NEW DRUGS

Dinutuximab beta

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Approved indication: neuroblastoma

Qarziba (EUSA Pharma)
vials containing 20 mg as concentrate

Neuroblastoma is an extracranial childhood cancer. While it accounts for about 12% of cancer deaths in children, some neuroblastomas regress spontaneously. Cases are classified according to prognostic factors such as age and the stage of the disease. Children with high-risk neuroblastomas have a poor prognosis. Treatment can include surgery, radiotherapy, high-dose chemotherapy and stem cell transplants. For children who survive, isotretinoin has been used as a maintenance therapy.

Neuroblastomas express an antigen called disialoganglioside 2 (GD2). This prompted research into whether immunotherapy could have a role in treatment. An antibody called ch14.18 was found to have a cytotoxic effect against cells expressing GD2. This monoclonal antibody can be produced by different methods. Dinutuximab beta is a form of ch14.18 recloned using Chinese hamster ovary cells.

The antibody is given in five consecutive cycles of 35 days duration. Dinutuximab beta is diluted in a solution of sodium chloride and albumin. It can be infused over eight hours on the first five days of each treatment cycle or given as a continuous infusion for the first 10 days. The maximum plasma concentration is reached on the last day of the infusions. Dinutuximab beta is then broken down like other antibodies. It has a half-life of eight days. Liver and kidney function, and a full blood count should be checked before each infusion.

An analysis of early non-randomised studies of ch14.18, after initial treatment of metastatic neuroblastoma, assessed the outcomes for 166 children who received the antibody. They were compared with 99 given maintenance therapy and 69 children given no additional therapy. This univariate analysis found that overall survival after three years was 68.5% in the antibody group, 56.6% in the maintenance group and 46.8% in the untreated group. However, there was uncertainty about the difference between these therapies depending on which statistical analysis was used.[1]

A phase III trial randomised 226 children with high-risk neuroblastoma which had responded to induction therapy and stem cell transplantation.[2] A group of 113 then received an immunotherapy regimen of the ch14.18 antibody with interleukin 2, granulocyte-macrophage colony-stimulating factor (GM-CSF) and isotretinoin. The other 113 patients were treated with isotretinoin alone. After a median follow-up of 2.1 years the trial was stopped early because of emerging differences in survival. Event-free survival at two years was estimated to be 66% with immunotherapy and 46% with isotretinoin alone. The estimated rates of overall survival were 86% and 75%.[2]

It was uncertain which components of the immunotherapy regimen were effective. Another phase III trial therefore compared treatment with dinutuximab beta, interleukin 2 and isotretinoin (206 children) to treatment with dinutuximab beta and isotretinoin (200). In effect, this trial was assessing whether including interleukin 2 in the regimen improved outcomes for patients with high-risk neuroblastoma.[3] The patients in the trial had received chemotherapy, stem cell transplant and radiotherapy. Their median age was around three years. The median follow-up was 4.7 years during which the children were monitored for events such as relapse, progressive disease or death. When assessed at three years, the event-free survival was 60% for the children treated with dinutuximab beta and interleukin 2 compared with 56% for those treated with dinutuximab beta alone. Three-year overall survival was 70% with interleukin 2 and 69% without it. At five years the overall survival was 62% versus 63%.[3]

Children with neuroblastoma have to endure many harmful treatments and dinutuximab beta is no exception. Infusing an antibody can cause severe reactions including anaphylaxis and cytokine-release syndrome. Patients require premedication with antihistamines before each infusion. Premedication is also required for the very common problem of pain. In addition to other analgesics, morphine infusions are required while dinutuximab beta is being delivered. Gabapentin is started three days before each infusion of dinutuximab beta. Pain still occurs in most patients despite giving analgesics. Other very common adverse events include capillary leak syndrome, haematological toxicity, infections, fever and neurological disorders of the eye. Such adverse reactions may require treatment to be interrupted.

While dinutuximab beta is toxic, using it alone results in less toxicity than combining it with interleukin 2. In that trial, serious adverse events which were less frequent with dinutuximab alone included hypersensitivity, infection, fever and pain.[3] As there was no difference in efficacy, this suggests dinutuximab beta should be used without interleukin 2 in the treatment of high-risk neuroblastoma after chemotherapy. Future research should investigate the optimum stage of the disease to use dinutuximab beta, the most effective regimens and how to reduce toxicity.

T T manufacturer provided additional useful information

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

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.