NEW DRUGS

New drugs

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Treosulfan

Approved indication: acute myeloid leukaemia and myelodysplastic syndrome in adults, and malignant and non-malignant haematological diseases in children

Trecondi (Link Medical Products)
vials containing 5 g powder for reconstitution

Before haematopoietic stem cell transplantation (HSCT), patients with haematological disorders routinely receive conditioning with radiation or chemotherapy regimens, such as busulfan with fludarabine. However, these regimens are associated with a high incidence of adverse events. The alkylating drug treosulfan, which has strong myelotoxic and immunosuppressive properties, may have less toxicity. The drug is indicated with fludarabine as part of conditioning treatment before allogeneic HSCT for acute myeloid leukaemia or myelodysplastic syndrome in adults who are at high risk of adverse effects from standard conditioning therapies. Treosulfan is also indicated, with or without thiotepa, in children older than one month of age with malignant or non-malignant haematological diseases.

The dose of treosulfan is adapted to the patient's body surface area and is given as a two-hour intravenous infusion on three consecutive days before HSCT. The drug is spontaneously converted to its active form in the body with a terminal half-life of about two hours, and 25–40% of the dose is excreted unchanged in the urine. In addition to patients with severe renal or hepatic impairment, treosulfan is contraindicated in patients with severe cardiac or lung impairment, active non-controlled infectious diseases, and DNA breakage repair disorders such as Fanconi anaemia. Live attenuated vaccines are also contraindicated during treatment. All concomitantly used drugs must be dosed two hours before or eight hours after the intravenous infusion of treosulfan. Drugs with a narrow therapeutic index (e.g. digoxin) that are substrates for cytochrome P450 (CYP) 3A4, CYP2C19 or P-glycoprotein should not be given during treatment with treosulfan. Interactions with high-dose chemotherapy have not been observed.

Treosulfan is an irritant and a human carcinogen. Care must be taken when handling the drug to avoid extravasation and contact with skin and mucous membranes.

In an open-label, multicentre, randomised controlled phase III trial, adults (18–70 years of age) with acute myeloid leukaemia or myelodysplastic syndrome received treosulfan (220 patients) or busulfan (240 patients) with fludarabine before HSCT. Two years later, the event-free survival rate was 64% in the treosulfan arm and 50% in the busulfan arm. There were no statistically significant differences between the treatment arms in terms of disease recurrence, progression after HSCT or platelet recovery after HSCT. The two-year overall survival (71% vs 56%), transplantation-related mortality (12% vs 28%) and non-relapse mortality (11% vs 23%) were all improved in the treosulfan arm compared with the busulfan arm. Graft failure occurred in eight patients in the busulfan arm.[1]

A prospective, multicentre, non-randomised phase II trial studied 65 children (28 days to 17 years of age) with acute lymphoblastic leukaemia, acute myeloid leukaemia, myelodysplastic syndrome or juvenile myelomonocytic leukaemia. They received a combined regimen of treosulfan, fludarabine and thiotepa before HSCT. Three years later, the cumulative incidence of non-relapse mortality was 3.1%. The three-year Kaplan–Meier estimate of relapse- or progression-free survival was 74% and that of overall survival was 83%. Eleven patients (17%) died in the trial due to relapse or progression (eight patients) and transplantation-related causes (three patients).[2]

Myelosuppression with pancytopenia is a desired therapeutic effect of conditioning regimens and, therefore, blood counts should be monitored frequently until recovery. The risk of infection is increased during severe neutropenia. Oral mucositis is a very common adverse effect and so mucositis prophylaxis is recommended.

During the phase III trial in adults, drug-related serious adverse events were reported in six patients (3%) in the treosulfan arm and eight patients in the busulfan arm (3%). The most common of these included infections (four patients in each arm) and hepatobiliary disorders (three patients in the busulfan arm). Adverse reactions did not result in any dose reductions or treatment discontinuation. Fifty-two patients (24%) in the treosulfan arm and 82 patients (34%) in the busulfan arm died. The most common causes of death were relapse and transplantation-related causes (including infection and graft-versus-host disease).[1]

The new drug commentaries in *Australian Prescriber* are prepared by the Editorial Executive Committee. Some of the views expressed 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.

During the phase II trial in children, treatment-emergent adverse events were reported in 97% (63/65) of the patients. The most common severe adverse events included oral mucositis (43%), infections and infestations (43%), nausea and vomiting (34%), and diarrhoea (15%).[2] Seizures might occur in infants 1–3 months of age. Dermatitis in the nappy area may occur in small children due to the excretion of treosulfan in urine.

Ovarian suppression and amenorrhoea with menopausal symptoms are common in pre-menopausal patients receiving treosulfan. The treatment can impair fertility in both men and women. Patients are advised to use effective contraceptive options during and for six months after stopping treatment.

Treosulfan was relatively well tolerated in the trials involving patients with haematological diseases. The low mortality and manageable adverse effects associated with treosulfan make it a suitable option for conditioning regimens in preparation for HSCT in both adults and children.

T manufacturer provided the product information

REFERENCES

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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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ANSWERS TO SELF-TEST QUESTIONS

1 True 2 True

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