

THERAPY

Lenvatinib and radioiodine-refractory thyroid cancers

Lara Dunn and James A. Fagin

Refers to Schlumberger, M. et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N. Engl. J. Med.* 372, 621–630 (2015).

Over the past decade, several multikinase inhibitors have shown considerable effectiveness against metastatic radioiodine-refractory thyroid cancers in early stage clinical trials. On the basis of some remarkable results in a phase III clinical trial, lenvatinib now joins sorafenib as another multikinase inhibitor approved by the FDA for this disease.

Traditionally, patients with radioiodine-refractory metastatic thyroid cancer who experience rapid disease progression have had limited therapeutic options, as conventional chemotherapy is largely ineffective for this disease. Lenvatinib^{1,2} and sorafenib³ are hypothesized to exert their actions by targeting tumour angiogenesis. Although both drugs are potent inhibitors of the vascular endothelial growth factor receptors, VEGFR-1, VEGFR-2 and VEGFR-3, they differ in their activity profiles against other kinases that might also contribute to disease pathogenesis. Sorafenib³ inhibits signalling through proto-oncogene tyrosine-protein kinase receptor Ret (commonly known as RET), RAF proto-oncogene serine/threonine-protein kinase and platelet-derived growth factor receptor (PDGFR) β , whereas lenvatinib^{1,2} blocks PDGFR α , RET, mast/stem cell growth factor receptor Kit and the fibroblast growth factor receptors FGFR-1, FGFR-2, FGFR-3 and FGFR-4. The two drugs seem to differ in their clinical efficacies, which suggests that the profile of kinases on which they act and the therapeutic window in which each agent inhibits their molecular targets might have practical clinical consequences.

Lenvatinib (E7080) was approved by the FDA on the basis of the SELECT multicentre trial that evaluated progression-free survival (PFS) in patients with progressive radioiodine-refractory thyroid cancer.⁴ The trial included 392 patients, who were randomly assigned at a ratio of 2:1 to receive either lenvatinib or placebo, respectively. Cross-over to open-label lenvatinib treatment

“...the SELECT study results are superior to those of the DECISION study...”

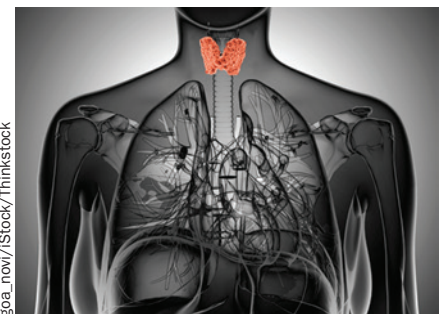
was permitted among patients in the placebo group at the time of disease progression, with appropriate analysis conducted per intention-to-treat. A significant improvement in PFS was observed in those receiving lenvatinib; the median PFS in the treatment group was 18.3 months compared with 3.6 months in the placebo group ($P < 0.001$). Treatment with lenvatinib also resulted in an impressive objective response rate (ORR) of 64.8%, with four (1.5%) complete responses and 165 (63.2%) partial responses, compared with only 1.5% (two partial responses) in the placebo group ($P < 0.001$).⁴

Importantly, comparisons between clinical trials must be made with caution. However, the SELECT study⁴ results are superior to those of the DECISION study,⁵ which was the phase III placebo-controlled trial that led to the FDA approval of sorafenib for radioiodine-refractory thyroid cancer. In the DECISION trial,⁵ treatment with sorafenib resulted in an overall PFS improvement of 5 months over placebo (median PFS 10.8 months versus 5.8 months, respectively) compared with PFS of 14.7 months for lenvatinib. Comparison of the response rates of the trials reveals an even greater disparity with an ORR for sorafenib of only 12.2% with no complete responses.

The differences in outcomes between the SELECT and DECISION trials are not readily explained by differences in the enrolled

patient populations. In fact, one could argue that the SELECT trial included a more challenging population than the DECISION trial, as 25% of patients in the lenvatinib group had previously received treatment with a multikinase inhibitor,⁴ whereas the sorafenib study excluded patients who had previously received multikinase inhibitor therapy.⁵ The PFS and ORR benefits with lenvatinib in patients who had previously received treatment was still impressive (median PFS 15.1 months; ORR 62.1%), which are comparable to the results observed across the entire SELECT study population and still superior to the DECISION results for first-line sorafenib. The impressive response rate and dramatic reduction in tumour volume that was achieved in some patients also suggests that the use of lenvatinib therapy might extend beyond the current use of multikinase inhibitors to control rapidly progressive multifocal disease.⁶ This expansion of treatment applications could include clinical scenarios that require considerable tumour shrinkage for local disease control, for which palliative surgical and radiotherapy approaches might have previously been prioritized.⁶

However, adverse effects associated with treatment with lenvatinib in the SELECT study were clinically relevant and maintenance of full-dose therapy proved to be a considerable challenge.⁴ The rates of dose interruption, dose reduction and discontinuation of therapy among patients who received lenvatinib were 82.4%, 67.8% and 14.2%, respectively. Dose interruptions and reductions of lenvatinib were most commonly due to diarrhoea (22.6% of patients), hypertension (19.9%) and proteinuria (18.8%); discontinuation of treatment was most commonly due to development of



goa_nov/f/stock/Thinkstock

hypertension (1.1%) and asthenia (1.1%).⁴ By contrast, hand–foot syndrome was the most common reason for dose interruption, dose reduction and discontinuation of sorafenib in the DECISION trial.⁵ Notably, six deaths in the lenvatinib group were considered to be related to the treatment, including one case of pulmonary embolism and one case of haemorrhagic stroke.⁴ The effects of lenvatinib on overall survival, quality-of-life and the long-term cumulative toxicities of therapy remain unexplored, such that a comprehensive picture of how this systemic therapy benefits patients is still open to question.

