NEW DRUGS

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Idelalisib

Aust Prescr 2016;39:60–2
http://dx.doi.org/10.18773/austprescr.2016.010
First published online 19 November 2015

Approved indication: chronic lymphocytic leukaemia, follicular lymphoma

Zydelig (Gilead)
100 mg and 150 mg tablets
Australian Medicines Handbook section 14.2.4

Like ibrutinib,[1] idelalisib is an oral anticancer drug that targets B-cell cancers. It works by inhibiting phosphatidylinositol 3-kinase. This enzyme is overactive in B-cell cancers and is involved in driving proliferation, migration and survival of malignant cells.

Idelalisib is registered for two indications:

- in combination with rituximab for chronic lymphocytic leukaemia and small lymphocytic lymphoma when chemotherapy is not suitable, in people who have relapsed after treatment or have the chromosome 17p deletion or TP53 mutation
- monotherapy for refractory follicular lymphoma.

Chronic lymphocytic leukaemia

The approval of idelalisib for relapsed chronic lymphocytic leukaemia is based on a pivotal phase III trial of 220 patients.[2] The median age of randomised patients was 71 years. Two-thirds of them had advanced disease and the median time since initial diagnosis was nine years. Patients were heavily pre-treated (regimens included rituximab, cyclophosphamide, fludarabine and bendamustine) and were considered too unwell for chemotherapy.

In total, 80% of the patients lacked somatic hypermutation of the gene encoding the immunoglobulin heavy-chain variable region, and 40% carried the 17p deletion or TP53 mutation. These genetic characteristics are generally associated with poorer outcomes.

Patients received intravenous rituximab with either oral idelalisib or placebo. After 24 weeks, the rate of progression-free survival was significantly higher with idelalisib than with placebo ($p<0.001$, see Table 1). The overall response rate, assessed using serial CT or MRI of the neck, chest, abdomen and pelvis, was significantly higher in the idelalisib group compared to the placebo group (81% vs 13%, $p<0.001$). These were all partial responses.[2]

Idelalisib was also better than placebo in subgroup analyses of patients with unmutated immunoglobulin

Table 1 **Efficacy of idelalisib in relapsed chronic lymphocytic leukaemia** [2]

Outcome	Idelalisib‡ plus rituximab§ (110 patients)	Placebo plus rituximab§ (110 patients)
Progression-free survival after 24 weeks	93%	46%
Median duration of progression-free survival	Not reached	5.5 months
Overall survival after one year	92%	80%
Overall response rate (all partial responses)#	81% (of a total of 88 patients that could be evaluated)	13% (of a total of 88 patients that could be evaluated)

‡ Oral idelalisib 150 mg twice a day
§ Intravenous rituximab 375 mg/m^2 body surface area, followed by 500 mg/m^2 body surface area every 2 weeks for 4 doses and then every 4 weeks for 3 doses, for a total of 8 infusions
# Assessed using serial CT or MRI of the neck, chest, abdomen and pelvis

heavy-chain variable region, or the 17p deletion or TP53 mutation. The trial was terminated at the interim analysis because of the superior efficacy of idelalisib combined with rituximab.

Single-arm trials of idelalisib combined with chemotherapy or immunotherapy generally found similar overall response rates (72% or above). However at the time of writing, these trials do not appear to have been published in full.

Follicular lymphoma

The approval of idelalisib as a monotherapy for refractory follicular lymphoma was based on a pivotal phase II uncontrolled trial of 125 patients with relapsed indolent lymphoma.[3] Of the participants, 72 had follicular lymphoma, 28 had small lymphocytic lymphoma, 15 had marginal-zone lymphoma and 10 had lymphoblastic lymphoma. Patients had received a median of four previous regimens and most of them were refractory to rituximab and an alkylating agent such as cyclophosphamide. Their median age was 64 years.

The median duration of treatment was 6.6 months. More than half of patients responded to treatment – these were mainly partial responses (see Table 2). Rates of response seemed to be comparable across the different disease subtypes.

Adverse effects and precautions

The most common adverse reactions (any grade) to idelalisib include neutropenia (50%), increased transaminases (50%), diarrhoea (38%), fever (32%), rash (24%) and pneumonitis (3%). These events can be serious (grade 3) in some cases and increased monitoring, dose interruption or treatment discontinuation may be needed.

In the indolent lymphoma trial there were 28 deaths. Most were related to disease progression (20 deaths). Other causes included pneumonia (3 patients), cardiac arrest, cardiac failure, splenic infarction, septic shock and pneumonitis (1 patient each).[3]

As elevated liver enzymes are so common, it is important to monitor alanine transaminase, aspartate transaminase and bilirubin fortnightly, at least for the first three months of treatment. Reactivation of hepatitis has occurred with idelalisib and all patients should be screened for hepatitis B and C before they start treatment. Close monitoring for toxicity is recommended if idelalisib is initiated in patients with severe hepatic impairment.

Severe diarrhoea or colitis occurred in 14% of patients across the trials. If diarrhoea occurs, make sure the patient is adequately hydrated, particularly those with pre-existing renal failure. Infections such as *Clostridium difficile* should be excluded. Intestinal perforation has been reported with idelalisib. This was fatal in some cases. Treatment should be stopped if perforation occurs.

Although live vaccines are not recommended during idelalisib treatment, they can be given to high-risk patients before treatment is started.

Pharmacokinetics

The recommended dose of idelalisib is 150 mg orally twice a day. Peak plasma concentrations are reached within 2–4 hours after oral administration. Idelalisib is mainly metabolised by aldehyde oxidase, but also by cytochrome P450 (CYP) 3A and UGT1A4. The elimination half-life is around eight hours and metabolites are excreted in the faeces (78%) and urine (15%).

Drug interactions

Concomitant strong CYP3A inducers (e.g. rifampicin, phenytoin, carbamazepine, St John's wort) may reduce plasma concentrations of idelalisib and should be avoided. Strong inhibitors may elevate idelalisib concentrations so increased monitoring for toxicity is recommended.

Caution is urged if idelalisib is given to patients taking CYP3A substrates with a narrow therapeutic index (e.g. cisapride, fentanyl). Idelalisib is a strong inhibitor of CYP3A and may increase exposure to substrates such as warfarin, some antiarrhythmic drugs, calcium channel blockers and statins.

Conclusions

Idelalisib seems to benefit pre-treated, older patients with chronic lymphocytic leukaemia and follicular lymphoma. However, adverse effects are common and often limit treatment. In chronic lymphocytic

Table 2 **Efficacy of idelalisib in relapsed indolent lymphoma** [3]

Outcome ‡	Idelalisib monotherapy §
Overall response rate	57% (71/125 patients) – 7 complete responses, 63 partial responses, 1 minor response
Median duration of response	12.5 months
Median progression-free survival	11 months
Median overall survival	20.3 months

‡ Tumour response and progression assessed by serial CT, laboratory testing and physical examination
§ Oral idelalisib 150 mg twice a day

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

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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