NEW DRUGS

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Plitidepsin

Approved indication: multiple myeloma

Aplidin (Specialised Therapeutics) vials containing 2 mg powder for reconstitution

Plitidepsin is a cytotoxic peptide originally found in the sea squirt *Aplidium albicans*. It interacts with a protein (eEF1A2) which is overexpressed in some cancers. This interaction leads to apoptosis. Synthetically produced plitidepsin has been found to have antiproliferative effects on cancer cells. Phase II trials have investigated its activity in tumours such as lung cancer, melanoma and multiple myeloma.

The drug has to be reconstituted and diluted. It is then infused over three hours. In the blood, 80% of plitidepsin is inside blood cells. The metabolism of plitidepsin includes cytochrome P450 3A4. It should therefore not be administered with inhibitors of this enzyme, such as clarithromycin, itraconazole and grapefruit juice. Plitidepsin should also not be administered with enzyme inducers such as carbamazepine, rifampicin or St John's wort. It is not recommended for patients with impaired liver function. Most of the drug is excreted in bile with a half-life of six days.

One of the phase II trials involved 51 patients with refractory or relapsed multiple myeloma. These patients were given an infusion of plitidepsin every two weeks. If the response was suboptimal, dexamethasone could be added. The median number of treatment cycles each patient received was four. In the 47 patients who were evaluable, six had a response to plitidepsin. Four of the 18 patients who added dexamethasone had a response. Progression-free survival was 2.3 months with plitidepsin alone and 3.8 months if dexamethasone was added.[1]

A subsequent open-label phase III trial in multiple myeloma randomised 171 patients to receive plitidepsin with dexamethasone and 84 to receive dexamethasone alone. These patients had previously been treated with at least three, but no more than six, therapies including bortezomib and lenalidomide or thalidomide. Plitidepsin was given on days 1 and 15 of the treatment cycle and dexamethasone was given on days 1, 8, 15 and 22. Patients in the dexamethasone group could cross over to the combined treatment group if there was disease progression after a minimum of eight weeks therapy.[2]

An analysis by an independent review committee found that progression-free survival was a median of 2.6 months with combined therapy and 1.7 months with dexamethasone alone. This difference was statistically significant, but there was no significant difference in overall survival (11.6 months vs 8.9 months).[2]

In patients with multiple myeloma that has not responded to several treatments, adverse events are common. Compared to those who were given dexamethasone alone, adverse events that were more frequent in patients taking plitidepsin included nausea, vomiting, diarrhoea, myalgia, peripheral oedema and fatigue. Liver enzymes are often increased and this can be an indication to interrupt treatment. Other indications for reducing treatment include anaemia, neutropenia, thrombocytopenia and increased creatine kinase. There is a risk of severe hypersensitivity reactions. To prevent infusion reactions, patients must be given intravenous ondansetron, ranitidine and an antihistamine.
The cardiac effects of plitidepsin are uncertain. Atrial fibrillation was more frequent than with dexamethasone alone and unstable atrial fibrillation is a reason for not using plitidepsin.

Patients with multiple myeloma that is refractory or has relapsed after multiple regimens do not have a good prognosis. While giving them plitidepsin and dexamethasone is more likely to induce a response than dexamethasone alone,[2] the consequences are less clear. The increase in progression-free survival is only about one month. Some of the uncertainty arises because in the phase III trial 44% (37/84) of the patients taking dexamethasone crossed over to the combined treatment group. A different analysis of the data allowing for the effect of these crossovers calculated a significant difference in overall survival. The median was then 11.6 months with plitidepsin and dexamethasone compared with 6.4 months for dexamethasone alone. This advantage has to be weighed against the greater toxicity of combination therapy. The trial also excluded sicker patients (Eastern Co-operative Oncology Group status >2).[3]

While the Therapeutic Goods Administration has decided that the balance favours plitidepsin, the European Medicines Agency refused to authorise the marketing of plitidepsin.

T manufacturer provided the product information

REFERENCES

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2. Spicka I, Ocio EM, Oakervee HE, Greil R, Banh RH, Huang SY, et al. Randomized phase III study (ADMYRE) of plitidepsin in combination with dexamethasone vs. dexamethasone alone in patients with relapsed/refractory multiple myeloma. Ann Hematol 2019;98:2139-50. https://doi.org/10.1007/s00277-019-03739-2

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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.