinoma (MTC) is a rare cancer arising from neural crest derived parafollicular C cells within the thyroid gland. In childhood, the age-adjusted incidence of MTC is <0.5 cases per million per year (1). Hereditary MTC is a manifestation of multiple endocrine neoplasia (MEN) type 2A and MEN2B, genetic cancer predisposition syndromes caused by germline, activating mutations in the RET (REarranged during Transfection) proto-oncogene (2–4). MEN2B is associated with a point mutation in exon 16 (codon 918) in more than 95% of cases (5); the associated MTC is characterized by a younger age of onset and a more aggressive clinical course (1).

Preventive thyroidectomy is recommended for patients known to have MEN2B (6–8); but patients with de novo germline mutations are not recognized early in life and present with locally advanced or metastatic MTC. MTC is the leading cause of death in patients with hereditary MTC, however, patients with locally advanced or metastatic disease can survive for years (9–12).

MTC secrete the polypeptide hormone, calcitonin, and the glycoprotein carcinoembryonic antigen (CEA), which are biomarkers that reflect tumor burden (13–15). Elevated serum calcitonin or other polypeptides may be associated with secretory diarrhea (16–18).

Vandetanib (Caprelsa, AstraZeneca Pharmaceuticals) is a small molecule receptor tyrosine kinase inhibitor of VEGF receptor 2 (VEGFR2), EGF receptor (EGFR), and RET tyrosine kinase activity as well as the mutated RET oncoproteins...
Translational Relevance

Ninety-five percent of children and adolescents with the cancer predisposition syndrome multiple endocrine neoplasia type 2B (MEN2B) harbor a germline mutation in the RET (REarranged during Transfection) proto-oncogene (exon 16 codon 918). All individuals with MEN2B develop medullary thyroid carcinoma (MTC); metastatic or locally advanced MTC is unresponsive to cytotoxic chemotherapy or radiation. Vandetanib is an oral inhibitor of tyrosine kinases including RET. This clinical trial of vandetanib in children and adolescents with MEN2B and MTC used a novel trial design and molecular selection of subjects to simultaneously and efficiently establish the recommended dose, tolerability of chronic dosing, and activity of vandetanib in this very rare population. The recommended dose is based on tolerability, pharmacokinetics, as well as biomarker and objective responses. Detailed pharmacokinetics at steady state support labeling in children. Therefore, this is an ideal dose-finding method for development of molecularly targeted agents in rare tumors.

In a randomized, placebo-controlled trial in adults with MTC, vandetanib 300 mg daily significantly prolonged progression-free survival and 45% of patients had objective responses. Adverse events included diarrhea, rash, nausea, hypertension, and headache (22). In adults receiving vandetanib 300 mg daily, the area under the concentration curve (AUC_{0–C}) after a single dose was 14 mcg·h/mL, half-life 109 ± 30 h, and apparent clearance was 4.7 L/h/m². The plasma concentration at steady state (C_{ss}) was 1 mcg/mL (23). Based on the randomized trial, the U.S. Food and Drug Administration has approved vandetanib for symptomatic or progressive MTC in adults with unresectable advanced or metastatic MTC (22).

In a phase 1 trial in children with pontine gliomas, the recommended dose of vandetanib was 145 mg/m²/d. The median [range] duration of treatment was 212 [3–674] days. Toxicities included hypertension, posterior reversible encephalopathy, photosensitivity, diarrhea, and prolonged QTc interval (24).

We designed a trial of vandetanib for children and adolescents with hereditary MTC to define the dose, toxicity profile, pharmacokinetics, and antitumor activity. This is the first clinical trial of an RET inhibitor in children and adolescents with MTC. Using intrapatient dose escalation meant that all patients with this very rare cancer were also evaluable for response and a therapeutic effect could be used to define the recommended dose.

Materials and Methods

Patients

Patients 5 to 18 years of age with measurable, locally advanced, or metastatic, hereditary MTC were eligible. Other eligibility criteria are provided as Supplementary Data.

