Summary

Thyroid cancer is a relatively rare malignancy, representing approximately 1% of all cancers, although it is the most common type of endocrine malignancy. In the UK, there were 2,154 newly diagnosed thyroid cancer cases in 2008 (3.5 cases per 100,000). Medullary thyroid cancer (MTC) is an uncommon histological subtype of thyroid cancer that accounts for approximately 3 to 5% of all thyroid cancer cases (or approximately 0.1 to 0.2 cases per 100,000 population).

Vandetanib (Caprelsa®) is licensed for the treatment of aggressive and symptomatic MTC in patients with unresectable, locally advanced or metastatic disease.

The license approval for the use of vandetanib for MTC is based on a phase III trial which evaluated the drug in patients with locally advanced or metastatic disease. The randomised, controlled trial involved 331 patients with measurable, unresectable diseases. At data cutoff, the median duration of follow up was 24 months, and 139 patients were continuing blinded treatment: 111 (48%) on vandetanib and 28 (28%) on placebo. The following results were reported:

- Statistically significant prolongation of PFS was observed for patients receiving vandetanib compared with placebo (hazard ratio [HR] 0.46; 95% CI, 0.31 to 0.69; \( P < 0.001 \)).
  
  The median PFS was 19.3 months in the placebo group and, although the median had not yet been reached for the vandetanib group, fitting a Weibull model indicated a predicted median of 30.5 months.

- Overall survival data were immature at data cutoff, with 14% of patients in the vandetanib group having died, as compared with 16% of patients in the placebo group (HR 0.89; 95% CI 0.48 to 1.65).

- At 6 months, the proportion of patients alive and progression-free was 192 (83%) for patients on vandetanib and 63 (63%) for patients on placebo.

- 56 patients in the placebo group (93%) subsequently received open-label vandetanib following progression of disease.

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- 56 patients in the placebo group (93%) subsequently received open-label vandetanib following progression of disease.

- Adverse effects occurring in more than 10% of patients and in greater numbers of patients on vandetanib compared to placebo were diarrhoea, rash, nausea, hypertension, headache, decreased appetite, acne, vomiting, and QT prolongation.

- Five patients in the vandetanib arm experienced adverse events leading to death during the randomised phase – these were single instances of aspiration pneumonia, respiratory arrest, respiratory failure, staphylococcal sepsis, and arrhythmia and acute cardiac failure in one patient. Two deaths in the placebo arm occurred due to an adverse event: one due to gastroenteritis, and one due to GI haemorrhage.

- Data from a meta-analysis evaluating the risk of rash associated with vandetanib has shown that patients who received vandetanib 300mg had a statistically significantly increased risk of developing all-grade rash in comparison with controls, with a relative risk of 2.43 (1.37 to 4.29, \( p = 0.002 \)).

Based on the PFS of 30 months, and the duration of administration of vandetanib would therefore be 30 months, then the average cost per 100,000 population for vandetanib would be £4500 for eligible patients starting treatment in year one (i.e. 0.03 patients). On a cumulative basis, the number of patients per 100,000 population receiving vandetanib would be 0.06 in year 2, and 0.075 per year thereafter, increasing the cost to £11,250 per 100,000 population per year from year 3.
Background

Medullary thyroid cancer
Thyroid cancer is a relatively rare malignancy, representing approximately 1% of all cancers, although it is the most common type of endocrine malignancy. In England and Wales, there were 1,918 newly diagnosed thyroid cancer cases in 2008. Medullary thyroid cancer (MTC) is an uncommon histological subtype of thyroid cancer that accounts for approximately 3 to 5% of all thyroid cancer cases. It arises from calcitonin-secreting parafollicular cells, and is a slow growing tumour with an indolent clinical course. MTC can occur spontaneously or be inherited on an autosomal dominant basis; hereditary forms include familial MTC and the multiple endocrine neoplasia type 2 (MEN 2) syndromes.

According to the European Thyroid Association guidelines on the management of metastatic medullary thyroid cancer (MTC) distant metastases in MTC often affect multiple organs including lungs, bones and liver, and more rarely brain, skin and breast, and are frequently associated with persistent disease in the neck. In patients with recurrent disease, an acceptable quality of life can usually be maintained for months or even years, but diarrhoea may be debilitating. Slow tumour growth is common, and distant metastases limited to a single organ may be considered for curative surgical resection or another local treatment modality. Patients with distant metastases and persistent/recurrent disease in the neck may benefit from treatment of neck disease depending on the extent of both neck and distant disease and of disease progression rate. Only patients with significant tumour burden and those with symptomatic or progressive disease according to the RECIST (Response Evaluation Criteria in Solid Tumour) criteria are candidates for systemic treatment.

