NEW DRUGS

Aust Prescr 2017;40:242–3
https://doi.org/10.18773/austprescr.2017.070
First published 3 October 2017

Lenvatinib

Approved indication: thyroid cancer, renal cell cancer

Lenvima (Eisai)

4 mg, 10 mg capsules

Australian Medicines Handbook section 14.2.4

In order to grow, cancers develop new blood vessels. This neovascularisation is the target of anticancer drugs such as the tyrosine kinase inhibitors.[1] Lenvatinib is a tyrosine kinase inhibitor which acts on a range of receptors including those for vascular endothelial growth factor and fibroblast growth factor. This action decreases the proliferation of endothelial cells.

Lenvatinib is well absorbed. Food does not affect the extent of absorption, but slows the rate. The drug is mainly metabolised by cytochrome P450 (CYP) 3A4. Although inducers or inhibitors of this enzyme will alter the concentrations of lenvatinib, no dose adjustments are recommended. The terminal half-life is 28 hours with metabolites appearing in the faeces and urine. A reduced starting dose is recommended for patients with severe hepatic or renal impairment.

Lenvatinib mesilate has been studied in a variety of solid tumours. Its initial approval is for progressive differentiated thyroid cancer that is refractory to radioactive iodine. Lenvatinib, in combination with everolimus, is also approved for advanced renal cancer that has not responded to therapy aimed at vascular endothelial growth factor.

The main trial in thyroid cancer randomised 261 patients to take daily doses of lenvatinib and 131 to take placebo. The median follow-up in the study was 17.1 months for the lenvatinib group and 17.4 months for the placebo group. Imaging revealed a 64.8% response rate with lenvatinib compared with 1.5% for placebo. The cancer progressed in 35.6% of the patients taking lenvatinib and 83.2% of those taking placebo. This led to a significant difference in progression-free survival – 18.3 months with lenvatinib and 3.6 months with placebo.[2]

The approval for lenvatinib in renal cell carcinoma appears to be based on an open-label phase II trial in 153 patients. These patients had advanced or metastatic disease and had previously been treated with a drug, such as sunitinib, aimed at vascular endothelial growth factor. They were randomised to take lenvatinib, everolimus or both drugs once daily and their radiographic response was assessed every eight weeks. The median duration of treatment was 7.4 months with lenvatinib, 4.1 months with everolimus and 7.6 months with the combination. The respective response rates were 27%, 6% and 43%. The median progression-free survival was significantly longer with the combination than with everolimus alone (14.6 months vs 5.5 months). Patients treated with lenvatinib alone also had a longer progression-free survival (7.4 months) than those taking everolimus.[3]

As tyrosine kinase inhibitors affect endothelial cells, they cause adverse effects such as thrombosis, bleeding and hypertension.[1] In the study of thyroid cancer, 68% of the patients taking lenvatinib developed hypertension compared with 9% of the placebo group.[2] In both trials frequent adverse events in patients taking lenvatinib included diarrhoea, fatigue, reduced appetite, nausea and vomiting. These were all more frequent than reported in patients taking everolimus or placebo.[2,3]

Adverse events led to the discontinuation of treatment in 14% of the patients taking lenvatinib for thyroid cancer.[2] In the study of renal cancer, 25% of the patients taking lenvatinib and 24% of those taking it with everolimus stopped treatment because of adverse events, compared with 12% taking everolimus alone.[3] Some adverse events, such as cerebral haemorrhage and pulmonary embolism, were fatal.[2,3]

Many patients will need to have their treatment reduced or interrupted because of toxicity. Patients with renal impairment are more prone to serious adverse effects. Lenvatinib may cause cardiac dysfunction and, as it can prolong the QT interval, the ECG should be regularly monitored. Monthly monitoring of thyroid function is recommended because lenvatinib can cause hypothyroidism. In the trial of renal cancer more than 35% of the patients taking lenvatinib developed hypothyroidism.[3] Liver function has to be frequently monitored because of the risk of hepatotoxicity. Other serious adverse effects include gastrointestinal fistula and perforation and proteinuria. Treatment should be permanently stopped if the patient develops nephrotic syndrome.

At present there is more published evidence about lenvatinib in thyroid cancer than in renal cancer. Further research will be needed to find out if overall survival improves. When the trial in thyroid cancer was published, there was no significant difference in overall survival between lenvatinib and placebo.[2] In the phase II trial in renal cancer, there were initially no significant differences in overall survival between the treatments. A later post hoc analysis found a significant difference between lenvatinib plus everolimus and everolimus alone (median 25.5 months vs 15.4 months). However, there was no significant difference between the combination and lenvatinib alone (median overall survival 19.1 months).[3]

Sorafenib is another tyrosine kinase inhibitor which improves progression-free survival in thyroid cancers refractory to radioactive iodine.[4] A systematic review has indirectly compared sorafenib and lenvatinib. It found that lenvatinib had more effect on progression-free survival, but there were not enough data to show a difference in overall survival.[5]

Patients considering treatment with lenvatinib need to be aware of the current uncertainty about its effect on survival. While this may be resolved with more research, it is inevitable that almost every patient will suffer adverse effects during treatment with lenvatinib.[2,3]

T T T Manufacturer provided the clinical evaluation

REFERENCES

1. Clarke SJ, Sharma R. Angiogenesis inhibitors in cancer - mechanisms of action. Aust Prescr 2006;29:9-12. http://dx.doi.org/10.18773/austprescr.2006.007
2. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med 2015;372:621-30. http://dx.doi.org/10.1056/NEJMoa1406470
3. Motzer RJ, Hutson TE, Glen H, Michaelson MD, Molina A, Eisen T, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. Lancet Oncol 2015;16:1473-82. http://dx.doi.org/10.1016/S1470-2045(15)00290-9
4. Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet 2014;384:319-28. http://dx.doi.org/10.1016/S0140-6736(14)60421-9
5. Kawalec P, Malinowska-Lipień I, Brzostek T, Kózka M. Lenvatinib for the treatment of radioiodine-refractory differentiated thyroid carcinoma: a systematic review and indirect comparison with sorafenib. Expert Rev Anticancer Ther 2016;16:1303-9. http://dx.doi.org/10.1080/14737140.2016.1247697

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.