Decitabine/cedazuridine

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Approved indication: chronic myelomonocytic leukaemia, myelodysplastic syndromes

Inqovi (Otsuka)
35 mg/100 mg tablets

Chronic myelomonocytic leukaemia and the myelodysplastic syndromes are disorders of stem cells. As many patients are not eligible for a stem cell transplant, they are treated with cytotoxic drugs such as azacitidine. Another option, not previously marketed in Australia, is decitabine. This inhibits DNA methyltransferase. As abnormal DNA methylation may be involved in myeloid malignancies, decitabine may improve the differentiation of cells and lead to apoptosis of abnormal cells.

Treatment with azacitidine or decitabine can require intravenous infusions for several consecutive days every month. By combining decitabine with cedazuridine, oral therapy is now possible.

The oral bioavailability of decitabine is low because the molecule undergoes first-pass metabolism by the enzyme cytidine deaminase found in the liver and gut. Cedazuridine inhibits this enzyme and therefore increases the bioavailability of oral decitabine. As the absorption of decitabine is reduced by food, the tablet should be taken on an empty stomach. The bioavailability of cedazuridine may be affected by gastric pH so drugs that increase pH should not be taken within four hours. Decitabine is mainly metabolised while the absorbed portion of the cedazuridine dose undergoes renal elimination. No dose modification is recommended for patients with mild hepatic impairment or mild to moderate renal impairment. The effects of more severe impairment are unknown.

A phase II trial compared patients' exposures to decitabine when it was given as 20 mg/m^2 intravenously and as 35 mg orally in combination with 100 mg cedazuridine. Eighty patients with chronic myelomonocytic leukaemia or myelodysplastic syndromes received one formulation for one cycle of treatment then switched to the other formulation for the second cycle. The oral formulation was used in subsequent cycles. For the fixed-dose combination, the exposure (area under the time–concentration curve) was 97.6% of that of the intravenous dose.[1]

The 80 patients in the phase II trial received treatment in cycles of five days every 28 days for a median of seven cycles. Based on blood counts and bone marrow examination, 60% of the patients responded to treatment with 21% having a complete response. The median duration of the complete responses was 13.3 months. For all patients, the median overall survival was 18.3 months.[1]

A phase III trial also used a crossover design between oral and intravenous therapy for the first two cycles followed by the fixed-dose combination. This also found that each formulation resulted in a similar exposure to decitabine. At the time of writing, the full results of the trial are yet to be published. Information on 133 patients treated for a median of 8.2 months shows a complete response in 21%. Some patients ceased to be dependent on transfusions.

Most patients will have serious adverse effects from decitabine/cedazuridine. These include neutropenia, anaemia, and thrombocytopenia which can lead to haemorrhage. Blood counts must be checked regularly as abnormalities will require treatment to be delayed or reduced. Dose adjustment may also be needed for non-haematological toxicity such as elevated creatinine or liver enzymes. Less serious, but frequent, adverse effects include fatigue, nausea, dizziness, diarrhoea and constipation. Five of the 80 patients in the phase II trial stopped treatment because of adverse effects.[1]

While decitabine/cedazuridine is easier to administer than azacitidine, it is uncertain how the outcomes of treatment compare. Evaluating the combination will be easier when the results of the phase III trial become available.

T manufacturer provided the AusPAR and the product information

REFERENCES

1. Garcia-Manero G, Griffiths EA, Steensma DP, Roboz GJ, Wells R, McCloskey J, et al. Oral cedazuridine/decitabine for MDS and CMML: a phase 2 pharmacokinetic/pharmacodynamic randomized crossover study. Blood 2020;136:674–83. https://doi.org/10.1182/blood.2019004143

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, the European Medicines Agency and the Therapeutic Goods Administration.