The guideline also stipulates that among cytotoxic drugs, the most frequently used agent in MTC patients is doxorubicin, used either alone or in combination with cisplatin. Response rates ranged from 0 to 22%, with all responses being partial and only lasting a few months. As MTC is a well-differentiated endocrine tumour, various combinations of 5-fluorouracil, dacarbazine, streptozocin, cyclophosphamide and vincristine have been used, leading to response rates of approximately 20%, with symptomatic improvement in a limited number of patients. Cytotoxic drugs, such as taxanes, gemcitabine or irinotecan have not been evaluated in significant series of MTC patients. Dendritic cell immunotherapy may be effective, but is still under evaluation.

Vandetanib
Vandetanib (Caprelsa) is licensed for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable, locally advanced or metastatic disease. For patients in whom Rearranged during Transfection (RET) mutation is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision.

Vandetanib is a potent inhibitor of vascular endothelial growth factor receptor-2 (VEGFR-2 also known as kinase insert domain containing receptor (KDR)), epidermal growth factor receptor (EGFR) and RET tyrosine kinases. Vandetanib is also a sub-micromolar inhibitor of vascular endothelial receptor-3 tyrosine kinase.

Vandetanib inhibits VEGF-stimulated endothelial cell migration, proliferation, survival and new blood vessel formation in in vitro models of angiogenesis. In addition, vandetanib inhibits epidermal growth factor (EGF)-stimulated EGF receptor tyrosine kinase in tumour cells and endothelial cells. Vandetanib inhibits EGFR-dependent cell proliferation and cell survival in vitro. Vandetanib also inhibits both wild type and the majority of mutated, activated forms of RET, and significantly inhibits the proliferation of MTC cell lines in vitro.

In vivo vandetanib administration reduced tumour cell-induced angiogenesis, tumour vessel permeability, tumour microvessel density, and inhibited tumour growth of a range of human xenograft tumour models in athymic mice. Vandetanib also inhibited the growth of MTC xenograft tumours in vivo.

The precise mechanism of action of vandetanib in locally advanced or metastatic MTC is unknown.

Epidemiology
Thyroid cancer is a relatively rare malignancy, representing approximately 1% of all cancers, although it is the most common type of endocrine malignancy. In the UK, there were 2,154 newly diagnosed thyroid cancer cases in 2008 (3.5 cases per 100,000). Medullary thyroid cancer (MTC) is an uncommon histological subtype of thyroid cancer that accounts for approximately 3 to 5% of all thyroid cancer cases (or approximately 0.1 to 0.2 cases per 100,000 population). Although the overall prognosis is good for the approximately 50% of patients with MTC who present with disease confined to the thyroid gland and the 35-50% of patients who present with lymph node involvement (10-year survival rates of 95% and 75-85% respectively), it is comparatively poor for the 10-15% of patients who have distant metastases at diagnosis (10-year survival rate of 40%).
Vandetanib for metastatic medullary thyroid carcinoma

Guidelines for the management of thyroid cancer or medullary thyroid cancer

The European Thyroid Association has recently published guidelines for the management of metastatic MTC. Whilst the guideline provides recommendations for the management of distant metastases using local treatment modalities, the following recommendations have been made for the systemic management of metastatic MTC:

- In patients with significant tumour burden and symptomatic or progressive disease according to RECIST, the use of standard chemotherapeutic agents should not be considered as first-line therapy for patients with persistent or recurrent MTC.
- Inhibitors of both Ret and VEGFR tyrosine kinases appear to be the most effective treatment modality in these MTC patients. Treatment with radio-labelled molecules may be considered in selected patients, ideally in the setting of a well-designed clinical trial.

An American guideline (published in 2009) and a British guideline (published in 2007) on the management of medullary thyroid carcinoma describe the diagnosis and management of patients with the condition. The guidelines describe surgical strategies used, but make no recommendations on the pharmacological management of persistent or relapsed disease. It appears that radiotherapy and chemotherapy have no place in the management of the condition, and vandetanib is the first and only drug licensed for metastatic medullary thyroid carcinoma.

More recently, the US National Comprehensive Cancer Network has also issued guidelines for the management of metastatic MTC, in which they recommend that vandetanib may be considered for recurrent or persistent disease, or disease with symptomatic distant metastases. However, increasing tumour markers, in the absence of structural disease progression are not an indication for treatment with vandetanib.

Published data

Vandetanib has been investigated in two phase II and one phase III clinical trial.

The license approval for the use of vandetanib for MTC is based on a recently published phase III trial which evaluated the drug in patients with locally advanced or metastatic disease. This is the largest study investigating vandetanib for MTC. The randomised, controlled trial involved a total of 331 patients with measurable, unresectable diseases. Submission of a tumour sample was required, except for patients with hereditary MTC who had a documented germline RET mutation. Other key inclusion criteria were:

- WHO performance status of 0 to 2, and serum calcitonin level >/= 500pg/mL.

