High-dose versus standard-dose imatinib for patients with metastatic gastrointestinal stromal tumours (GIST): results after 10 years of treatment

The 'Advanced GIST' trial, also known as EORTC 62005, has helped researchers answer an important health question. It has provided evidence that has changed the way some GISTs—a relatively rare type of stomach and intestinal cancer—are treated.

We appreciate the part played by our volunteer participants. Without them, this trial would not have been possible. It has helped to improve the medical treatment of patients. Here is a summary of the trial and results.

What was the trial about?

Imatinib (Glivec or Gleevec) is a biological therapy that blocks some chemical messenger proteins between cells (tyrosine kinases) and therefore hinders the growth of cancer cells.

Imatinib changed the lives of many people with advanced gastrointestinal stromal tumours (or GISTs) when it was discovered that imatinib could shrink their cancers and extend their lives.

The 62005 trial, described here, started when imatinib was a new drug. The drug was known to work, but the best dosage to balance benefit and side-effects was not known. The trial was designed to compare two dosages.

Patients were recruited from Australia, New Zealand, Singapore and 10 countries in Europe.

946 patients with cancer that had spread or returned after treatment were enrolled in the trial. They were randomly allocated to 1 tablet (400 mg) a day or two tablets a day (800 mg).

Their average age was 60, and about 60% were men.

They continued treatment until their disease became worse, or they had toxic side-effects, or chose to discontinue for other reasons.

The dose could be reduced if they had side-effects. Patients taking the lower dose (once a day) could change to the higher dose group (twice a day) if their disease became worse.

How was the effect of treatment measured?

The researchers measured the proportion of patients surviving after 10 years had passed. They also measured progression-free survival—that is, the time between the participant's entry into the trial until the disease became worse.

Patients had CT scans and tests every 3 months.

Also, pathologists analysed the patients' tumour samples to detect the types of mutations in the cells. When this trial started, this was not routine, so only about half had this testing.

Was the new treatment better?

Over the first few months, progression-free survival was similar for the two dosages. After 2 years, the group on the higher dosage were doing slightly better.

When the results were analysed again at an average of 11 years, the two groups were similar. The average survival in both groups was 3.9 years.

What were the side-effects of the treatment?

Most patients had medical problems due to the cancer or the treatment during the trial. Drug side-effects usually occurred during the first 2 months. The most common were anaemia (93% of patients) and other blood-related disorders. Patients had swelling (80%), fatigue (74%), nausea (55%), chest pain (53%), diarrhoea (52%) and rashes (37%).

Were there any serious side-effects requiring hospital admission?

41% on once-a-day treatment and 50% on twice-a-day treatment had a serious toxic event. Many of them then had their dosage reduced to make imatinib more tolerable. 18 participants died of causes that could have been related to the drug.

Over a long period, many cancers became resistant to imatinib. Imatinib stopped working and the tumour started growing again. During the trial, and even now, which ones these are and when it will happen can't be easily predicted.

What does this mean for trial patients?

Both the high and low dosages of imatinib benefited many of the patients. After 2 years, nearly three-quarters of them were still alive. Without imatinib, only about 20% would have survived.

After 10 years, the high and low dosages had similar results. About 20% of patients survived to 10 years, and 9% had no worsening of disease.

Pathology testing done after the trial started showed that patients with tumours with a specific mutation (exon 9), did better than patients without mutation on the higher dose but worse on the lower dose of imatinib.

How will the results help patients and doctors in future?

This trial began when imatinib was a fairly new drug. The patients in this trial had advanced disease and large tumours. Now, patients with smaller tumours are starting this treatment and so may have better prospects.

The trial has already resulted in over 20 scientific articles and new research projects.

What will the researchers do next?

The investigators and others will continue to study the characteristics of individual patients that may predict survival with use of imatinib.

The trial has stimulated new laboratory research on drugs like imatinib, particularly on why the drug some tumours become resistant to the drug.

Where can I find out more about the trial?

Talk with your GP or oncologist.

The results have been published in a scientific journal

Casali PG, and others. Ten-year progression-free and overall survival in patients with unresectable or metastatic GI stromal tumors. *Journal of Clinical* Oncology 2017; volume 35, issue 15: pages 1713–1720. Summary

Trial registration

Australian New Zealand Clinical Trials Registry
www.anzctr.org
Registration number 12605000138684

Australasian Gastro-Intestinal Trials Group

See further information about the trial here

The sponsors were the European Organisation for Research and Treatment of Cancer, the Italian Sarcoma Group, and the Australasian Gastrointestinal Trials Group. The trial was supported by an unrestricted grant from Novartis. The long-term follow-up study was supported by the European Organisation for Research and Treatment of Cancer Cancer Research Fund.

Some of the authors of the articles reporting on this study have received research funding or have had advisory roles for the pharmaceutical industry, including Novartis, the manufacturer of Glivec. Full disclosures are listed in the article with the results.

Results of any clinical trial do not represent complete knowledge about treatment. Patients should not change their therapy on their understanding of the results or the results provided herein.