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NEURO-ONCOLOGY

Everolimus for astrocytoma in tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is a genetic disorder characterized by benign tumours in various organs. Now, a phase III study in patients with TSC has shown that the drug everolimus significantly reduces the volume of subependymal giant cell astrocytomas in these patients, providing hope that the first approved treatment for this aspect of TSC could be on the horizon.

Mutations in tuberous sclerosis genes *TSC1* or *TSC2* underlie the disease, and mediate their pathogenic effects through aberrant control of mammalian target of rapamycin (mTOR)—an important regulator of cell growth and proliferation. Neurological symptoms such as epilepsy and intellectual disability are common in TSC, and about one-fifth of patients develop subependymal giant cell astrocytomas. Although such tumours are benign, as they continue to grow they can cause life-threatening symptoms such as hydrocephalus, leading to requirement for surgery. Moreover, such intervention carries a substantial risk of postoperative morbidity.

How might treatment options for this important manifestation of TSC be improved? A series of preliminary studies had previously indicated the potential of everolimus, an approved mTOR inhibitor, to reduce the volume of subependymal giant cell astrocytomas. Now, a double-blind, placebo-controlled, phase III study to assess whether such benefits can be achieved in patients with TSC has been completed.

117 patients with TSC in 24 centres across 10 countries worldwide were randomly assigned to receive oral everolimus or placebo. After 24 weeks, 42% of patients in the everolimus group versus only 3% in the placebo group met the primary end point, defined as at least 50% reduction in volume of subependymal giant cell astrocytomas as measured on MRI. "This therapy gives patients a new and, I believe, a superior option to neurosurgical treatment," says David Franz, who was lead author on the paper.

> "This therapy gives patients a new ... option to neurosurgical treatment"

Treatment was also associated with reductions in the skin lesions and kidney tumours that occur in TSC. About half of the patients receiving everolimus experienced adverse events, such as stomatitis and mouth ulceration, but these effects did not lead to treatment discontinuation and were consistent with the known adverse event profile of the drug.

In previous open-label trials, regrowth of subependymal giant cell astrocytomas occurred in some patients after discontinuation of everolimus. An ongoing extension phase of the current study will follow up patients for 4–5 years, providing long-term data to determine whether continuous everolimus is required to maintain clinical benefit.

As Franz points out, mTOR inhibitors can increase clearance of proteins that cause Huntington disease, Parkinson disease and Alzheimer disease. "These drugs may be useful for treatment of various neurological disorders," he concludes.

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Original article Franz, D. N. *et al.* Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet* doi:10.1016/S0140-6736(12)61134-9