Proteasome inhibition: the dawn of novel therapies in multiple myeloma

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TITLE	Bortezomib or high-dose dexamethasone for relapsed multiple myeloma.
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Nowadays for multiple myeloma (MM) experts it is well established that the prognosis of this often evil disease has improved. Numerous novel anti-MM agents have shown impressive activity, inducing longevity or chronic disease courses. The currently available anti-MM drug options include proteasome inhibitors (PI), immunomodulatory agents (IMiD), immunotherapies, such as monoclonal antibodies (mAb), antibody drug conjugates, bispecific antibodies, chimeric antigen receptor T cells, chemotherapy (CTx) and others. Moreover, MM biology and genomic heterogeneity are better understood, suggesting that it is important to enumerate the extent of clonal heterogeneity and to interpret the results of subsequent therapy in light of this heterogeneity. Effective targeted therapy requires drug combinations which target distinct subclones, and the employment of targeted therapies only in patients for whom the drug target is entirely clonal,[1] the former being common and the latter scarce. This provides the rationale for doublet, triplet and quadruplet therapies.

At the time of the APEX study,[2] the inhibition of the proteasome was a completely novel therapeutic approach, with remarkable preclinical activity in MM.[3] The drug bortezomib was the first in class for clinical application (Figure 1A).[2] This large randomized open-label phase III study compared bortezomib/dexamethasone (VD) *versus* single agent dexamethasone (D) in 669 patients with relapsed/refractory MM (RRMM), who had one to three prior lines of therapy. It was also the first major international phase III study in RRMM that brought together the MM community in Europe and North America. Notably, after the interim analysis determined superiority of VD over D, patients in the D arm were permitted to cross over to receive bortezomib (Bz) after disease progression. This study illustrated higher responses, longer time to progression and extended overall survival in

