leukaemia, the long-term safety and effectiveness of idelalisib remains to be determined.

T T manufacturer provided additional useful information

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Nintedanib

Aust Prescr 2016;39:62–3
http://dx.doi.org/10.18773/austprescr.2016.031
First published online 22 February 2016

Approved indications: idiopathic pulmonary fibrosis, non-small cell lung cancer

Ofev (Boehringer Ingelheim)
100 mg and 150 mg capsules
Australian Medicines Handbook section 14.2.3

Growth factors contribute to the proliferation of cells in cancers and conditions such as pulmonary fibrosis. This proliferation involves tyrosine kinases such as fibroblast growth factor, vascular endothelial growth factor and platelet-derived growth factor. Nintedanib inhibits these growth factors by binding to their receptors intracellularly. This disrupts the signalling needed for cell proliferation.

Nintedanib capsules are taken twice daily with food. There is extensive first-pass metabolism so the bioavailability is under 5%. The drug is also mainly cleared by metabolism with most of the metabolites being excreted in the faeces. The terminal half-life is 10–15 hours. As nintedanib is a substrate of P-glycoprotein, inducers of this transporter, such as phenytoin and St John's wort, will reduce the concentration of nintedanib. Its plasma concentration will be increased by inhibitors of P-glycoprotein such as ketoconazole.

Idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis is one of the interstitial lung diseases. A proliferation of fibroblasts leads to progressive breathlessness. The median survival is 3–5 years.

The main clinical trials of nintedanib in pulmonary fibrosis were INPULSIS-1 and -2.[1] In these trials a total of 638 patients were randomised to take 150 mg nintedanib twice daily for 52 weeks and 423 were given a placebo. These patients all had a forced vital capacity (FVC) that was at least 50% of the predicted value. In INPULSIS-1 the FVC fell by 239.9 mL/year with placebo and by 114.7 mL/year with nintedanib. The respective figures in INPULSIS-2 were reductions of 207.3 mL/year and 113.6 mL/year. The smaller decline in lung function with nintedanib was statistically significant.

In INPULSIS-1, 21% of the patients had to discontinue nintedanib because of adverse events. In both trials more than 60% of the patients taking nintedanib developed diarrhoea compared with about 18% of the placebo group. Other adverse events that were more common with nintedanib than with placebo included nausea, vomiting, weight loss and elevated liver enzymes.[1]

Lung cancer

The inhibition of growth factors by nintedanib has been studied in patients with non-small cell lung cancer of different histological types. The LUME-Lung 1 trial involved 1314 patients with locally advanced, metastatic or recurrent disease that had not responded to first-line chemotherapy. All the patients were given an infusion of docetaxel every 21 days and 652 also took 200 mg nintedanib twice daily on days 2–21 of the cycle. The median duration of treatment was 2.8 months with docetaxel alone and 3.4 months with the combination. After a median follow-up of 7.1 months, progression-free survival was 2.7 months in the control group and 3.4 months in the combination group. This difference is statistically significant.[2]

Adverse events led to 21.7% of the patients taking docetaxel and 22.7% of those taking docetaxel and nintedanib withdrawing from the trial. Deaths from adverse events were more frequent with the combination treatment. Nausea, vomiting, diarrhoea, altered liver function and febrile neutropenia were also more frequent.[2]

Precautions

The adverse effects of nintedanib may require treatment to be interrupted or reduced. Blood counts and liver function should be regularly monitored. Nintedanib is not recommended for patients with moderate or severe liver disease. In addition to the common adverse effects, there may also be an increased risk of gastrointestinal perforation, impaired wound healing, bleeding and thromboembolism. Although patients with a history of myocardial infarction or stroke were excluded from the INPULSIS

trials, myocardial infarctions were more frequent with nintedanib than placebo (1.6 vs 0.5%).

Conclusion

Idiopathic pulmonary fibrosis has a poor prognosis, so reducing the decline in lung function is a benefit. However, in a pooled analysis of the INPULSIS trials, nintedanib had no significant advantage over placebo in preventing acute exacerbations in pulmonary fibrosis or in health-related quality of life.[1]

In non-small cell lung cancer adding nintedanib to docetaxel increases progression-free survival, but the median overall survival is not significantly increased unless the cancer is an adenocarcinoma. The median overall survival for patients with an adenocarcinoma given the combination was 12.6 months compared with 10.3 months for patients treated with docetaxel alone. Pemetrexed is another drug that can be used to treat non-small cell lung cancer. In March 2015 the Pharmaceutical Benefits Advisory Committee concluded that an indirect comparison did not show that the effectiveness of nintedanib and docetaxel was non-inferior to pemetrexed.[3]

T T manufacturer provided additional useful information

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Ramucirumab

Aust Prescr 2016;39:63–4
http://dx.doi.org/10.18773/austprescr.2016.030
First published online 22 February 2016

Approved indication: gastric cancer

Cyramza (Eli Lilly)
vials containing 100 mg in 10 mL and 500 mg in 50 mL as concentrate
Australian Medicines Handbook section 14.2.1

Ramucirumab is indicated for patients with advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma when the disease has progressed after cytotoxic chemotherapy. This drug is used in combination with paclitaxel or as monotherapy if paclitaxel cannot be given.

Ramucirumab is a monoclonal antibody that binds to the vascular endothelial growth factor (VEGF) receptor 2. This blocks the binding of several vascular endothelial growth factors (A, C and D) to the receptor. Signalling mediated by these growth factors in endothelial cells is important in the progression of gastric cancer.

The efficacy and safety of ramucirumab has been assessed in two trials – RAINBOW[1] and REGARD.[2] The trials enrolled patients who had locally advanced or metastatic gastric adenocarcinoma which had progressed after chemotherapy with platinum, fluoropyrimidine or both. Patients with a history of arterial thromboembolic events, gastrointestinal bleeding, or uncontrolled hypertension were excluded from the trials. Participants received treatment until their disease progressed (confirmed by radiography) or they had unacceptable adverse effects. In both trials, the primary end point was overall survival.

The RAINBOW trial randomised patients to ramucirumab plus paclitaxel or placebo plus paclitaxel. Ramucirumab (8 mg/kg) or placebo was given on day 1 and 15 and paclitaxel (80 mg/m^2) was given on days 1, 8 and 15 of a 28-day cycle. Median overall survival was significantly longer in the ramucirumab arm than in the placebo arm (9.6 vs 7.4 months) (see Table).[1]

Table **Efficacy of ramucirumab alone and in combination with paclitaxel for gastric cancer**

RAINBOW trial [1]	**Ramucirumab + paclitaxel**	**Placebo + paclitaxel**
Number of patients	330	335
Median duration of treatment	18 weeks	12 weeks
Median duration of overall survival	9.6 months	7.4 months
Overall survival at 12 months	40%	30%
Median progression-free survival	4.4 months	2.9 months
REGARD trial [2]	**Ramucirumab**	**Placebo**
Number of patients	238	117
Median duration of treatment	8 weeks	6 weeks
Median duration of overall survival	5.2 months	3.8 months
Overall survival at 12 months	17.6%	11.8%
Median progression-free survival	2.1 months	1.3 months