The majority of patients presented with sporadic disease, and most had metastatic disease at study entry. Exclusion criteria included significant cardiac, haematopoietic, hepatic, or renal dysfunction and administration of chemotherapy and/or radiation therapy within 4 weeks before random assignment. Patients were randomised to receive vandetanib 300mg once daily (n=231) or placebo (n=100). The primary objective was to determine whether vandetanib, compared with placebo, prolonged progression-free survival (PFS). Secondary assessments included objective response rate, disease control rate at 24 weeks, duration of response, overall survival, biochemical response (decrease in serum levels of calcitonin, and carcinoembryonic antigen (CEA)), and time to worsening of pain.

At data cutoff, the median duration of follow up was 24 months, and 139 patients were continuing blinded treatment: 111 (48%) on vandetanib and 28 (28%) on placebo. The following results were reported:

- Statistically significant prolongation of PFS was observed for patients receiving vandetanib compared with placebo (HR, 0.46; 95% CI, 0.31 to 0.69; P<0.001.) The median PFS was 19.3 months in the placebo group and, although the median had not yet been reached for the vandetanib group, fitting a Weibull model indicated a predicted median of 30.5 months.
- At 6 months, the proportion of patients alive and progression-free was 192 (83%) for patients randomised to vandetanib and 63 (63%) for patients randomised to placebo.
- In the vandetanib arm, a total of 73 (32%) patients progressed: 64 (28%) by response evaluation criteria in solid tumours (RECIST) progression and 9 (4%) by death in the absence of progression. The remaining 158 patients (68%) were censored in the analysis of PFS.
- In the placebo arm, a total of 51 (32%) patients progressed: 46 (28%) by response evaluation criteria in solid tumours (RECIST) progression and 5 (4%) by death in the absence of progression. The remaining 158 patients (68%) were censored in the analysis of PFS.
Vandetanib for metastatic medullary thyroid carcinoma

- Overall survival data were immature at data cutoff, with 14% of patients in the vandetanib group having died, as compared with 16% of patients in the placebo group (hazard ratio [HR] 0.89; 95% CI 0.48–1.65).
- A total of 31 patients discontinued treatment during the randomised phase, 28 patients in the vandetanib group (12%), vs. 3 patients in the placebo group (3%).
- More patients required dose reduction of vandetanib compared with placebo for adverse events or QT prolongation (35% vs. 3%).
- In terms of patient reported outcomes, patients receiving vandetanib had a 4.6 month delay in time to worsening of pain vs. placebo (HR 0.61; 95% CI 0.43 to 0.87, p=0.006).
- Adverse effects occurring in more than 10% of patients and in greater numbers of patients on vandetanib compared to placebo were diarrhoea, rash, nausea, hypertension, headache, decreased appetite, acne, vomiting, and QT prolongation.
- Five patients in the vandetanib arm experienced adverse events leading to death during the randomised phase – these were single instances of aspiration pneumonia, respiratory arrest, respiratory failure, staphylococcal sepsis, and arrhythmia and acute cardiac failure in one patient. Two deaths in the placebo arm occurred due to an adverse event: one due to gastroenteritis, and one due to GI haemorrhage.

The researchers concluded that in this clinical study, vandetanib has shown efficacy in patients with locally advanced or metastatic MTC, a challenging group of patients for whom there has been no effective therapy. A subgroup analysis concluded that the benefit that was demonstrated in PFS for patients receiving vandetanib compared with placebo was observed in patients with the hereditary or the sporadic form of MTC. However, because of the small number of patients with sporadic MTC who were confirmed RET negative and the large number of patients who were RET unknown, the subgroup analyses of PFS and objective response rate by RET mutation status are inconclusive. If data from the ARMS assay are taken into account, patients with sporadic MTC received benefit from vandetanib whether their tumours were M918T positive or negative; however, the response rate was greater in those who had an M918T mutation.

A phase II trial with vandetanib, targeting the kinases of Ret, EGFR and VEGFR, was evaluated at a maximal tolerated dose (300 mg/day) in 30 hereditary MTC patients. A partial response was observed in 10 patients, among whom 6 had a confirmed partial response, and stable disease longer than 24 weeks was established in another 16 patients. Another phase II trial with vandetanib (100 mg/day) included 19 hereditary MTC patients, and a partial response was observed in 3 patients, and stable disease longer than 24 weeks in another 10 patients, demonstrating antitumour activity in this setting. However, it was not clear whether there was a relationship between dose and efficacy, as well as between dose and toxicity.

