New drugs

Avelumab

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Approved indication: Merkel cell carcinoma

Bavencio (Merck)
vials containing 200 mg/10 mL for dilution
Australian Medicines Handbook section 14

The Therapeutic Goods Administration has an orphan drug program to encourage pharmaceutical companies to market treatments for rare conditions in Australia. Avelumab is an immune checkpoint inhibitor that has been designated as an orphan drug for the treatment of metastatic Merkel cell carcinoma. This is a rare form of skin cancer but, due to an association with ultraviolet radiation, Australia has the highest incidence in the world (1.6/100 000 people). The cancer is also associated with immunosuppression and Merkel cell polyomavirus. It presents as a rapidly growing painless nodule and has a poor prognosis. Patients can be given chemotherapy, but the median progression-free survival is only about two months. The mortality rate is higher than that of melanoma and patients with metastatic Merkel cell carcinoma only have a median survival of 9.6 months.

Avelumab acts against cancer cells by altering the immune response. Some cancer cells express a protein called programmed cell death ligand 1. This reduces the activity of T-lymphocytes against the tumour. Avelumab is a monoclonal antibody that binds to the ligand preventing it from binding to its receptor. This encourages reactivation of the immune response to cancer cells.

The drug has to be diluted and given by slow intravenous infusion. It is catabolised like other proteins. The half-life is six days, but clearance may decrease during treatment. Renal disease has no significant effect, but the effect of severe hepatic impairment on the drug's pharmacokinetics is unknown.

In Australia the approval of avelumab for Merkel cell carcinoma is based on one uncontrolled, open-label, phase II study. This enrolled 88 patients who had already been treated for metastatic disease. They were given infusions at a dose of 10 mg/kg every two weeks and assessed by the Response Evaluation Criteria in Solid Tumours. The median duration of treatment was 17 weeks and the median follow-up was 10.4 months.[1]

The primary outcome of the trial was the overall response to treatment. Eight patients had a complete response and 20 had a partial response giving an overall response rate of 31.8%. At six months, 69% of the patients were still alive. The median overall survival was 11.3 months.[1]

Treatment-related adverse events affected 70% of the patients. Some adverse effects are the predictable consequences of infusing a drug that alters the immune system. These include immune-mediated pneumonitis, hepatitis, nephritis, colitis and endocrinopathies. Infusion reactions are common and premedication with antihistamines and paracetamol is recommended. Other frequent adverse reactions include fatigue, peripheral oedema, musculoskeletal pain, diarrhoea, nausea and anaemia. Avelumab should be avoided in pregnancy and lactation because of its potential for harm.

Another immune checkpoint inhibitor pembrolizumab has also shown some efficacy in Merkel cell carcinoma, so this class of drugs may have an increasing role in treatment. However, in the phase II trial of avelumab only a minority of the 88 patients responded and 43 patients died, with most of these deaths being due to progressive disease. Median progression-free survival was 2.7 months.[1] As the trial excluded patients with significant comorbidities or immunosuppression, avelumab will not be suitable for all patients. Further research will reveal whether avelumab is effective earlier in the course of the disease.

T manufacturer provided the product information

REFERENCES

1. Kaufman HL, Russell J, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol 2016;17:1374-85. https://doi.org/10.1016/S1470-2045(16)30364-3

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 and the European Medicines Agency.

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.