Effect of an outreach programme on vandetanib safety in medullary thyroid cancer

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Supplementary information

Supplementary Table 1. Toxicity management

Toxicity	Action
Cardiac toxicity – QTc prolongation	
1. QTc ≥550 ms	Withhold vandetanib. Follow for resolution of QTc prolongation. Vandetanib to be resumed at lower dose after QTc recovers to <480 ms or baseline.
2. QTc ≥500 ms and <550 ms	Continue vandetanib. Repeat ECG to be obtained within 48 hours. If QTc ≥550 ms, step 1 to be followed. If repeat ECG does not meet criteria for QTc prolongation, patient to continue vandetanib and resume ECG according to study plan.

Toxicity	Action
Gastrointestinal toxicity	
Nausea, vomiting	May be controlled with anti-emetic therapy.
Diarrhoea	Diarrhoea to be treated with standard medications to avoid dose modification or interruption, if possible.
Grade 1 or 2	No dose modifications required; however, electrolyte supplementation with regular laboratory monitoring to be used, when appropriate, to maintain electrolytes within normal limits.
Grade 3 or 4	Vandetanib to be withheld until diarrhoea resolves to CTCAE grade 1 or baseline; vandetanib can then be restarted at a permanently reduced dose. Any electrolyte imbalance to be corrected promptly.
Cutaneous toxicity	
General	All patients strongly recommended to follow a programme of sun protective measures while receiving study treatment and for 3–4 weeks after discontinuing study treatment. Patients were instructed to apply sunscreen whenever they go outdoors during daylight hours to areas of the skin that will be exposed to the sun.

Toxicity	Action
Skin rash	Treated with a variety of agents, including mild- to moderate-strength steroid creams, either topical or systemic antibiotics, topical or systemic antihistamines, and occasionally retinoid creams. Rash to be graded as soon as possible according to CTCAE cutaneous toxicity criteria.
Grade 2 or higher	Immediate symptomatic treatment to be provided.
Grade 3 or 4	Vandetanib to be withheld until rash resolves to CTCAE grade 1 or baseline; vandetanib can then be restarted at a permanently reduced dose.
Hypertension	
Grade 3	Vandetanib can be continued if blood pressure is controlled (to CTCAE grade 1 or baseline) on increased antihypertensive medication. If blood pressure cannot be stabilized with increased antihypertensive medication, vandetanib to be withheld and resumed only when blood pressure is controlled to baseline level. Upon recovery, vandetanib can be restarted at a permanently reduced dose.

Toxicity	Action
Grade 4	Vandetanib to be withheld and resumed only when blood pressure is controlled to baseline level. Upon recovery, vandetanib can be restarted at a permanently reduced dose.

Materials and methods

Standard AE monitoring schedule

The standard AE monitoring schedule received by patients was similar to that used in previous studies [1-3]. Patients were asked about their AEs at scheduled visits (approximately 2, 4, 8, 13, 26, 39, 52 and 60 weeks after starting vandetanib) and had the option to contact the investigator at any time if they were experiencing any AEs or symptoms and to discuss appropriate treatment options. Patients in the vandetanib control arm only underwent standard AE monitoring.

Outreach programme

In the outreach arm, in addition to the standard AE review during scheduled visits, patients were contacted by study site personnel or the study coordinator at week 1 and every 2 weeks thereafter, either by telephone or at standard clinic visits during the first 52 weeks of study treatment, in order to detect and possibly treat AEs at an earlier time point than would be possible without patient outreach. During these frequent contacts, patients were asked if they had experienced diarrhoea, rash, nausea/vomiting, headache or fatigue since the last contact. Symptoms of the above, and any other symptoms, were discussed with the study investigator and appropriate treatment regimens were implemented as required. These included concomitant medication, having the patient come to the study site for evaluation, or other measures to treat the AE (eg dose reductions). In addition, at randomization, patients in the outreach arm were given a patient information card and a rescue package that consisted of loperamide for treatment of diarrhoea and sunscreen (sun protection factor [SPF] ≥45) for prevention of skin conditions.

Exclusion criteria

Exclusion criteria included significant cardiac, haematopoietic, hepatic or renal dysfunction. Patients with brain metastases or spinal cord compression were ineligible unless they had been treated at least 4 weeks before study entry and were clinically stable without steroid treatment for 10 days. Patients were also excluded if they had received prior chemotherapy within 3 weeks of initiation of study therapy, if radiation therapy was ongoing prior to initiation of study treatment, or if major surgery was performed within 4 weeks of initiation of study therapy.

