VERTU: A randomised phase II trial of veliparib, radiotherapy and temozolomide in patients with unmethylated *MGMT* glioblastoma

The VERTU trial tested a promising drug called veliparib for people with primary brain tumours. It was conducted in Australia between 2015 and 2018.

We thank the participants, their families and all staff members who contributed to the trial. Here is a summary of the trial and results.

What was the trial about?

Glioblastoma is the most common primary brain tumour. The standard treatment for glioblastoma consists of neurosurgery, then radiotherapy and temozolomide. Despite this, glioblastoma is aggressive and people usually die within 1–2 years.

About 1 in 2 people have glioblastoma which is '*MGMT*-unmethylated'. This means that a repair gene called *MGMT* is active in these tumour cells. Unfortunately, *MGMT*-unmethylated glioblastoma is resistant to the standard treatment. Novel treatments are greatly needed.

In the VERTU trial, we tested a promising drug called veliparib. Veliparib works by stopping tumour cells from being able to repair themselves. Previous research suggested that:

a) Veliparib can easily enter the brain
b) Veliparib can stop tumour cells from repairing the radiotherapy damage
c) Veliparib can stop tumour cells from repairing the temozolomide damage

People with a new diagnosis of *MGMT*-unmethylated glioblastoma were randomly allocated to receive either:

a) Veliparib treatment (radiotherapy with veliparib for 6 weeks, then a break for 4 weeks, then temozolomide and veliparib for 24 weeks)
b) Standard treatment (radiotherapy with temozolomide for 6 weeks, then a break for 4 weeks, then temozolomide alone for 24 weeks)

We enrolled 125 people from 16 hospitals across Australia. There were 87 men and 38 women, with an average age of 61 years.

How was the effect of treatment measured?

We measured how long it took for the glioblastoma to grow, despite the veliparib or standard treatment.

We also measured:

a) How long people lived
b) 'Quality of life' based on questionnaires that they filled out during the trial
c) The side-effects of the treatment

Was the new treatment better?

There was not enough evidence to show that veliparib was useful for people with *MGMT*-unmethylated glioblastoma.

For 46% of the people receiving the veliparib treatment, the tumour was under control at the 6-month mark. For 31% of the people receiving the standard treatment, the tumour was under control at the 6-month mark. Based on previous research, we expected this to be 53%. Evidently, the outcomes were poor in both groups.

Overall, people who received the veliparib treatment lived a similar length of time to those who received the standard treatment. Likewise, the quality of life outcomes were similar in both groups.

What were the side-effects of the treatment?

The number and severity of side-effects were similar in both groups.

For people receiving the veliparib treatment, serious side-effects included low platelets (17%), low neutrophils (12%), seizures (11%) and fatigue (7%). For people receiving the standard treatment, serious side-effects included low platelets (8%), seizures (5%), high blood sugar levels (5%) and diarrhoea (5%).

How will the results help patients and doctors in future?

The results add to our knowledge base about the treatment of primary brain tumours. Although veliparib is well-tolerated, there is not enough evidence to support its use for *MGMT*-unmethylated glioblastoma. The standard of care remains unchanged. Building on these results, researchers are investigating newer generation drugs acting on similar pathways as veliparib, and rational combinations with other targeted and immunotherapy drugs.

What will the researchers do next?

Additional research is underway to explore why some people benefited from the veliparib treatment but others did not. This includes:

a) Biological analysis of the tumour samples from the VERTU trial. We will search for biomarkers (molecular properties of the tumour) which predict benefit from veliparib. In this process of searching for biomarkers, we may also identify novel molecular pathways to target with drugs in future trials.
b) Advanced imaging analysis of the MRI scans from the VERTU trial. This will include verifying the accuracy of the MRI assessments in the VERTU trial, as well as developing novel methods to improve the utility of MRI scans.

Also, we await the completion of a similar trial which tested veliparib in people with *MGMT*-methylated glioblastoma. Your oncologist can discuss these results once available.

Where can I find out more about the trial?

The preliminary results have been presented at the Society of Neuro-Oncology Annual Meeting 2019:

Khasraw M, McDonald KL, Rosenthal M, Lwin Z, Ashley DM, Wheeler H, and others. ACTR-24: A randomized phase II trial of veliparib, radiotherapy and temozolomide in patients with unmethylated *MGMT* glioblastoma: The VERTU study. *Neuro-Oncology* 2019, volume 21, issue supplement 6, page vi18.
https://doi.org/10.1093/neuonc/noz175.067

Talk with your oncologist.

Trial registration:

Australian New Zealand Clinical Trials Registry
Registration number: ACTRN12615000407594
https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=ACTRN12615000407594

Cooperative Trials Group for Neuro-Oncology:

https://cogno.org.au/content.aspx?page=currenttrials

Preparations are underway for the results to be published in a peer-reviewed journal.

The sponsor of the VERTU trial was The University of Sydney. The trial was a collaboration between the Cooperative Trials Group for Neuro-Oncology (COGNO) and the National Health and Medical Research Council Clinical Trials Centre (NHMRC CTC). The trial was funded by grants from The Cure Brain Cancer Foundation, Cancer Council New South Wales, and AbbVie Pharmaceuticals, including veliparib supply. AbbVie Pharmaceuticals was not involved in any aspects of trial conduct or reporting.

Some authors of the VERTU trial have received research funding or have had advisory roles for the pharmaceutical industry. Full disclosures will be listed in the manuscript.