New drugs

Romidepsin

Approved indication: peripheral T cell lymphoma
Istodax (Celgene)
vials containing 10 mg powder for reconstitution
Australian Medicines Handbook section 14.2

Peripheral T cell lymphomas are a rare group of cancers that result from clonal proliferation of mature T cells. They account for up to 5–10% of all non-Hodgkin's lymphomas and multiple sites are usually involved including blood, bone marrow, lymph nodes, spleen and skin. These T cell neoplasms are generally aggressive. They do not respond well to chemotherapy and are associated with a poor prognosis.

Romidepsin, which is isolated from *Chromobacterium violaceum*, is a new drug for peripheral T cell lymphomas in patients who have already had previous systemic treatment. The drug is thought to reduce the growth and division of cancer cells by inhibiting histone deacetylases involved in gene regulation.

Romidepsin has been studied in a phase II trial involving 130 pre-treated patients.[1] They had had 1–8 previous therapies and some had had autologous stem cell transplants. There was no comparator in the study so all participants received romidepsin 14 mg/m^2 as a four-hour infusion on days 1, 8 and 15 of a 28-day cycle. Six cycles were planned but treatment was stopped if disease progressed or toxicity occurred. The median duration of treatment was 1.4 months. According to an independent review committee, 25% of patients responded to romidepsin but 49% progressed despite treatment. The overall median progression-free survival was 4 months. However, this was longer for responders (see Table).

Adverse events in the trial were common. Over half of the patients had nausea (59%), infections (55%) or fatigue (55%). Other common events included vomiting (39%), diarrhoea (36%), fever (35%), constipation (30%), reduced appetite (28%) and dysgeusia (21%). Thrombocytopenia (41% of patients), neutropenia (30%) and anaemia (24%) were frequently observed and were serious (grade 3 or more) in many cases. Blood monitoring is therefore recommended during treatment and the dose may need to be reduced or stopped if abnormalities occur.

Four patients had a prolonged QTc interval but no other concurrent cardiac problems. An ECG should be performed at baseline and during treatment in patients taking other medicines that prolong the QT interval. Serum potassium and magnesium should be within the normal range before treatment is started.

Just under half of the patients required a dose interruption. Thrombocytopenia, infections and neutropenia were the most common reasons for this. Treatment was discontinued in 19% of patients because of an adverse reaction – events included thrombocytopenia, pneumonia, fatigue, dyspnoea and sepsis. Eight patients died within 30 days of receiving treatment – three deaths were due to progressive disease and five were related to an infection.

Following intravenous administration for four hours, romidepsin is metabolised by cytochrome (CYP) P450 enzymes – mainly CYP3A4. Strong inhibitors or inducers of CYP3A4 are best avoided as they may alter romidepsin concentrations. This drug is a substrate of P-glycoprotein so care should be taken

Table **Efficacy of romidepsin in a single-arm phase II trial in patients with peripheral T cell lymphoma** [1]

	Proportion of patients	Median progression-free survival
Overall objective response	25% (33/130)	4 months (overall)
Complete response	15% (19‡/130)	18 months
Partial response	11% (14/130)	7 months
Stable disease	25% (33/130)	6 months
Progressive disease or not evaluable	49% (64/130)	<2 months

‡ six of these were unconfirmed

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

if the patient is taking inhibitors of this transporter. Prolonged prothrombin time and INR have been observed in patients taking concomitant warfarin so increased monitoring is recommended.

A quarter of patients with peripheral T cell lymphoma responded to romidepsin. However because there was no control arm in the trial, it is not possible to quantify how much of the clinical benefit was due to romidepsin and how much was due to the patients' underlying condition. It is also difficult to assess whether the benefits of treatment outweigh the risks. Because of these reasons, the application for licensing romidepsin in Europe was rejected.

T T manufacturer provided additional useful information

REFERENCE *†

1. Coiffier B, Pro B, Prince HM, Foss F, Sokol L, Greenwood M, et al. Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T cell lymphoma after prior systemic therapy. J Clin Oncol 2012;30:631-6.

First published online 3 October 2013

The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2011;34:26–7.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).