Treatments administered

Dose reductions were permitted for patients with toxicity related to vandetanib. In general, if any CTCAE grade 3 or 4 toxicity developed and was attributable to vandetanib, the study drug was withheld until the toxicity resolved to CTCAE grade 1 or baseline. Upon recovery, treatment could resume at a permanently reduced dose. Patients starting vandetanib at 300 mg could have two dose reductions: 300 mg to 200 mg and a further reduction from 200 mg to 100 mg; patients starting vandetanib at 200 mg were allowed one dose reduction to 100 mg. If CTCAE grade 3 or 4 toxicity recurred on the lowest reduced dose or if vandetanib was withheld for >6 weeks for resolution of toxicity, study treatment was permanently discontinued for that patient. Specific dose reduction plans were in place for management of skin toxicity, gastrointestinal toxicity, QTc prolongation and hypertension (Supplementary Table 1); these events are known to occur following treatment with vandetanib in patients with MTC and should be monitored and managed appropriately [2].

For patients who permanently discontinued treatment at or before 52 weeks, a final discontinuation visit occurred and the patient was contacted 60 days later for AE/serious AE (SAE) follow-up. Patients who wished to remain on therapy after completing 52 weeks of treatment attended a final analysis visit and were contacted every 13 weeks thereafter for collection of SAE information and drug accountability only until permanent discontinuation of treatment. At this stage, patients had a final discontinuation visit and were contacted 60 days later for SAE follow-up. These patients were then considered to have completed the study.

Statistical analysis

The percentage of time that patients experienced at least one AE of CTCAE grade ≥2 during their first 12 months of vandetanib treatment (primary outcome) was calculated as the number of days with at least one AE of CTCAE grade ≥2 divided by 365 and multiplied by 100. If the patient discontinued vandetanib treatment prior to 12 months, the endpoint was calculated as the number of days that the patient experienced at least one AE of CTCAE grade ≥2 divided by the total number of days that the patient received vandetanib and multiplied by 100.

Assuming 60% as a true percentage of time that patients experienced at least one AE of grade ≥2 in the first 12 months of treatment in the control arm and based on a standard deviation (SD) of 33% (as observed in the Phase III study) [2], a target sample size of 206 patients (103 in each treatment arm) was calculated in order to achieve 90% power at a 5% significance level of detecting a 15% difference between treatment arms.

Results

AEs with an outcome of death

In the outreach arm: one patient experienced cardiac arrest 1 day after receiving their last dose of vandetanib, having been treated for 70 days, with the direct cause of death recorded as MTC; the second experienced cardiac arrest 10 days after receiving their last vandetanib dose, having been treated for 285 days; the third died of cachexia due to progressive disease 55 days after receiving their last vandetanib dose, having been treated for 62 days; and the fourth patient died of unknown cause 2 days after the last vandetanib dose, having been treated for 221 days. In the vandetanib control arm, the two patients died of unknown cause: one 2 days after their last vandetanib dose, having been treated for 159 days; and the other 20 days after their last vandetanib dose, having been treated for 56 days. None of the AEs with an outcome of death were considered related to vandetanib. A total of 11 (5.4%) patients discontinued treatment because of an AE (eight [7.8%] in the outreach arm versus three [2.9%] in the vandetanib control arm). AEs leading to discontinuation of vandetanib were myocardial infarction (two [1.0%] patients), iron deficiency anaemia, eyelid oedema, large intestine perforation, increased blood creatinine, prolonged QT, cachexia, migraine with aura, dyspnoea, and chronic renal failure (one [0.5%] patient each).

Clinical laboratory evaluation, vital signs and ECG changes

Three patients experienced elevations in ALT, aspartate aminotransferase (AST), and total bilirubin; however, these abnormalities resolved without the requirement for dose modifications of vandetanib or other medications. Mean ALT, creatinine and thyroid-stimulating hormone (TSH) levels were higher during

treatment, although the elevated ALT later reverted to baseline levels. An increase in TSH levels was observed in 73 patients, with a median time to TSH elevation of 17 days. Hypothyroidism as an AE was reported in 30 patients. Overall, 16 (7.8%) patients had at least one QTc interval >500 ms (eight in each treatment arm). One patient discontinued treatment because of QT prolongation.

References

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