MedicalXpress

New pill could offer hope to bowel cancer and gastrointestinal stromal tumor patients after failure of standard treatmen

November 21 2012

Two phase 3 trials, published in *The Lancet*, have shown that a novel oral drug called regorafenib could offer survival benefits to people with bowel cancer or gastrointestinal stromal tumor following failure of existing treatments.

Globally, nearly 1.25 million people are diagnosed with bowel cancer every year, and in at least 50% of patients the cancer spreads to other parts of their body (which doctors refer to as the cancer becoming metastatic). Metastatic bowel cancer tends not to be treatable by surgery, and although there are a number of existing drugs which can be used to treat the cancer, resistance develops eventually to all therapies, and patients then have poor prognosis.

Gastrointestinal stromal tumours (GISTs) belong to a type of cancer known as soft tissue sarcomas, and although they are relatively rare, there are thought to be at least 8000 new cases in Europe every year. While GISTs can be surgically removed in their early stages, more than 40% of cases recur and begin to spread. There are currently only two drugs – 'molecular targeted' therapies called imatinib and sunitinib – approved to treat GISTs.

In one trial, led by Professor Eric Van Cutsem, at the University Hospitals Leuven in Belgium, and Professor Axel Grothey at the Mayo Clinic, Rochester, Minnesota, USA, researchers assessed the effect of

regorafenib on patients with bowel cancer which was progressing after the patients had received all available standard therapies (classic chemotherapy, and other targeted agents). In a group of 760 patients, 505 were assigned a daily 160mg dose of regorafenib for three weeks, followed by a one week break, and 255 patients were assigned a placebo delivered to the same schedule. The cycle was then repeated if necessary. All patients received the best available supportive care throughout the trial.

The trial participants were monitored for up to 16 months after the trial began, and the researchers found that overall, patients who received regorafenib had an overall survival of an average (median) of 6.4 months, compared to 5.0 months for those who were given placebo. The authors noted also that regorafenib delayed progression compared to placebo, and more frequently controlled metastatic disease compared to placebo.

According to Professor Van Cutsem, "Our results show that in patients with progressive bowel cancer which still progresses after standard treatments, regorafenib can significantly prolong survival, compared with placebo. This provides further evidence for the role of targeted therapies, and should offer hope for a new standard of care in bowel cancer patients who have no other treatment options left to them. In future, we hope to find subgroups of patients, based on molecular markers, who may experience significantly better survival times on regorafenib and are likely to benefit from it the most."

In another trial, researchers led by Professor George Demetri, at the Dana-Farber Cancer Institute and Harvard Medical School in Boston, USA, examined the effect that regorafenib had on patients with GIST which was worsening, despite prior treatment with both imanitib and sunitinib. In a group of 199 patients, 133 received a daily 160mg dose of regorafenib for three weeks, followed by a one week break, and 66

patients received a matching placebo delivered to the same schedule, with the cycle of treatment repeated as long as benefit was maintained. Again, all patients received the best available supportive care throughout the trial. Trial participants were monitored for at least 12 months after the trial began, and those patients who started by receiving regorafenib had an average (median) progression-free surivival time of 4.8 months, compared to 0.9 months to those in the matched placebo group.

According to Professor Demetri, "When added to best supportive care, regorafenib significantly improves disease control, as measured by progression-free survival time, in patients with GIST after progression following failure of all other therapies. We know that regorafenib can inhibit many of the mutated proteins and abnormal signals which cause this cancer, and the next step will be to investigate the molecular mechanisms by which this new treatment can control GIST after resistance appears to other 'targeted therapy' drugs for this aggressive malignancy."

In both trials, regorafenib resulted in a high rate of adverse effects, the most severe of which were hypertension (high blood pressure), fatigue, diarrhoea and hand-foot skin reaction (reddening, swelling, numbness, and peeling of the skin). These effects were expected from experiences of earlier regorafenib trials, and the authors state that, in most cases, they were able to manage them by reducing or interrupting the dose.

Writing in a linked Comment, Professor David Cunningham and Dr Tom Waddell, of The Royal Marsden Hospital in Sutton, UK, state that, "On the basis of the reported data from these two clinical trials, regorafenib would seem to have a future in the treatment of gastrointestinal malignant disease. In the relatively rare GIST, the case for routine use of this drug in patients who have failed imatinib and sunitinib is strong, despite the apparent absence of a benefit in terms of overall survival, which is probably attributable to planned extensive

crossover to regorafenib. By contrast, and somewhat paradoxically, in colorectal cancer for which a statistically significant improvement in survival is reported, the overall clinical effect of the drug seems to be more modest and the case is less compelling, but would be greatly enhanced by the identification of a biomarker that allows selection of the subset of patients who really benefit from regorafenib."

More information: Regorafenib for bowel cancer (Grothey, Van Cutsem et al): www.thelancet.com/journals/lan … (12)61900-X/abstract

Regorafenib for GIST (Demetri et al): www.thelancet.com/journals/lan … (12)61857-1/abstract

Provided by Lancet