New drugs

Vandetanib

Approved indication: medullary thyroid cancer
Caprelsa (AstraZeneca)
100 mg and 300 mg film-coated tablets
Australian Medicines Handbook section 14.2.3

Medullary thyroid cancer is a rare malignancy stemming from parafollicular C cells which produce calcitonin in the thyroid gland. Treatment is mainly by thyroidectomy and over three-quarters of patients survive for more than 10 years if treated early. However, options are limited for patients with distant metastases as these do not respond well to radiation or chemotherapy.

Vandetanib, an orphan drug, is a tyrosine kinase inhibitor. It is thought to work by blocking signalling via growth factors VEGFR (vascular endothelial growth factor receptor), EGFR (epidermal growth factor receptor) and the oncogenic RET (rearranged during transfection) kinase.

Following oral administration, peak plasma concentrations are reached after 4–10 hours. Excretion of the dose is slow, with a half-life of approximately 19 days, and 44% of the drug is recovered in the faeces and 25% in the urine.

The efficacy of daily vandetanib 300 mg has been assessed in one phase III placebo-controlled trial in 331 patients with advanced inoperable or metastatic disease. Most of these patients (90%) had had their thyroid removed. The median follow-up of two years was too short to detect significant differences in overall survival (see Table). The estimated median progression-free survival was 11 months longer in the vandetanib group than in the placebo group. This was an estimate due to the lack of events at data cut-off.

In the trial, diarrhoea (56%), rash (45%), nausea (33%), hypertension (32%), fatigue (24%), headache (26%), decreased appetite (21%) and acne (20%) were the most common adverse events with vandetanib. Just over a third of patients needed to have their dose reduced and 12% stopped treatment because of an adverse event or QTc prolongation. Asthenia and rash led to treatment discontinuation in 1.7% and 1.3% of patients. There were five deaths relating to adverse events in the vandetanib arm. The causes were aspiration pneumonia, respiratory arrest, respiratory failure and sepsis in single patients, and arrhythmia and acute cardiac failure in one patient.

Vandetanib 300 mg was associated with substantial QTc prolongation in the trial. Torsades de pointes, ventricular tachycardia and sudden death have been reported with vandetanib, and the drug is contraindicated in those with congenital long QTc syndrome or a long QTc interval (>480 milliseconds). Vandetanib is also not recommended in patients with a history of ventricular arrhythmias or those taking concomitant drugs that prolong the QTc interval.

ECG monitoring is recommended before and during treatment. If a patient develops a prolonged QTc interval, treatment should be interrupted. It can be resumed at a lower dose only if ECG findings improve. Electrolytes should also be monitored, especially if the patient has diarrhoea. Hypocalcaemia, hypomagnesaemia and hypokalaemia should be corrected if they occur. As vandetanib has a long half-life, patient monitoring should be continued for at least three weeks after the dose is stopped.

Vandetanib is not recommended in severe renal impairment and a reduced starting dose is recommended in moderate impairment. As with other VEGF inhibitors, proteinuria can occur with vandetanib. Elevations in alanine aminotransferase are also common and treatment may need to be interrupted. Pancreatitis has been reported with vandetanib.

Thyroid-stimulating hormone should be measured before and during treatment as almost half of patients taking vandetanib in the trial needed an increase in their thyroid replacement therapy.

Bleeding is an adverse event and has been fatal in some cases. Treatment should be stopped in severe

Table  Efficacy of vandetanib 300 mg/day in advanced or metastatic medullary thyroid cancer

<table>
<thead>
<tr>
<th></th>
<th>vandetanib 300 mg/day</th>
<th>placebo</th>
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</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>231</td>
<td>100</td>
</tr>
<tr>
<td>Median progression-free survival</td>
<td>30.5 months (estimated)</td>
<td>19.3 months</td>
</tr>
<tr>
<td>Deaths</td>
<td>32/231 (13.9%)</td>
<td>16/100 (16%)</td>
</tr>
</tbody>
</table>

1 this value was estimated using the Weibull model of probability

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haemorrhage and vandetanib should not be given to patients with a recent history of haemoptysis. As photosensitivity is increased with vandetanib, prescribers should advise their patients to wear sunscreen or avoid sun exposure during and for four months after treatment.

Vandetanib caused fetal abnormalities in animal studies and is classified as a pregnancy category D drug. It may be excreted in breast milk and should be avoided during lactation.

Vandetanib is a substrate of cytochrome P450 (CYP) 3A4, so co-administration of potent CYP3A4 inhibitors (itraconazole, ketoconazole, clarithromycin) or inducers (rifampicin, carbamazepine, St John’s wort) could affect vandetanib exposure. Avoidance or dose adjustment is recommended. Vandetanib is also a moderate inducer of CYP3A4 so caution is urged with concomitant CYP3A4 substrates such as cyclosporin and docetaxel.

Because vandetanib is a weak inhibitor of P-glycoprotein, it may increase plasma concentrations of drugs excreted by this transporter such as dabigatran and digoxin. Vandetanib also inhibits the organic cation transporter 2 (OCT2) and may increase concentrations of substrates such as metformin. In both instances, careful monitoring is recommended and dose adjustments may be needed.

Co-administration with proton pump inhibitors could potentially decrease exposure to vandetanib and is not recommended. Increased INR monitoring may be necessary in patients receiving vitamin K antagonists.

Although vandetanib may prolong the onset of progressive disease in some patients with advanced inoperable or metastatic medullary thyroid cancer, benefits to overall survival have not yet been shown. Patients and doctors need to balance this against the drug’s potentially life-threatening adverse effects.

**T** manufacturer provided clinical evaluation

**REFERENCE**


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The Transparency score (    ) is explained in ‘New drugs: T-score for transparency’, Aust Prescr 2011;34:26-7.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).