Proteasome inhibitors: Really a targeted therapy?

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Disclosure slide

• I have no Conflicts of Interest to declare
Proteasome inhibitors were not initially considered as drug candidates at all, due to the assumption that the inhibition of this basic cellular pathway would disrupt the homeostasis of all tissues.

This view was overturned by the discovery that proteasome inhibition preferentially induced apoptosis in transformed cells, ie, rapidly proliferative cells with deregulated cell cycle or other signaling, or cells with abnormally upregulated activities.
Timeline of the evolution of proteasome inhibition

Figure 2. The ubiquitination pathway in the UPS results in the polyubiquitination of substrate proteins, which are recognized and unfolded by the 19S cap and then degraded into peptide fragments within the 20S core; bortezomib inhibits proteolysis at the β5-site, resulting in multiple downstream effects.
Bortezomib has demonstrated substantial benefit alone or as part of combinations inducing chemo- or radiosensitization in several hematological malignancies, mainly in multiple myeloma and mantle cell lymphoma

Less effective in solid tumors
Mantle Cell Lymphoma (MCL): disease features and biology

- Mature B-cell phenotype (CD19, CD20, CD22, CD79) and coexpression of CD5.
- Genetic hallmark t(11;14)(q13;q32) Cyclin D1 overexpression
- Many secondary genomic aberrations:
  - Cell cycle and senescence: BMI-1/INK4/ARF/CDK4/RB
  - DNA damage: ATM/CHK2/p53
- Up to 30% of MCL show leukemic involvement
Mantle Cell Lymphoma: current therapies

- Intensive immuno-chemotherapy regimens, highly effective in other aggressive lymphomas such as DLBCL, induces only transient remissions in MCL.
Bortezomib: initial rationale to use in MCL

Bortezomib induces remissions in relapsed and refractory MCL

1.5 mg/m²
Response rate 41.5%
Time to response 1 month
29 Patients Goy A, JCO 2005
10 Patients O'Connor O, JCO 2005

FDA approval in 2006 as second line treatment in MCL

Goy A, JCO 2005
O'Connor O, JCO 2005
Bortezomib: proposed mechanism of action

Bortezomib

ER stress
ROS generation

Unfolded Protein Response (UPR)

Adaptive response

↑ Undegraded proteins

↑ ATF3  ATF4

H2A

↑ Noxa

↑ Mcl-1

Bax

Bak

↓ ΔΨm

Smac
Cyt C

APOPTOSIS

Perez-Galan et al, Blood 2006;107:257-264
Wang Q et al, PNAS 2009; 106(7):2200-5
Weniger et al, CCR 2011. 17(15):5101-12
However, still more than half of MCL cases fail to respond to bortezomib

The explanation for these differential responses remains unanswered

1. Point mutations or overexpression of β5 (PSMB5) subunit in MM
2. High proteasome activity

BR cell lines have acquired a partial plasmacytic phenotype without full differentiation to plasma cells.

**IRF4 high plasma cell vs B-cell**

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<td>TNFAIP3</td>
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<td><strong>FDR=0.04; NES= 1.44</strong></td>
<td><strong>FDR&lt;0.001; NES= 1.91</strong></td>
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**Plasma cell vs B-cell**

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<td><strong>FDR=0.08; NES =1.52</strong></td>
<td><strong>FDR=0.03; NES= 1.65</strong></td>
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Intrinsic bortezomib resistance MCL cell lines (MINO and REC) show plasmacytic features

IRF4 is highly expressed in MINO and REC

XBP-1 is not spliced in MINO and REC

Bortezomib resistant MCL patients show higher CD38 and IRF4 expression

Paradox

MCL with features of partial plasma cell differentiation (upregulation of IRF4 and CD38)

MCL with features of partial plasma cell differentiation (upregulation of IRF4 and CD38)

Bortezomib resistant

Bortezomib sensitive

MM (Plasma Cells)

SECRETION


Extensive Immunoglobulin Production Sensitizes Myeloma Cells for Proteasome Inhibition

Silke Meister,1 Ulrich Schubert,3 Kirsten Neubert,1 Kai Herrmann,4 Renate Burger,5 Martin Gramatzki,5 Sabine Hahn,3 Sandra Schreiber,3 Sabine Wilhelm,1 Martin Herrmann,2 Hans-Martin Jäck,4 and Reinhard E. Voll12
A model for bortezomib resistance in MCL

IRF4 → BLIMP → XBP-1


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Advantages bortezomib

• Malignant cells harbor elevated proteasome activity compared with normal cells.
• Cancer cells are more dependent on proteasome activity for their survival and drug resistance; therefore, malignant cells should be more sensitive to treatment with proteasome inhibitors.
• Bortezomib sensitizes cancer cells to conventional chemotherapeutic agents, and appears to overcome drug resistance.
HSP inhibitors
- Tanespimycin
- Retaspimycin

Deacetylase inhibitors (DACI)
- Vorinostat
- Panabinostat
- Belinostat
- Romidepsin

AKT/mTOR inhibitors
- Perifosine
- Tensirolimus
- Everolimus

Pan-BCL2 inhibitors
- Obatoclax

Farnesyl transferase inhibitors (FTIs)
- Tipifarnib
- Lanafarnib

Immuno modulating agents
- Thalidomide
- Lenalidomide
- Pomalidomide

DNA damaging agents
- Alkylators
- Antracyclines
- bendamustine

Monoclonal antibodies
- Elotuzumab (CD319)
- Mapatumumab (trail receptors)
- Siltuximab (IL-6)
Disadvantages bortezomib

• **Toxic side effects** (asthenia, gastrointestinal events, hematological toxicity, peripheral neuropathy and a high rate of shingles).

• Bortezomib is particularly effective in MM and MCL. However, **only about 40 – 50% of MCL are sensitive to bortezomib**, indicating that some patients possess intrinsic resistance to proteasome inhibition.
FUTURE
Targeting regulators of protein homeostasis

Inhibitors against specific E3 ligases. These ligases act on an early step in the ubiquitin-proteasome system.

Proteasome Inhibitors:
- reversible: BORTEZOMIB- FDA approved
  MLN9708 (Millennium)- phase I/II
  Oprozomib ONX 0912 (Onyx)- phase I
  Delanzomib (Cephalon) - phase III
- irreversible: Carfilzomib PR-171 (Onyx) phase III
  Marizomib (Nereus)- phase Ib
Targeting the tumor ubiquitin-proteasome degradation pathway continues to be a promising strategy for human cancer therapies.
Research team Therapeutic targets and new diagnostic strategies in lymphoid neoplasms

Molecular bases of apoptosis regulation induced by drugs in lymphoid neoplasms. Evaluation of new strategies for the treatment of these disorders.

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