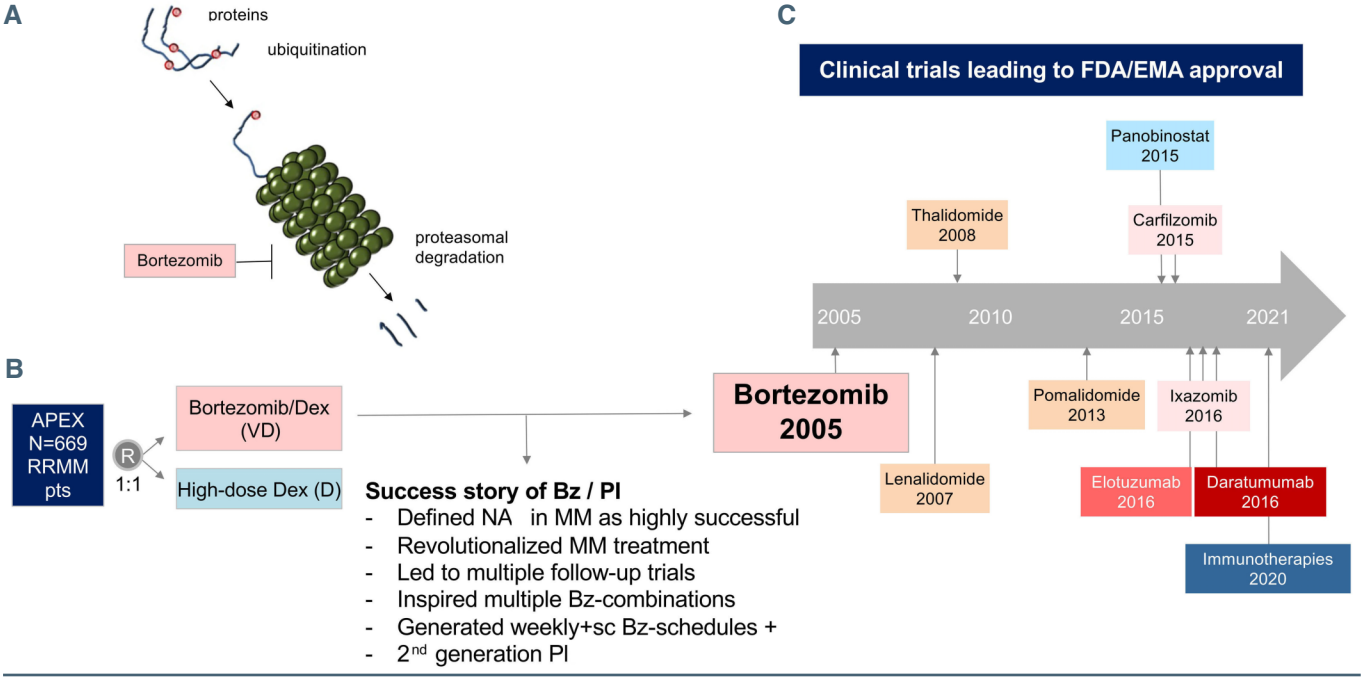

Figure 1. Proteosome inhibition. (A) Mechanism of proteasome inhibition. (B) APEX trial randomizing 669 patients (pts) 1:1 to bortezomib (Bz)/dexamethasone (D) (VD) vs. D alone and the achievements evolving from this pivotal trial. (C) Key clinical trials that led to Food and Drug Adminstration (FDA) and European Medicines Agency (EMA) approval of various novel agents (NA). The proteosome inhibitor (PI) Bz in the APEX trial was established as one fundamental NA and was the clinical study that led others to follow and likewise achieve clinical significance in multiple myeloma (MM). Dex: dexamethasone; RRMM: relapsed/refractory MM (RRMM).

patients treated with VD *versus* D alone, despite this crossover. The combined complete and partial response rates were 38% *versus* 18% (P<0.001), median progression-free survival was 6.22 months *versus* 3.49 months (hazard ratio [HR] 0.55; P<0.0001), the 1-year overall survival was 80% *versus* 66% (HR 0.57; P=0.001) and grade 3/4 adverse events occurred in 75% *versus* 60%, respectively.[2] This study led to swift approval of VD in RRMM and established that novel agents (NA), far more active than dexamethasone, should be developed. In fact, with myriads of papers in MM, numerous publications exist for RRMM, illustrating the widespread use of PI and the important follow-up studies evolving after the *New England Journal of Medicine* publication.[2] The enormous success of APEX and its worldwide implication are exemplified in Figure 1B and C, namely that PI were defined as key NA and induced impressive responses not only in RRMM, but also in induction, consolidation and maintenance, and stood at the beginning of the rapid development of several NA which have revolutionized MM treatment. APEX has stimulated multiple follow-up research, including papers on lines of therapy and response, earlier *versus* later relapse treatment, side effect management, cytogenetics/high-risk patients, PI retreatment, and avoidance and recovery of peripheral neuropathy. It allowed the exploration of multiple highly potent Bz combinations beyond D, namely employing IMiD, CTx, mAb and others. It encouraged the development of second generation PI and novel PI schedules, i.e., with subcutaneous and weekly applications, rather than intravenous and twice a week applications. It has demonstrated that NA are a vital treatment armamentarium that has even challenged the replacement of standard autologous stem cell transplantation with NA treatment alone.

Disclosures

The authors participated in the APEX study at the University of Freiburg (UKF) / Comprehensive Cancer Center Freiburg (CCCF), but other than receiving study support (UKF/CCCF) for the patients being included and meticulously documented in APEX, declare no competing financial interest related to this historic report.

Contributions

ME wrote this report, JMW and RW provided comments and approved the paper.

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References

1. Lohr JG, Stojanov P, Carter SL, et al. Widespread genetic heterogeneity in multiple myeloma: implications for targeted therapy. Cancer Cell. 2014;25(1):91-101.
2. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med. 2005;352(24):2487-2498.
3. Orlowski RZ. The ubiquitin proteasome pathway from bench to bedside. Hematology Am Soc Hematol Educ Program. 2005;220-225.