Another phase II study published more recently evaluated the efficacy of vandetanib in patients with locally advanced or metastatic differentiated thyroid cancer (note: vandetanib is not currently licensed for differentiated thyroid cancer). The phase II study involved 145 patients aged 18 years or older with histologically confirmed differentiated disease. All patients had target lesions according to RECIST version 1.0 and were unsuitable for radioiodine therapy because of progression after previous radioiodine treatment, or had one or more lesion without detectable radioiodine uptake. Additionally, eligible patients had:

- A WHO performance status of 2 or less
- A life expectancy of 12 weeks or more, and
- Normal cardiac, hepatic and renal function

Patients were randomised to receive vandetanib 300mg per day (n=72) or placebo (n=73). The primary endpoint was progression-free survival (PFS) defined as the time from randomisation to the date of objective progression, or death by any cause. By data cut-off, approximately 14 months after the start of enrolment, the following results were reported:

- 113 (78%) patients had progressed (52 [72%] patients in the vandetanib group and 61 [84%] in the placebo group) and 40 (28%) had died (19 [26%] patients in the vandetanib group and 21 [29%] in the placebo group).
- Patients who received vandetanib had longer PFS than those who received placebo (hazard ratio [HR] 0.63, 60% CI 0.54–0.74; one-sided p=0.008): median PFS was 11.1 months (95% CI 7.7–14.0) for patients in the vandetanib group and 5.9 months (4.0–8.9) for patients in the placebo group.
- The most common grade 3 or worse adverse events were QTc prolongation (ten [14%] of 73 patients in the vandetanib group vs none in the placebo group), diarrhoea (seven [10%] vs none), asthenia (five [7%] vs three [4%]), and fatigue (four [5%] vs none).
- Two patients in the vandetanib group and one in the placebo group died from treatment-related serious adverse events (haemorrhage from skin metastases and pneumonia in the vandetanib group and pneumonia in the placebo group).
Finally, a meta-analysis evaluating the risk of developing rash, and the incidence of rash has also been published. This meta-analysis included data from 9 studies (n=2961) which met inclusion criteria. The summary incidence of all-grade and high-grade rash were 46.1% (95% CI 40.6 to 51.8%), and 3.5% (95% CI 2.5 to 4.7%) respectively. Patients who received vandetanib 300mg had a statistically significantly increased risk of developing all-grade rash in comparison with controls, with a relative risk of 2.43 (1.37 to 4.29, p=0.002).

**Cost**

The cost of a 30-tablet pack of the 100-mg strength is £2500, whilst the cost of the 30-tablet pack of the 300mg-strength is £5000. Based on the phase III trial dose of 300mg per day, the cost of treating a single patient would therefore be £5000 per month, or £120,000 if treated for an average median duration of 24 months (i.e. the duration of follow-up).

If it is assumed that 5% of all newly diagnosed thyroid cancer is MTC, this would equate to diagnosis of MTC for 96 patients in England and Wales in 2008 (0.2 per 100,000 population). If 15% of these patients would be eligible for treatment due to aggressive or metastatic disease, this would equate to 0.03 patients per 100,000 population.

Based on the PFS of 30 months, and the duration of administration of vandetanib would therefore be 30 months, then the average cost per 100,000 population for vandetanib would be £4500 for eligible patients starting treatment in year one (i.e. 0.03 patients). On a cumulative basis, the number of patients per 100,000 population receiving vandetanib would be 0.06 in year 2, and 0.075 per year thereafter, increasing the cost to £11,250 per 100,000 population per year from year 3.

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<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Incidence (number of patients per 100,000 eligible for this treatment)</th>
<th>Average duration of treatment</th>
<th>Cost per 100,000 population per month (£)</th>
<th>Cost per 100,000 for average treatment duration – 30 months (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vandetanib</td>
<td>Treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable, locally advanced or metastatic disease.</td>
<td>0.03</td>
<td>30 months (based on duration of PFS)</td>
<td>150</td>
<td>4500</td>
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Service implications

Although not particularly recommended, if the current standard strategy required the administration of doxorubicin with or without cisplatin, and oral vandetanib was replacing this standard strategy, there would be an expected decrease in service implications as patients can be managed via outpatient appointments.
Vandetanib for metastatic medullary thyroid carcinoma

References

3. Vandetanib SPC (Caprelsa); Date of revision = 17 Feb 2012
5. Robinson BG. Vandetanib (100 mg) in patients with locally advanced or metastatic hereditary medullary thyroid cancer. J Clin Endocrinol Metab 2010; 95: 2664–2671.

Details of search strategy:

1. Vandetanib SPC (Caprelsa); Date of revision = 17 Feb 2012
2. Cochrane Library
3. NICE (accessed 13 December 2012)
5. PubMed
   #4 Select 5 document(s) 5
   #3 Search (#1) AND #2 36
   #2 Search Thyroid Neoplasms[MeSH Terms] 35937
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6. EMBASE
   1. *VANDETANIB/ 329
   2. *THYROID MEDULLARY CARCINOMA/ 2553
   3. 1 AND 2 28

The document reflects the views of LCNDG and may not reflect those of the reviewers

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