Protocol-specific exclusion criteria included elevated plasma metanephrines (evidence of pheochromocytoma); prolonged QTc, or requirement for medications known to prolong QTc (see Supplementary Data); hypertension defined as diastolic blood pressure above the 95th percentile for sex and age. The NCI Institutional Review Board approved the trial. Consent and assent were obtained.

Study design

The primary objectives this phase I/II trial were to assess the drug’s safety, tolerance, and pharmacokinetics at 2 dose levels within the 100 to 300 mg/day dose range used in adults and to assess the antitumor activity of vandetanib in children and adolescents with measurable hereditary MTC.

Vandetanib was supplied by AstraZeneca Pharmaceuticals as 50 and 100 mg tablets and as a 10 mg/mL oral solution. The starting dose was 100 mg/m²/d (equivalent to 180 mg in an adult) administered orally, once daily, continuously for 28-day cycles. Because of the limited safety data available in the pediatric population, adolescents (13–18 years) were enrolled before children (5–12 years) using a 3+3 design in each age group. To ensure safety and tolerance at steady-state drug concentrations, toxicity was monitored during the initial 2 cycles of vandetanib before dose escalation. For individual patients, if dose-limiting toxicity (DLT) was not observed during cycles 1 and 2, intrapatient escalation to 150 mg/m²/d (equivalent to an adult fixed dose of 270 mg) occurred on cycle 3. Intrapatient dose escalation was conducted first in adolescents. Once 100 mg/m²/d was shown to be safe (≤33% DLT) during cycles 1 and 2 in at least 3 adolescents, children were enrolled at the 100 mg/m²/d dose level. Children were not considered for intrapatient dose escalation until this dose was proven to be tolerable in adolescents. The starting dose level on cycle 1 could be escalated to 150 mg/m²/dose if DLT was ≤33% during cycles 1 and 2 in each age group. In the absence of DLT, patients remained on treatment until there was radiographic evidence of tumor progression.

Toxicity assessment and definition of DLT

The CTEP Common Terminology Criteria for Adverse Events Version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm) was used for quantifying the severity of adverse events. Toxicity monitoring included physical exams, laboratory tests including thyroid stimulating hormone, blood pressure monitoring, and serial MRIs of the knee to quantify growth plate volume and monitor for potential bone toxicity from VEGFR inhibition (25). Frequency of each observation is included in Supplementary Data.

Hematologic DLT included grade 3 neutropenia or thrombocytopenia on 2 consecutive measurements at least 72 hours apart or a single episode of grade 4 neutropenia or thrombocytopenia. Nonhematologic DLT included any grade 3 or higher nonhematologic toxicity, except for transient grade 3 nausea, vomiting, or electrolyte abnormalities that could be ameliorated within 48 hours and grade 3 serum transaminase elevation (ALT/AST) that returned to

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With hereditary MTC, was comparable to the preliminary response rate of 30% in adults (28). If there were 5 objective responses among up to 21 patients, using an exact binomial test (one-sided alpha = 0.1), the single-stage design provided 80% power to rule out a response rate of <10% in favor of a response rate of 30%. Adverse events, pharmacokinetics, biomarker, and clinical response rates are reported as median (range) values. The Wilcoxon signed rank test was used to compare height and weight percentiles for age at baseline and last evaluation; reported P values are two-tailed and have not been adjusted for multiple comparisons.

Results

Patient characteristics
Between July 2007 and July 2011, 16 patients were accrued to this study at the NIH Clinical Center, 10 in the adolescent cohort (age 13–18 years) and 6 in childhood cohort (age 5–12 years). Patient characteristics are presented in Table 1. All patients harbored a germline RET mutation in codon 918 except patient 03 who had a polymorphism (G691S) in the RET proto-oncogene. All patients except subject 15 had de novo RET mutations with no family history of MEN2B or MTC. All subjects were evaluable for toxicity and response (Fig. 1).

