CO.17 trial: Cetuximab for bowel cancer

The CO.17 trial has helped researchers answer an important health question. It has provided evidence on whether cetuximab (Erbutix), an antibody drug acting on the immune system and through a cancer growth pathway, benefits people with advanced bowel cancer.

We appreciate the part played by our volunteer participants. This may help to improve the medical treatment of patients in the future. Here is a summary of the trial and results.

What was the trial about?

Cetuximab is a fairly new treatment that blocks the growth of some cancers. Before the trial, it was known that it had some effect on bowel cancer, but there was no trial evidence that it increased the survival of patients with advanced bowel cancer who had not been helped by chemotherapy or who had cancer that returned after chemotherapy.

In the CO.17 trial, patients with bowel cancer that had spread and were no longer responding to chemotherapy were randomly allocated to have an infusion of cetuximab each week or not. Both groups also had supportive care (nursing and other care to maintain their quality of life).

572 participants enrolled in the trial between December 2003 and August 2005 and gave tumour samples. Most gave permission for their tumour tissue to be used for research.

How was the effect of treatment measured?

Patients had a clinic assessment every four weeks. They had scans every eight weeks and also completed questionnaires on their quality of life at some visits.

The patients' survival was the main measure. The researchers also measured quality of life, change in the size of the tumour, and progression-free survival—that is, the time between the participant's entry into the trial until the disease became worse.

Participants' tumour samples were examined in the laboratory for some molecular markers, changes in small structures and in the DNA of the cancer cells that might correspond with treatment success.

Was the new treatment better?

The people in the cetuximab group lived longer than those in the group who had supportive care only, although because they all had very advanced cancer, their survival was not long. In the cetuximab group, 50% were alive at six months and 21% were alive at one year. In the supportive care group, 33% were alive at six months and 16% at one year.

During the trial, the investigators noticed that some of the cancers did not respond to the drug. They sent tumour samples to the laboratory to look for particular gene mutations in the cancer to see if there was a connection between the presence of the mutation and the response to treatment.

When the results of gene mutations were analysed at the end of the trial, it was found that patients with a mutated K-*ras* gene did not benefit from the drug. Their survival was no longer than for those who had only supportive care. Only patients with the-non-mutant gene had benefit. Their survival was twice as long.

According to the questionnaires, the cetuximab treatment also improved quality of life in the participants who had the non-mutant gene.

What were the side-effects of the treatment?

The most common side-effect was fatigue. However this was similar in the groups with and without the cetuximab. More people having the drug had a rash or an infection. The rash was

known to be a side-effect of cetuximab. About 20% of patients had a type of allergic reaction when the drug was being given through a vein (an infusion reaction).

Were there any serious side-effects?

13 participants had a severe infusion reaction, which was 4.5% of those who had the drug. 45 people had one of their infusions interrupted, most often because of a reaction to it. 34 had a severe rash (12%). 33 people had a reduction in their dose, usually because of a rash.

What does this mean for trial patients?

Patients given the new treatment who had the non-mutated gene survived, on average, nearly five months longer than those having supportive care only.

How will the results help patients and doctors in future?

The finding in the CO.17 trial that tumours with a specific genetic marker would respond to cetuximab treatment was a major discovery that has changed bowel cancer treatment and medical research worldwide.

Now, people with advanced bowel cancer can have a genetic test performed on their cancer specimen before treatment. This is a test looking for the gene mutation (a change in the DNA of the cancer). Cetuximab treatment can be given to some patients with confidence that it will help them. Those who have the K-ras gene mutation are unlikely to benefit from cetuximab.

Cetuximab, like most cancer drugs, is expensive, and the cost is saved when treatment only given to those most likely-to-benefit.

What will the researchers do next?

Even in patients that benefited from the drug, their tumours eventually developed resistance to treatment. The investigators are doing further gene studies to try to find out why this happened.

Where can I find out more about the trial?

Talk with your GP or oncologist.

The results have been published in a scientific journal

Karapetis C, and others. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *New England Journal of Medicine* 2008; volume 359, issue 17, page 175. link to article

Jonker D, and others. Cetuximab for the treatment of colorectal cancer. *New England Journal of Medicine* 2007, volume 357, issue 20, page 2040. link to article

Trial registration

Australian New Zealand Clinical Trials Registry
www.anzctr.org
Registration number ACTRN12606000112561

Disclaimer and conflict of interests

The sponsors were the National Cancer Institute of Canada and the Australasian Gastro-Intestinal Trials Group (AGITG). The study was funded by Bristol-Myers Squibb and Im-Clone Systems, which developed Cetuximab (Erbitux). Cetuximab is now owned by Lilly. The trial was coordinated by the NHMRC Clinical Trials Centre, University of Sydney.

Two of the investigators, Drs Langer and Khambata-Ford, own equity and are employed by Bristol-Myers Squibb. Some of the investigators have received lecture or consulting fees from Bristol-Myers Squibb. Full disclosures are listed in the journal articles above.

Results of any clinical trial do not represent complete knowledge about treatment. Patients should discuss the results of this trial with their treating doctor before making changes therapy.