TRIAL WATCH

Multikinase-targeting therapy finds potential niche in thyroid cancer

The US Food and Drug Administration (FDA) has approved the use of lenvatinib, an orally available multikinase inhibitor, for the treatment of patients with locally recurrent or metastatic, progressive, radioactive-iodine-refractory, differentiated thyroid cancer. This approval is based on results in the Phase III SELECT trial, in which lenvatinib extended the median progression-free survival of these patients from 3.6 months to 18.3 months (*N. Engl. J. Med.* **372**, 621–630; 2015).

Although the current treatment regime for patients with low-grade thyroid cancer is often curative, patients with radioiodine-resistant tumours fare poorly; only 10% of these patients are alive a decade after the detection of metastases. Thus, new treatments are needed. Lenvatinib targets vascular endothelial growth factor receptor 1 (VEGFR1), VEGFR2 and VEGFR3; fibroblast growth factor receptor 1 (FGFR1), FGFR2, FGFR3 and FGFR4; platelet-derived growth factor receptor- α (PDGFR α); the tyrosine-protein kinase receptor RET; and the mast or stem cell growth factor receptor KIT. Inhibiting the angiogenic activity of VEGF or VEGFRs in particular is thought to have an important role in slowing the growth of these tumours. Although other multikinase inhibitors are licensed by the FDA for the treatment of thyroid cancer, Enrique Grande, an oncologist from the Hospital Universitario Ramón y Cajal in Madrid, Spain, who specializes in thyroid cancer, thinks that lenvatinib could “completely change the natural history of radioiodine-refractory

thyroid cancer,” owing to its substantially increased antitumour activity relative to its predecessors.

“The first [multikinase inhibitor] drugs — sorafenib, vandetanib, sunitinib and axitinib — induced a few partial responses,” explains Martin Schlumberger, a professor of oncology at the Université Paris-Sud, France, and a lead investigator in the lenvatinib trial. “The more recent drugs — lenvatinib, pazopanib and cabozantinib — induce a much higher response rate.” Response rates for the first group of drugs hovered at around 20% or lower, whereas response rates for the second wave of compounds are 50–60%. In addition, lenvatinib induced a complete response in four patients (1.5%); complete responses have not been observed with any of the other compounds, including cabozantinib.

This high response rate, however, has come at a cost. “The Achilles heel of lenvatinib is the toxicity profile,” says Grande. In the SELECT trial, over 97% of patients taking lenvatinib had at least one treatment-related adverse effect, such as hypertension, diarrhoea or

asthenia. Six treatment-related deaths (2.3% of patients) occurred, and 30% of patients had serious treatment-related adverse events. “All these drugs are quite toxic, and treatment lasts months or years, so toxicity is a very big issue,” agrees Schlumberger. However, decreasing the dose will probably decrease the treatment effects as well as the incidence of adverse events; Grande and Schlumberger both highlight the importance of monitoring patients carefully and dealing with the adverse events without substantially reducing the dose.

Compounds that target molecules in pathways downstream of the receptors inhibited by lenvatinib — particularly the kinases BRAF and MEK — are also being investigated as potential treatments in ongoing clinical trials. Schlumberger thinks that thyroid cancers might also be effectively treated with immunotherapy, possibly in combination with a compound like lenvatinib. Most cases of thyroid cancer present with mutant proteins, infiltration of inflammatory cells and evidence of programmed cell-death protein 1 (PD1) activity — all of which suggests that an anti-PD1 strategy could be effective.

On the basis of the SELECT trial results, lenvatinib will probably feature in many of the combination strategies that will emerge in the coming years for radioiodine-resistant thyroid cancers. “If the toxicity can be controlled, I think that clinicians will always give the drug that is more potent,” says Schlumberger — and so far, that drug is lenvatinib.

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