The use of proteasome inhibitors (PI) with the first-in class drug Bortezomib (Btz) has improved the outcome of multiple myeloma (MM) patients. However, Btz resistance frequently emerges in patients with advanced disease. The second generation PI Carfilzomib (Czf) and additional PI (including Delanzomib (Dlz), ixazomib (Ixa), Oprozomib (Oprz), and AMO-1) are in advanced clinical development. All these PI are designed to target the β\textsubscript{5} subunit which is the rate-limiting protease. The protease in addition contains β\textsubscript{1} and β\textsubscript{5} protease subunits that differ from β\textsubscript{5} in their substrate specificity. The degree of cytoxicity in MM is correlated with the degree of inhibition of proteasomal subunits β\textsubscript{1} and/or β\textsubscript{5} in addition to β\textsubscript{5} and Btz-refractory MM cells upregulate activity of β\textsubscript{1}, the subunit not targeted by Btz. The "optimum" pattern of proteasome inhibition to reach maximum cytotoxicity in MM, either Btz-sensitive or -resistant is unknown, as well as the individual patterns of proteasome subunit inhibition (i.e. co-inhibition of β\textsubscript{1} and/or β\textsubscript{5}) of the non-approved PI in MM.

**MATERIALS & METHODS**

We developed a set of subunit-selective PI as well as fluorophore-labelled activity-based probes (ABP) capable to visualize the individual activities of the β\textsubscript{1}, β\textsubscript{5}, and β\textsubscript{5} subunits of the constitutive- and immuno-proteasome in intact cells. Equimolar concentrations of PI were used to assess the inhibition profiles of the different drug candidates. Btz/Czf-resistant MM cell lines were generated by continuous drug exposure from AMO-1 cells (AMOQbtz/ AMOQczt). Viability was estimated by MTS and plotted against the inhibition of the individual β-subunits (alone or with various combinations of proteasome inhibitors). In addition, recently synthesized inhibitors with dual specificity for β\textsubscript{1} and β\textsubscript{5} (Xin550, Xin551) were used to improve the efficacy of protease inhibition in PI resistant cells.

**REFERENCES**


**DISCLOSURES**

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