A once-daily, interferon-free treatment, which in most cases only needs to be taken for 12 weeks, that has very high efficacy is an advance. While further research is needed for other genotypes, the combination of ledipasvir and sofosbuvir is probably the treatment of choice for genotype 1 hepatitis C infection in 2015. However, until similar antiviral drugs arrive, cure comes with a high cost.[5] The Pharmaceutical Benefits Advisory Committee estimates that the cost of treatment in Australia will exceed $3 billion over five years.[6]

T manufacturer provided the product information

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First published online 14 October 2015

Ponatinib

Approved indication: chronic myeloid leukaemia, acute lymphoblastic leukaemia

Iclusig (Ariad Pharmaceuticals)

15 and 45 mg film-coated tablets

Australian Medicines Handbook section 14.2.3

Along with imatinib (Aust Prescr 2001;24:129), dasatinib (Aust Prescr 2007;30:50-5) and nilotinib (Aust Prescr 2008;31:49-55), ponatinib is a tyrosine kinase inhibitor for patients who have leukaemia with the Philadelphia chromosome (Ph). This chromosome results in an abnormal tyrosine kinase that causes uncontrolled growth of malignant cells. Almost all patients with chronic myeloid leukaemia and approximately 20–25% of those with acute lymphoblastic leukaemia have the chromosome.

Ponatinib is indicated for patients with chronic myeloid leukaemia who are resistant or intolerant to at least two previous tyrosine kinase inhibitors, or have the T315I mutation. Patients with this mutation are resistant to imatinib, dasatinib and nilotinib.

Ponatinib is also indicated for those with Ph-positive acute lymphoblastic leukaemia who are resistant or intolerant to dasatinib, cannot be given imatinib or have the T315I mutation.

The approval of ponatinib is primarily based on a phase II, single-arm trial. The study enrolled 449 people with chronic myeloid leukaemia (n=417) or Ph-positive acute lymphoblastic leukaemia (n=32). Almost all of the patients had experienced treatment failure with imatinib.[1]

Patients were started on ponatinib 45 mg once a day. Those with chronic myeloid leukaemia were grouped into cohorts according to whether they had chronic-, accelerated- or blast-phase disease. The primary end point for those with chronic-phase disease was a major cytogenetic response (when the proportion of Ph-positive white blood cells has fallen to 35% or less) within the first 12 months. For patients with accelerated- and blast-phase chronic myeloid leukaemia or Ph-positive acute lymphoblastic leukaemia, the primary end point was a major haematological response (normal number of white blood cells or no evidence of leukaemia) in the first six months.[1]

Just over half of the patients with chronic- and accelerated-phase chronic myeloid leukaemia responded to treatment. Response rates were lower in people with blast-phase chronic myeloid leukaemia and Ph-positive acute lymphoblastic leukaemia (see Table). Pre-specified subgroup analyses revealed that fewer previous treatments, younger age and shorter duration between diagnosis and treatment tended to predict a better response to ponatinib.[1]

Adverse reactions were very common in the trial with 67% of patients having at least one dose interruption because of an adverse event. The most common treatment-related events (any grade) were thrombocytopenia (37% of patients), rash (34%), dry skin (32%), vascular occlusion (23%), abdominal pain (22%), neutropenia (19%) and anaemia (13%).[1] Infections occurred in over half of the people who received ponatinib – these were serious in 20% of cases and some were fatal.

Serious adverse events (grade 3 or 4) included pancreatitis (5%), abdominal pain (2%), increased lipase (2%), thrombocytopenia (2%), diarrhoea (1%), fever (1%), myocardial infarction (1%), anaemia (1%), neutropenia (1%), febrile neutropenia (1%) and pancytopenia (1%).[1] Thrombocytopenia was the most common reason for treatment interruption.

During the study, 18/449 patients died. Five deaths were thought to be related to treatment and were a result of pneumonia, fungal pneumonia, gastric haemorrhage, acute myocardial infarction and cardiac arrest. Other deaths deemed unrelated to

NEW DRUGS

Table **Efficacy of once-daily ponatinib 45 mg in Ph-positive leukaemias** [1]

Cohort (number of patients)	Patients with a major cytogenetic response‡	Patients with a major haematological response§	Progression-free survival	Overall survival
	by 12 months	by 6 months	estimated at 12 months	
Chronic-phase CML (267 patients)	56%	-	80%	94%
Accelerated-phase CML (83 patients)	-	55%	55%	84%
Blast-phase CML (62 patients)	-	31%	19%	29%
Ph-positive acute lymphoblastic leukaemia (32 patients)	-	41%	7%	40%

CML chronic myeloid leukaemia
Ph Philadelphia chromosome
‡ Primary outcome for chronic-phase CML (when the proportion of Ph-positive white blood cells has fallen to 35% or less)
§ Primary outcome for accelerated- and blast-phase CML and acute lymphoblastic leukaemia (when the number of white blood cells has returned to normal or there is no evidence of leukaemia)

treatment were due to sepsis (4 people), cardiac arrest (2 people), congestive cardiac failure (2 people), cardiopulmonary failure (1 person), disease progression (1 person), dehydration (1 person), hyperviscosity syndrome (1 person) and intestinal obstruction (1 person).[1]

Vascular occlusion is a problem with ponatinib. Arterial and venous occlusive events occurred in 23% (101/449) of patients in the trial. These events were serious in 18% (81/449). Heart failure and left ventricular dysfunction also occurred and were serious in 5% (23/449) of patients.[1] The cardiovascular status of patients should be assessed and treated before starting ponatinib. Monitoring is recommended and treatment should be discontinued if problems develop.

As thrombocytopenia is a common adverse effect, there is an increased risk of bleeding, particularly in patients with accelerated- or blast-phase chronic myeloid leukaemia and acute lymphoblastic leukaemia. Fortnightly blood counts are recommended for the first three months then monthly after that. Serum lipase should also be regularly monitored as the majority of patients who develop pancreatitis do so in the first two months of treatment. The product information gives specific recommendations for reducing or stopping the ponatinib dose if myelosuppression or pancreatic abnormalities occur.

Increased liver enzymes and fatal liver failure have occurred with ponatinib so liver function tests before and during treatment are recommended. Caution is urged when treating patients with moderate to severe hepatic impairment.

Ponatinib is a category D drug in pregnancy. In animal studies, it was toxic and teratogenic to the developing fetus. Breastfeeding is not recommended during treatment.

Following oral administration of ponatinib, peak plasma concentrations are reached within four hours. The terminal half-life is 22 hours and steady state is reached within a week. Most of the dose is eliminated in the faeces.

Ponatinib is extensively metabolised by cytochrome P450 (CYP) 3A4, and to a lesser extent by CYP2C8 and 2D6. CYP3A4 inhibitors (e.g. ketoconazole) may increase ponatinib exposure whereas CYP3A4 inducers (e.g. rifampicin) may lead to a decrease. Caution is urged with concomitant use of these drugs. As ponatinib inhibits P-glycoprotein, it may increase concentrations of co-administered drugs that are substrates of this transporter, such as digoxin or pravastatin. Monitoring for adverse events with these drugs is recommended.

Ponatinib may offer benefit for people with Ph-positive leukaemias who have limited treatment options. However, as there was no comparator in the trial, it is difficult to quantify the benefit. Ponatinib has serious adverse effects that often limit treatment and are sometimes fatal, so regular patient monitoring is essential. The drug comes with a black box warning about vascular occlusion and heart failure.

T T manufacturer provided additional useful information

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First published online 18 September 2015