NEW DRUGS

Aust Prescr 2017;40:118–9
http://dx.doi.org/10.18773/austprescr.2017.041
First published 10 May 2017

Venetoclax

Approved indication: chronic lymphocytic leukaemia
Venclexta (Abbvie)
10 mg, 50 mg, 100 mg film-coated tablets

Like ibrutinib and idelalisib, venetoclax is a small-molecule oral anticancer drug that targets B-cell cancers. It works by blocking the action of the BCL2 molecule. This protein is overexpressed in chronic lymphocytic leukaemia cells and prolongs cell survival by inhibiting apoptosis.

Venetoclax is indicated for patients with relapsed or refractory chronic lymphocytic leukaemia who have the 17p genetic deletion. This mutation is associated with a poor prognosis. Venetoclax can also be given to those without the mutation if there are no other treatment options.

Venetoclax has been investigated in two published open-label trials.[1,2] An initial dose-escalation study found that when treatment was started at doses of 50 mg or more, or had been increased to 150 mg or above, tumour lysis syndrome was observed in 10 of 56 patients. One of the patients died and another developed acute renal failure. After the regimen was changed to a starting dose of 20 mg/day and more gradual titration to 400 mg/day with additional prophylaxis (e.g. hydration) and monitoring, the risk seemed to reduce. Only one of the 60 patients given the new regimen developed tumour lysis syndrome.[1]

The activity of venetoclax was studied in an uncontrolled phase II trial of 107 patients. They had previously been treated with a median of two therapies and over half of them were resistant to fludarabine or bendamustine. After a stepwise increase in the venetoclax dose from 20 mg/day to 400 mg/day over 4–5 weeks, patients were treated for a median of 12.1 months. Overall, 79 patients (74%) responded to venetoclax (based on an investigator assessment) – 17 were complete remissions (with or without recovery of blood counts), 4 were nodular partial remissions and 58 were partial remissions.[2]

Just over 40% of patients taking venetoclax developed serious neutropenia.[2] Blood monitoring is therefore recommended during treatment and the venetoclax dose should be reduced or stopped if neutropenia develops. Other common serious adverse events were infection (20%), anaemia (18%) and thrombocytopenia (15%). Milder but frequently reported events included diarrhoea (29%), nausea (28%), fatigue (22%), fever (19%), vomiting (14%) and constipation (10%).[2]

Tumour lysis syndrome occurred in 5 of 107 patients during the dose-titration phase of the efficacy trial.[2] Two of the patients had to have their treatment interrupted. Tumour lysis syndrome is more likely to occur in people with a high tumour burden. Reduced renal function also increases the risk. Monitoring of blood chemistry is recommended during treatment and venetoclax should be interrupted or stopped if tumour lysis syndrome occurs.

There were 11/107 deaths within a month of the last venetoclax dose – seven were due to disease progression, and the other four were a result of adverse events which included stroke, liver derangement, septic shock and cardiorespiratory insufficiency. None of these events was deemed to be related to venetoclax.[2]

Venetoclax tablets should be taken with food. Maximum serum concentrations are reached 5–8 hours after oral administration. The drug's elimination half-life is about 26 hours and most of the dose is excreted in the faeces.

Venetoclax is mainly metabolised by cytochrome P450 (CYP) 3A so the concomitant use of inhibitors of this enzyme (e.g. ketoconazole, clarithromycin) is contraindicated during the dose-titration phase as they may increase venetoclax concentrations. Moderate CYP3A inhibitors (e.g. erythromycin and ciprofloxacin) and P-glycoprotein inhibitors should also be avoided during the titration phase. Once a steady venetoclax dose has been reached, CYP3A inhibitors can be used but with a lower venetoclax dose. Concomitant use of CYP3A inducers (e.g. carbamazepine, rifampicin, St John's wort) should be avoided. Venetoclax could potentially affect concentrations of co-administered warfarin so close monitoring is recommended in these patients.

Although this drug is not curative, almost three-quarters of patients in the uncontrolled phase II trial responded to venetoclax. Improvements in overall survival and progression-free survival have not yet been established. Serious adverse events are common with this drug and regular blood monitoring is important.

T T manufacturer provided additional useful information

REFERENCES

1. Roberts AW, Davids MS, Pagel JM, Kahl BS, Puvvada SD, Gerecitano JF, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. N Engl J Med 2016;374:311-22. http://dx.doi.org/10.1056/NEJMoa1513257
2. Stilgenbauer S, Eichhorst B, Schetelig J, Coutre S, Seymour JF, Munir T, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label phase 2 study. Lancet Oncol 2016;17:768-78. http://dx.doi.org/10.1016/S1470-2045(16)30019-5

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA and the European Medicines Agency.

A:

ANSWERS TO SELF-TEST QUESTIONS

1 False 2 True
3 False 4 False

Correction

Extemporaneously compounded medicines

Aust Prescr 2017;40:119
http://dx.doi.org/10.18773/austprescr.2017.042
First published 10 May 2017

The article by James R Falconer and Kathryn J Steadman on extemporaneously compounded medicines (Aust Prescr 2017;40:5-8) has been corrected.

In Table 1 classifying simple versus complex compounding, the example given for simple capsules, tablets and powders was incorrect. It should have been boric acid capsules (not ethinylestradiol capsules, which are an example of complex compounding).

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