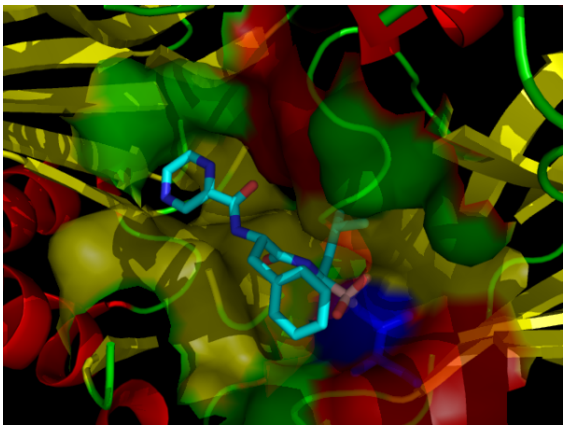
Bortezomib

Bortezomib (BAN, INN and USAN. Originally codenamed **PS-341**; marketed as **Velcade** by Millennium Pharmaceuticals; **Neomib** by Getwell and **Bortecad** by Cadila Healthcare) is the first therapeutic proteasome inhibitor to be tested in humans. Proteasomes are cellular complexes that break down proteins. In some cancers, the proteins that normally kill cancer cells are broken down too quickly. Bortezomib interrupts this process and lets those proteins kill the cancer cells. It is approved in the U.S. for treating relapsed multiple myeloma and mantle cell lymphoma.[1][2] In multiple myeloma, complete clinical responses have been obtained in patients with otherwise refractory or rapidly advancing disease.



Bortezomib bound to the core particle in a yeast proteasome. The bortezomib molecule is in the center colored by atom type (boron = pink, carbon = cyan, nitrogen = blue, oxygen = red), surrounded by the local protein surface. The blue patch is catalytic threonine residue whose activity is blocked by the presence of bortezomib.

1 Origin and development

Bortezomib was originally synthesized in 1995 at Myogenics. The drug (PS-341) was tested in a small Phase I clinical trial on patients with multiple myeloma. It was brought to further clinical trials by Millennium Pharmaceuticals in October 1999.

In May 2003, seven years after the initial synthesis, bortezomib (marketed as Velcade by Millennium Pharmaceuticals Inc.) was approved in the United States by the Food and Drug Administration (FDA) for use in multiple myeloma, based on the results from the SUMMIT Phase II trial.[3] Bortezomib is approved for initial treatment of patients with multiple myeloma by the U.S. FDA in 2008.[4]

Later in August 2014, this Administration approved Velcade for the retreatment of adult patients with multiple myeloma[5] who had previously responded to Velcade therapy and relapsed at least six months following completion of prior treatment.

2 Pharmacology

2.1 Structure

The drug is an N-protected dipeptide and can be written as Pyz-Phe-boroLeu, which stands for pyrazinoic acid, phenylalanine and Leucine with a boronic acid instead of a carboxylic acid. Peptides are written N-terminus to C-terminus, and this convention is used here even though the "C-terminus" is a boronic acid instead of a carboxylic acid.

2.2 Mechanism

The boron atom in bortezomib binds the catalytic site of the 26S proteasome[6] with high affinity and specificity. In normal cells, the proteasome regulates protein expression and function by degradation of ubiquitylated proteins, and also cleanses the cell of abnormal or misfolded proteins. Clinical and preclinical data support a role in maintaining the immortal phenotype of myeloma cells, and cell-culture and xenograft data support a similar function in solid tumor cancers. While multiple mechanisms are likely to be involved, proteasome inhibition may prevent degradation of pro-apoptotic factors, permitting activation of programmed cell death in neoplastic cells dependent upon suppression of pro-apoptotic pathways. Recently, it was found that bortezomib caused a rapid and dramatic change in the levels of intracellular peptides that are produced by the proteasome.[7] Some intracellular peptides have been shown to be biologically active, and so the effect of bortezomib on the levels of intracellular peptides may contribute to the biological and/or side effects of the drug.

2.3 Pharmacokinetics and pharmacodynamics

After subcutaneous administration, peak plasma levels are ~25-50 nM and this peak is sustained for 1-2 hrs.

After intravenous injection, peak plasma levels are ~500 nM but only for ~5 minutes, after which the levels rapidly drop as the drug distributes to tissues (volume of distribution is ~500 L).[8][9] Both routes provide equal drug exposures and generally comparable therapeutic efficacy. Elimination half life is 9–15 hours and the drug is primarily cleared by hepatic metabolism.[10]

Pharmacodynamics are measured by measuring proteasome inhibition in peripheral blood mononuclear cells. The much greater sensitivity of myeloma cell lines and mantle cell lines to proteasome inhibition compared with normal peripheral blood mononuclear cells and most other cancer cell lines is poorly understood.

3 Costs

3.1 UK

NICE recommended against Velcade in Oct 2006 due to its cost. Treatment costs about £18,000 per patient, and studies reviewed by NICE reported that it could extend the life expectancy by an average of six months over standard treatment.[11]

The company proposed a cost reduction for multiple myeloma,[12] and this was taken up in the UK.[13]

4 Adverse effects

Bortezomib is associated with peripheral neuropathy in 30% of patients; occasionally, it can be painful. This can be worse in patients with pre-existing neuropathy. In addition, myelosuppression causing neutropenia and thrombocytopenia can also occur and be dose-limiting. However, these side effects are usually mild relative to bone marrow transplantation and other treatment options for patients with advanced disease. Bortezomib is associated with a high rate of shingles,[14] although prophylactic acyclovir can reduce the risk of this.[15] Acute interstitial nephritis has also been reported.[16]

Gastro-intestinal (GI) effects and asthenia are the most common adverse events.[17]

5 Drug interactions

Green tea extract epigallocatechin gallate (EGCG), which had been expected to have a synergistic effect, was found by Encouse B. Golden, *et al.* to reduce the effectiveness of bortezomib.[18]

6 Therapeutic efficacy

Two open-label, phase II trials (SUMMIT and CREST) established the efficacy of bortezomib 1.3 mg/m^2 (with or without dexamethasone) administered by intravenous bolus on days 1,4,8, and 11 of a 21-day cycle for a maximum of eight cycles in heavily pretreated patients with relapsed/refractory multiple myeloma.[19] The phase III APEX trial demonstrated the superiority of bortezomib 1.3 mg/m^2 over a high-dose dexamethasone regimen (e.g. median TTP 6.2 vs 3.5 months, and 1-year survival 80% vs 66%).[19]

7 Experimental use

Bortezomib has been trialled for SLE and appeared to reduce disease activity and plasma cell numbers, however 7 of 12 patients dropped out due to side effects, some of which were severe.[20]

8 References

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9 External links

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- Myeloma patients campaigning for access to a life prolonging cancer drug
- Millennium Pharmaceuticals website on Velcade
- Multiple Myeloma Research Foundation article on Velcade
- International Myeloma Foundation article on Velcade
- U.S. Food and Drugs Administration on Velcade
- Dedicated website for European audience

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