Trifluridine/tipiracil

Approved indication: colorectal cancer

Lonsurf (Servier)
film-coated tablets containing 15 mg/6.14 mg or 20 mg/8.19 mg
Australian Medicines Handbook Appendix A

This fixed-dose combination therapy is indicated for people with metastatic colorectal cancer who have previously been treated with (or not considered candidates for) fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies, and drugs targeting vascular endothelial growth factor (VEGF) such as bevacizumab, and epidermal growth factor receptor (EGFR) such as cetuximab and panitumumab. Currently, only the tyrosine kinase inhibitor regorafenib is indicated for these patients.

Tablets contain trifluridine, a thymidine-based nucleoside analogue, and tipiracil, a thymidine phosphorylase inhibitor. Once trifluridine enters cells, it is phosphorylated to its active form and incorporated into DNA. This interferes with DNA synthesis and inhibits proliferation of rapidly dividing cells. Tipiracil boosts the effect of trifluridine by reducing its degradation.

Treatment is given in 28-day cycles. The recommended starting dose is trifluridine 35 mg/m^2 twice a day on days 1–5 and days 8–12. Tablets should be taken within one hour after eating in the morning and evening. After administration, peak plasma concentrations of trifluridine and tipiracil are reached in two and three hours. The majority of the trifluridine dose (55%) is eliminated in the urine.

Approval of this combination therapy is based on a randomised, placebo-controlled trial in 800 patients with previously treated metastatic colorectal cancer.[1] After enrolment, 534 patients were given the trifluridine combination and 265 were given placebo. All patients received supportive care. Median overall survival increased from 5.3 months with placebo to 7.1 months with the trifluridine combination. The corresponding median duration of progression-free survival was 1.7 months and 2 months.[1]

Serious adverse events were more common with the active treatment than with placebo. Over half of patients receiving the trifluridine combination delayed starting their next cycle of treatment because of toxicity. The most common serious adverse effects were neutropenia (38% of patients), leukopenia (21%) and anaemia (18%). Thrombocytopenia was also reported. Other common events with this combination included nausea, decreased appetite, fatigue, diarrhoea, vomiting and respiratory tract infections. Four per cent of patients had febrile neutropenia and there was one treatment-related death from septic shock.[1]

As myelosuppression is such a problem with this product, dose modification is common. Full blood counts are needed before treatment is started and to monitor for toxicity during treatment. Life-threatening infections are a risk and antimicrobials and granulocyte-colony stimulating factor may be required.

Higher exposure to trifluridine and tipiracil was observed in moderate renal impairment. This corresponded with more serious adverse events requiring dose reductions in these patients compared to those with normal or mild renal impairment. More frequent monitoring for haematological toxicities is therefore required. The drug is not recommended in severe renal impairment or end-stage renal disease as there are no data in these populations. There was a higher incidence of grade 3 or 4 hyperbilirubinaemia in moderate–severe hepatic impairment so the combination is not recommended for these patients.

Trifluridine is primarily metabolised by thymidine phosphorylase. In vitro studies have found that neither drug is metabolised by cytochrome P450 enzymes.

The combination of trifluridine and tipiracil prolonged overall survival of pre-treated patients with metastatic colorectal cancer by a median of seven weeks. However, treatment causes gastrointestinal toxicity and serious bone marrow suppression so close patient monitoring is paramount.

TT manufacturer provided additional useful information

REFERENCES

1. Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med 2015;372:1909-19. https://doi.org/10.1056/NEJMoa1414325

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.

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