Everolimus for tuberous sclerosis complex

Everolimus, an inhibitor of mTOR, could be an effective treatment for subependymal giant cell astrocytomas associated with tuberous sclerosis complex, according to the results of a phase 3 trial.

Tuberous sclerosis complex is an autosomal-dominant genetic disorder in which mTOR is constitutively activated and benign tumours (hamartomas) grow in several organs, including the brain, kidneys, eyes, heart, lung, liver, and skin. The disease usually affects the CNS, with symptoms including seizures, intellectual disability, and neurobehavioural problems.

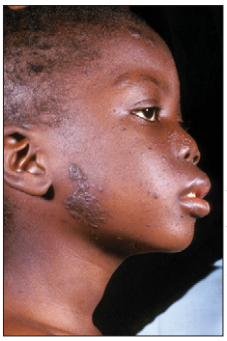
Investigators of the EXIST-1 trial randomly assigned 78 patients to receive everolimus and 39 to receive placebo. 27 (35%) patients in the everolimus group had a reduction in astrocytoma volume of at least 50%, compared with none in the control group. The trial has been extended to assess whether the results can be safely maintained over a longer period.

"This is the first placebo-controlled trial confirming the efficacy of everolimus in the treatment of the growing hamartomas associated with tuberous sclerosis complex", said study coauthor Michael Kohrman (University of Chicago, Chicago, IL, USA). "In addition to the primary efficacy for the treatment of subependymal giant cell astrocytomas…angiomyolipomas of the kidney and facial angiofibromas also responded to everolimus."

Lead investigator David Neal Franz (Cincinnati Children's Hospital, OH, USA) told *The Lancet Oncology* that the latest study confirms the positive results of a previous phase 1–2 everolimus trial. Patients "now have a medical option instead of surgical resection, as well as the chance to improve many of the varied manifestations of their disease with a single intervention". Franz added that future research will investigate the effects of mTOR inhibition on seizures and cognitive impairment in people with the disease.

Chris Kingswood (Tuberous Sclerosis Association, Woking, UK), commented: "Subependymal giant cell astrocytomas in young people with tuberous sclerosis complex are common, often dangerous, and challenging to treat. To date, treatment options have been limited, and because of this, outcomes for some patients with more difficult-to-treat subependymal giant cell astrocytomas have been suboptimal. Everolimus, as an innovative and less invasive treatment…is certainly to be welcomed."

Neil Bennet



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Published **Online**
November 23, 2012
http://dx.doi.org/10.1016/S1470-2045(12)70535-1

For the **trial** see **Articles** http://dx.doi.org/10.1016/S0140-6736(12)61134-9

Novel therapeutic target in aggressive paediatric AMKL

The fusion of *CBFA2T3* and *GLIS2* via chromosomal rearrangement has recently been shown to promote development of acute megakaryoblastic leukaemia (AMKL), which constitutes about 10% of paediatric acute myeloid leukaemias. AMKL in children with Down's syndrome has a favourable outcome; however, children with non-Down's syndrome AMKL (non-DS-AMKL) have a very poor prognosis, with 3-year survival under 40%.

The *CBFA2T3-GLIS2* fusion was discovered during a sequencing study of paediatric non-DS-AMKL samples, and was detected in 27% of the 48 cases analysed. For patients with childhood non-DS-AMKL, expression of *CBFA2T3-GLIS2* was associated with significantly worse overall survival than was seen in the absence of this genomic alteration.

In laboratory studies, expression of the CBFA2T3-GLIS2 fusion protein in haematopoietic cells caused activation of signalling through the bone morphogenic protein (BMP) pathway. Dorsomorphin, a small molecule inhibitor targeting the BMP pathway, inhibited the proliferation of these cells in a dose-dependent fashion.

Senior author James Downing (St Jude Children's Research Hospital, Memphis, TN, USA) said that, as part of the Pediatric Cancer Genome Project, this study "was focused on the biology of paediatric AMKL. The observation of the cryptic translocation…could be used as a prognostic marker to identify those patients who do not do well on current therapy." Coauthor Tanja Gruber (St Jude Children's Research Hospital) agreed: "If patients do have the fusion, these are patients where you do need to try new agents". Ongoing studies include "building mouse models of the disease and exploring a variety of chemicals to inhibit the BMP pathway", Downing said. "Map[ping] out other pathways that are involved, with a goal of identifying targeted agents that inhibit multiple pathways utilised by the tumour cells", Gruber added.

For Michelle Le Beau (University of Chicago, IL, USA), "the results provide good reason to study BMP signalling in this model. We would want to know exactly what the fusion protein is doing, as well as to identify the cooperating mutations that work together with the fusion protein to drive leukaemogenesis. There is no effective treatment for this type of AMKL. That's the promise here—once you understand the biology of the disease, then you have the potential for developing targeted therapy."

Judith A Gilbert

Published **Online**
November 23, 2012
http://dx.doi.org/10.1016/S1470-2045(12)70536-3

For the **study** see http://dx.doi.org/10.1016/j.ccr.2012.10.007