Toxicity
Three adolescents were enrolled at the 100 mg/m^2/d dose level, none had DLT in cycle 1 or 2, the protocol was then open to both children and adolescents at this dose level. Overall, 9 adolescents enrolled at the 100 mg/m^2/d; none had DLT in cycle 1 or 2. Six children were enrolled at the 100 mg/m^2 dose level, one had dose-limiting diarrhea during cycle 2. One adolescent enrolled at starting dose of 150 mg/m^2/d required enalapril for hypertension during cycle 1 and had a dose reduction to 100 mg/m^2/d for bradycardia in cycle 3. No additional subjects were enrolled at a starting dose of 150 mg/m^2/d.

Seven adolescents met criteria for intrapatient dose escalation to 150 mg/m^2/d, one experienced dose-limiting diarrhea in cycle 3 and was dose reduced to 100 mg/m^2/d then reduced to 67 mg/m^2/d in cycle 6 due to intolerable diarrhea. Two adolescents did not intrapatient dose escalate. Subject 03 with the G691S RET polymorphism discontinued vandetanib after cycle 2 due to progressive disease and subject 07 declined intrapatient dose escalation due to non-dose-limiting diarrhea (grade 2) and hypertension requiring enalapril during cycle 2. Subject 07 subsequently required dose reduction to 67 mg/m^2/d in cycle 3 due to dose-limiting diarrhea.

As of July 2011, 392 cycles of vandetanib were administered at 150 mg/m^2/d (n = 144 cycles), 100 mg/m^2/d (n = 153 cycles), or doses ≤70 mg/m^2/d (n = 95 cycles). The median number of cycles administered per subject was 27 (range 2–52). Diarrhea was the primary DLT. No grade 4 toxicities attributable to vandetanib were observed. Adverse events attributed to vandetanib are presented in Fig. 2. Common non-dose-limiting toxicities included prolonged QTc, hypertension, diarrhea, rash, and TSH.
elevation necessitating an increase in levothyroxine dosage in athyrotic patients who were previously on a stable dose.

The median (range) baseline QTc was 438 (352–472) milliseconds. During therapy, 387 ECGs were performed in 16 subjects. No subject had dose-limiting prolongation of QTc. The median (range) QTC increase was 38 milliseconds (11–71). Subject 10 receiving 100 mg/m²/d, had a baseline QTc = 438 milliseconds, a QTc = 509 milliseconds on cycle 3, and a QTc = 500 milliseconds on cycle 13. These asymptomatic QTc prolongations were not verified on repeat ECG conducted within 24 hours.

Four patients required enalapril to control hypertension. In patients receiving levothyroxine at enrollment (n = 13), the levothyroxine dose increased by 15% during cycles 1 and 2 and by 75% (0–175%) during all vandetanib courses. Thirteen patients developed vandetanib-associated rash that responded to topical therapy with hydrocortisone, fluclonolone acetonide, dapsone, or clindamycin. Three patients required oral minocycline or tetracycline for acneiform rash. All patients required loperamide intermittently for diarrhea.

Serial MRI measurements of growth plate volume were completed in 13 subjects. Subjects 04, 08, 11 had increases in growth plate volume of 240%, 39%, and 52%, respectively. Despite an increase in height, these growth plate volume changes were not significant.


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therapy. One had bone metastases. Eleven patients remain on protocol cycles. For 7 patients with confirmed partial responses, only bone after 28 cycles. One patient discontinued therapy with disease (subject 07) developed a new metastatic lesion in of vandetanib, one patient with best response of stable disease (subject 04) subsequently had progressive disease after 44 or 48 cycles. Two patients who achieved partial response (subject 01 and 02) had confirmed partial response in calcitonin during subsequent cycles (cycle 5+). Because of dose-limiting diarrhea in adolescents, intrapatient dose escalation was not permitted in children. One adolescent was enrolled at the starting dose of 150 mg/m2/d; that subject had hypertension and was dose reduced to 100 mg/m2/d in cycle 3. The recommended dose of vandetanib (100 mg/m2/d) was determined based on extended tolerability, pharmacokinetics, and demonstration of activity (objective response).

9 (<3–96)% and increased to 20 (<3–91)% at last evaluation (P = 0.48).

