Selinexor

Approved indication: multiple myeloma

Xpovio (Antengene)
20 mg film-coated tablets

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Exportin-1 is an essential nuclear exporter of many tumour suppressor proteins, growth regulator proteins and several classes of messenger RNAs, including those of oncogenic proteins. It is overexpressed in several cancers including multiple myeloma. Selinexor is a selective inhibitor of exportin-1. This inhibition leads to marked accumulation of the tumour suppressor proteins and growth regulator proteins in the nucleus and reduced expression of several oncoproteins, resulting in cell cycle arrest and apoptosis of cancer cells.

Selinexor is indicated in combination with bortezomib and dexamethasone as a treatment for multiple myeloma in patients who have received at least one therapy previously. The drug is also indicated with dexamethasone as a treatment for relapsed or refractory multiple myeloma in patients who have received at least three therapies previously and whose disease is refractory to at least one proteasome inhibitor, at least one immunomodulatory medicinal product and an anti-CD38 monoclonal antibody.

Selinexor should be swallowed whole with water, with or without food, and should not be crushed, chewed, broken or divided. For multiple myeloma, the dose is based on a 35-day cycle and is given with bortezomib and dexamethasone. For relapsed or refractory multiple myeloma, selinexor is given with dexamethasone. Treatment should be continued until disease progression or unacceptable toxicity.

Selinexor is a substrate of cytochrome P450 (CYP) 3A4, and so its exposure might be reduced with the concomitant use of strong CYP3A4 inducers, such as rifampicin, St John's wort and phenytoin. The drug's mean half-life after an 80 mg dose is 6–8 hours. The dose does not need to be adjusted in patients with renal impairment or mild to moderate hepatic impairment.

Selinexor with dexamethasone was studied in the single-arm, open-label phase II STORM trial, which included 122 patients with triple-class refractory multiple myeloma. They had previously been treated with bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab, glucocorticoids and an alkylating drug and had disease that was refractory to at least one proteasome inhibitor, one immunomodulatory drug and daratumumab. When assessed by the reduction in myeloma protein concentration, a partial response or better was observed in 26% of the patients. The median progression-free survival was 3.7 months.[1]

Selinexor in combination with bortezomib and dexamethasone was studied in the open-label, active-controlled, phase III BOSTON trial. This randomised 402 patients with multiple myeloma who had previously been treated with one to three lines of therapy, including proteasome inhibitors. In this trial, the median progression-free survival was 13.9 months in the 195 patients who received the triplet combination, compared with 9.5 months in the 207 patients who received bortezomib and dexamethasone only. The objective response rate was also significantly higher in the patients who received the triplet combination (76.4% vs 62.3%).[2]

In the STORM trial, the most common grade 3–4 adverse events were thrombocytopenia (59%, which then resulted in grade 3 or higher bleeding events in six patients), anaemia (44%), hyponatraemia (22%) and neutropenia (21%). Treatment-emergent adverse events led to discontinuation in 18% of the patients and two deaths.[1] In the BOSTON trial, the most frequent grade 3–4 adverse events in the patients who received the triplet combination were thrombocytopenia (39% vs 17% without selinexor), fatigue (13% vs 1%), anaemia (16% vs 10%) and pneumonia (11% vs 11%). Grade 2 or higher peripheral neuropathy was less frequent with the triplet combination (21% vs 34% without selinexor). Treatment-emergent adverse events led to discontinuation in 21% of the patients and four deaths with the triplet combination compared with 16% of patients and one death without selinexor.[2]

Thrombocytopenia, neutropenia, neurological toxicities, hyponatraemia and infections are all potential adverse reactions to selinexor that can be life-threatening. The drug can also lead to severe gastrointestinal toxicities, fatigue, weight loss, anorexia, dizziness, tumour lysis syndrome and new onset or exacerbation of cataracts. Patients are advised to avoid driving or operating machines if they experience dizziness or a confusional state. Most patients will require dose reductions to manage adverse events. Detailed dosage modification guidelines to manage adverse haematologic and nonhaematologic reactions are provided in the Australian product information for selinexor.

Based on animal studies, selinexor might impair fertility. Patients are advised to use effective contraceptive options during and for one week after stopping treatment. The drug has not been studied in children or pregnant women. The drug has similar efficacy in patients older than 75 years of age, but they have a higher incidence of adverse effects.

NEW DRUGS

A once-weekly regimen of selinexor with dexamethasone alone or with dexamethasone and bortezomib is an effective treatment option for patients with multiple myeloma. It has modest efficacy in patients with triple-class refractory disease. However, patients and clinicians must be mindful of the many potential adverse reactions, which should be managed appropriately.

T T manufacturer provided additional useful information

REFERENCES

1. Chari A, Vogl DT, Gavriatopoulou M, Nooka AK, Yee AJ, Huff CA, et al. Oral selinexor–dexamethasone for triple-class refractory multiple myeloma. N Engl J Med 2019;381:727-38. https://doi.org/10.1056/NEJMoa1903455
2. Grosicki S, Simonova M, Spicka I, Pour L, Kriachok I, Gavriatopoulou M, et al. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. Lancet 2020;396:1563-73. https://doi.org/10.1016/s0140-6736(20)32292-3

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, the European Medicines Agency and the Therapeutic Goods Administration.