NEW DRUGS

Trabectedin

Approved indication: soft tissue sarcoma

Yondelis (Specialised Therapeutics)
vials containing 0.25 mg or 1 mg powder for reconstitution

Soft tissue sarcomas are rare cancers that have a poor prognosis with up to 50% of patients developing metastases. Chemotherapy is not very effective, so the median survival with metastatic disease is about one year. The search for new treatments has led to the study of trabectedin. This is an alkaloid that was originally extracted from a sea squirt (*Ecteinascidia turbinata*). The molecule can now be synthesised.

Trabectedin is thought to act by binding to DNA. This distorts the DNA, which affects transcription and DNA repair mechanisms. These changes lead to multiple effects including cytotoxic, antiproliferative and antiangiogenic actions.

The drug has to be infused over 24 hours every three weeks. Trabectedin is widely distributed after infusion. It is metabolised by cytochrome P450 3A4 so plasma concentrations are likely to be altered by inducers and inhibitors of this enzyme system. Trabectedin is also a substrate of P-glycoprotein, so it may interact with drugs such as verapamil. Most of the metabolites are excreted in the faeces. The terminal half-life is about 180 hours. Liver impairment will increase concentrations of trabectedin. Renal impairment is unlikely to have much effect as little drug is excreted in the urine, but there have been no studies in patients with severe impairment.

The main clinical trial of trabectedin enrolled patients with unresectable, locally advanced or metastatic leiomyosarcoma or liposarcoma. These patients had previously been treated with at least an anthracycline regimen. A group of 345 patients was randomised to receive trabectedin and 173 were randomised to receive dacarbazine. They were treated every 21 days until the disease progressed or toxicity became unacceptable. An interim analysis took place after 188 patients had died. This found that there had been an objective response in 9.9% of the patients given trabectedin and 6.9% of those given dacarbazine. Progression-free survival was 4.2 months with trabectedin and 1.5 months with dacarbazine, but there was little difference in median overall survival (12.4 vs 12.9 months).[1]

The trial continued with eventually 384 patients in the trabectedin group and 193 in the dacarbazine group. In the final analysis 67% of the trabectedin group had died compared with 64% of the dacarbazine group. The median overall survival was 13.7 months with trabectedin and 13.1 months with dacarbazine.[2]

Trabectedin is a very toxic drug. Nearly all patients will experience adverse effects and in 63% of cases these will be serious. Approximately 4% of the patients had a fatal adverse reaction to trabectedin. In the clinical trial, dose reductions were required in 42% of the patients and 63% required a delay in treatment. The corresponding figures for dacarbazine were 12% and 42%.[2] Reasons for revising the trabectedin regimen include neutropenia, thrombocytopenia and increases in bilirubin or liver enzymes. Treatment must stop if the patient develops rhabdomyolysis, cardiomyopathy, or capillary leak syndrome. There can be severe injection-site reactions with tissue necrosis if there is extravasation of trabectedin. It is therefore strongly recommended that the drug is infused through a central venous line. Patients should be given intravenous dexamethasone half an hour before the infusion. This may provide some protection for the liver as well as reducing the nausea and vomiting associated with trabectedin.

Despite the significant hepatic and haematological toxicity, patients were able to endure trabectedin for longer than dacarbazine. The median number of treatment cycles was four versus two for dacarbazine.[2] There was no difference in overall survival between the drugs, but switching patients from dacarbazine to other drugs may have affected this result. The median time to starting another therapy was 3.5 months in the dacarbazine group and 6.8 months with trabectedin. However, a post hoc analysis taking these factors into account did not show a great advantage for trabectedin.[2] In Australia its use will be limited to patients with unresectable or metastatic liposarcoma or leiomyosarcoma who have already been treated with a regimen containing an anthracycline.

T T manufacturer provided additional useful information

REFERENCES

1. Demetri GD, von Mehren M, Jones RL, Hensley ML, Schuetze SM, Staddon A, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. J Clin Oncol 2016;34:786-93. https://doi.org/10.1200/jco.2015.62.4734
2. Patel S, von Mehren M, Reed DR, Kaiser P, Charlson J, Ryan CW, et al. Overall survival and histology-specific subgroup analyses from a phase 3, randomized controlled study of trabectedin or dacarbazine in patients with advanced liposarcoma or leiomyosarcoma. Cancer 2019;125:2610-20. https://doi.org/10.1002/cncr.32117

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Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, 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. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

NEW DRUGS

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.