Pharmacokinetics
Steady-state pharmacokinetic sampling was completed in 11 subjects receiving vandetanib 100 mg/m2/dose. The median (range) apparent clearance was 5.9 (3.9–7.3) L/h/m2; the area under the concentration-time curve was 16 (13.5–23.3) mcg·h/mL. All subjects achieved steady state. The average ± SD Css was 0.73 ± 0.14 mcg/mL (Supplementary Fig. S1). The small sample size and low frequency of toxicity and progression of disease precluded formal correlations.

Response
All 15 subjects with M918T RET germline mutations experienced a decrease tumor size (Figs. 3 and 4), and 7 of 15 achieved a confirmed partial response (objective response rate 47%; 95% CI, 21%–73%). The overall objective response rate was 7 of 16 (44%; 95% CI, 20%–70%). The number of cycles to achieve a partial response was 6 (6–20). Two patients who achieved partial response (subject 01 and 04) subsequently had progressive disease after 44 or 48 cycles of vandetanib, one patient with best response of stable disease (subject 07) developed a new metastatic lesion in bone after 28 cycles. One patient discontinued therapy with 25% decrease in tumor diameter (stable disease) after 29 cycles. For 7 patients with confirmed partial responses, only one had bone metastases. Eleven patients remain on protocol therapy.

Subject 03 with an RET polymorphism was enrolled on the trial 2 months after initial diagnosis of widely metastatic MTC. Compared to baseline, he had increased CEA and calcitonin during initial 2 cycles of vandetanib and clinical progression of disease in cervical vertebral bodies requiring surgery and discontinuation of vandetanib. He died from progression of disease 8 months after initial diagnosis.

Serum calcitonin and CEA are presented in Fig. 5. Fifteen of 16 patients had a rapid decline in calcitonin. The decrease in calcitonin from baseline was 59 (35–84)% during cycle 1. Biomarker partial response in calcitonin was confirmed in 12 subjects at median (range) 3 (3–5) cycles. CEA was more variable, in part, because of the clinical laboratory change in the assay methodology during the study. Three subjects had baseline CEs that were not evaluable for biomarker response. Two subjects (03 and 05) had increases in CEA, 8 had confirmed partial biomarker response in CEA by cycle 5 (3–17). No subject achieved a complete biomarker response (normalization of calcitonin or CEA).

Baseline performance status was 90 (80–100) and did not change significantly during therapy. Two patients had calcitonin-mediated diarrhea (≥5 watery stools per day) at enrollment, none achieved a complete response. Subject 07 presented with Cushing’s syndrome and ectopic secretion of ACTH (urine cortisol 745 mcg/24 hours; serum ACTH 95 pg/mL). The Cushing’s syndrome resolved, urine cortisol and serum ACTH normalized within 4 weeks of starting vandetanib.

### Figure 1.
Clinical trial flow diagram. The starting dose of vandetanib was 100 mg/m2/d. Adolescents (age 13–18 years of age) were enrolled at the starting dose (100 mg/m2/d) before children. Enrollment of the younger age cohort (children age 5–12 years old) and intrapatient dose escalation in adolescents to 150 mg/m2/d commenced after vandetanib 100 mg/m2/d was shown to be tolerable in adolescents (<33% dose-limiting toxicity during cycles 1 and 2). Because of dose-limiting diarrhea in subsequent cycles (cycle 5+), intrapatient dose escalation was not permitted in children. One adolescent was enrolled at the starting dose of 150 mg/m2/d; that subject had hypertension and was dose reduced to 100 mg/m2/d in cycle 3. The recommended dose of vandetanib (100 mg/m2/d) was determined based on extended tolerability, pharmacokinetics, and demonstration of activity (objective response).
Discussion

MTC associated with activating germline mutations of RET is a rare cancer in children and adolescents. Conducting sequential phases I and II trials to define the dose and antitumor activity was impractical. We developed an innovative trial design to simultaneously determine the recommended dose using intrapatient dose escalation and antitumor activity of vandetanib, and restricted enrollment to patients with mutated RET proto-oncogene and measurable MTC. Dose escalation was limited to 2 dose levels with...
Figure 4. Radiographic objective responses in adolescents and children with MEN2B and MTC. A, CT of chest and neck in patient 1 (15-year-old female). B, CT of chest in patient 4 (11-year-old male). CT, computer tomography.
evidence of activity in adults with MTC. Safety was maintained by enrolling adolescents before children and by requiring DLT evaluation period to extend for 2 cycles to ensure steady-state drug concentrations had been achieved and tolerated.