The mechanisms by which multikinase inhibitors, and lenvatinib in particular, are active against cancers remain elusive, primarily because they inhibit multiple oncologic targets. Three tumours that respond positively to treatment with multikinase inhibitors (renal cell carcinoma, hepatocellular carcinoma and thyroid cancer) originate from cell types that require direct contact with capillaries to exert their normal functions. One might speculate that these cells emit trophic signals for capillary endothelial cells, which upon loss of polarity lead to development of a disorganized tumoural vasculature and promotion of tumour cell hypoxia. The hypoxic state might, in turn, result in loss of immune surveillance, selection of more aggressive tumour clones, increased VEGFR activation and dependence on VEGFR signalling that can be targeted therapeutically.^{7,8} Evidence supports the importance of concomitantly inhibiting multiple receptor tyrosine kinases (for example, VEGFR-2, PDGFR and, possibly, FGFR) to effectively block tumour-dependent angiogenesis.⁸ The highly selective VEGF-trapping agent aflibercept, which is a soluble decoy receptor for VEGF, had no activity in radioiodine-refractory thyroid cancers.⁹ This

observation strengthens the assertion that the benefits of multi-targeted kinase inhibitors in thyroid cancer likely stem from more than inhibition of VEGFR signalling alone.⁹

Inhibition of angiogenesis in renal cell carcinoma and hepatocellular carcinoma is appealing given the lack of cell autonomous oncogenic drivers that can be pharmacologically targeted. By contrast, radioiodine-refractory thyroid cancers frequently have genetic alterations in the MAPK signalling axis (including *BRAF*, *RAS* and fusions of genes encoding receptor tyrosine kinases) that generate dependencies and can be exploited with targeted therapies.¹⁰ This feature of thyroid cancers offers two potential treatment strategies: blocking the primary oncogenic driver and disrupting the disorganized tumour vasculature. The ultimate application of these two distinct approaches, either sequentially or in combination, remains to be defined but offers much promise.

Lenvatinib is an exciting, new treatment option with potential to modify the role of systemic treatment in the management of patients with radioiodine-refractory thyroid cancer. Information on overall survival and quality-of-life will be important as clinicians implement this new therapy. Moreover, continued research into the molecular mechanisms of thyroid cancer remains central to developing rational biologic therapies with increased selectivity and potent targeted activity to maximize efficacy and limit toxicity.

Department of Medicine, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA (L.D., J.A.F.).
Correspondence to: J.A.F.
faginj@mskcc.org

doi:10.1038/nrendo.2015.53
Published online 31 March 2015

Acknowledgements

We are grateful to Alan L. Ho for helpful comments on the manuscript. This work was supported, in part, by NIH grants CA50706, CA72597, P50-CA72012 and P30-CA008748.

Competing interests

The authors declare no competing interests.

1. Matsui, J. *et al.* Multi-kinase inhibitor E7080 suppresses lymph node and lung metastases of human mammary breast tumor MDA-MB-231 via inhibition of vascular endothelial growth factor-receptor (VEGF-R) 2 and VEGFR3 kinase. *Clin. Cancer Res.* **14**, 5459–5465 (2008).
2. Matsui, J. *et al.* E7080, a novel inhibitor that targets multiple kinases, has potent antitumor activities against stem cell factor producing human small cell lung cancer H146, based on angiogenesis inhibition. *Int. J. Cancer* **122**, 664–671 (2008).
3. Wilhelm, S. M. *et al.* BAY 43–9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res.* **64**, 7099–7109 (2004).
4. Schlumberger, M. *et al.* Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N. Engl. J. Med.* **372**, 621–630 (2015).
5. Brose, M. S. *et al.* Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. *Lancet* **384**, 319–328 (2014).
6. Tuttle, R. M. *et al.* NCCN clinical practice in oncology for thyroid carcinoma. Version 2.2014. *National Comprehensive Cancer Network* [online] http://www.nccn.org/professionals/physician_gls/f_guidelines.asp (2014).
7. Jain, R. K. Normalizing tumor microenvironment to treat cancer: bench to bedside to biomarkers. *J. Clin. Oncol.* **31**, 2205–2218 (2013).
8. Jain, R. K. Antiangiogenesis strategies revisited: from starving tumors to alleviating hypoxia. *Cancer Cell* **26**, 605–622 (2014).
9. Sherman, E. J. *et al.* A phase II study of VEGF trap in patients with radioactive iodine (RAI)-refractory thyroid carcinoma. *J. Clin. Oncol.* **29** (Suppl.), a5566 (2011).
10. Knauf, J. A. & Fagin, J. A. Role of MAPK pathway oncoproteins in thyroid cancer pathogenesis and as drug targets. *Curr. Opin. Cell Biol.* **21**, 296–303 (2009).