In adults with advanced solid tumors receiving vandetanib for 2.7 (0.1–14) months, the maximum tolerated and recommended dose of vandetanib was 300 mg daily. In the randomized phase III trial in adults with MTC, the median duration of vandetanib administration was 22.5 months, 35% required dose reductions for toxicity and one third discontinued therapy due to an adverse event (22). Vandetanib 100 mg/d (\( \frac{C_{24}}{C_{24}} \) \( \frac{55 \text{ mg/m}^2}{\text{d}} \)) daily has shown activity in adults with MTC with fewer and less severe toxicities, and a lower frequency of dose reductions during 8.7 (0.03–16.7) months of therapy (29).

In our study, the toxicity profile in adolescents and children was similar to adults. Vandetanib did not impair linear growth. The vandetanib \( C_{\text{ss}} \) in children receiving 100 mg/m\(^2\)/d is similar to the \( C_{\text{ss}} \) in adults receiving 300 mg/d fixed dose. Durable responses were achieved in children and adolescents at 150 mg/m\(^2\)/d (\( n = 2 \), duration 40–52 cycles), 100 mg/m\(^2\)/d (\( n = 4 \), duration 20–44 cycles) and 67 mg/m\(^2\)/d (\( n = 1, 48 \) cycles). Therefore, based on a therapeutic endpoint and long-term tolerability, we recommend vandetanib 100 mg/m\(^2\)/d for children with locally advanced or metastatic MTC.

Vandetanib is active in adults with sporadic and hereditary MTC (22, 28, 30). The objective response rate in children and adolescents with germline M918T RET mutations is comparable to adults with hereditary MTC and adults with sporadic MTC harboring the M918T in the tumor (22). In our study, the subject with RET polymorphisms G691S, S836S had rapid progression of disease. The role of the RET variant allele G691S in MTC has been controversial. A recent metanalysis concluded that the G691S increases the risk of several cancers including MTC via a recessive mechanism of action (31). Evidence that RET variants G691S, L769L, S836S, and S904S are disease modifiers in sporadic MTC remains inconclusive (32). The compelling antitumor activity of vandetanib in children with germline M918T RET mutations may reflect a RET-specific response to the drug. However, vandetanib is an inhibitor of VEGFR and EGFR, and inhibition of these targets may contribute to the clinical responses. In addition, the direct effect of RET kinase inhibitors on the secretion of calcitonin may contribute to the rapid reduction in
calcitonin, and perhaps other hormones. Resolution of Cushing's syndrome (subject 07) occurred before a decrease in tumor size (33). In our study, the TSH elevations in athyrotic subjects cannot be attributed to a decrease in thyroid hormone production, suggesting that vandetanib, like other VEGFR inhibitors may antagonize or increase metabolism of thyroid hormone (34).

Although we observed a high response rate, the responses have been partial and 3 children have experienced progression after an initial decrease in tumor size. Disease control rather than cure may be a more realistic goal of molecularly targeted anticancer drugs. The development of resistance to vandetanib through somatic mutations in \( \text{RET} \) is the likely explanation for tumor progression after an initial response. Other \( \text{RET} \) inhibitors are currently in clinical development (35).

Using an innovative trial design and selecting patients based on target gene expression, we conclude that vandetanib 100 mg/m\(^2\)/d is a well-tolerated, active treatment for children and adolescents with MEN2B and locally advanced or metastatic MTC.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References


Vandetanib in Children and Adolescents with MEN2B and MTC

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