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EDITORIAL

Novel mechanism of drug resistance to proteasome inhibitors in multiple myeloma

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Abstract

Multiple myeloma (MM) is a cancer caused by uncontrolled proliferation of antibody-secreting plasma cells in bone marrow, which represents the second most common hematological malignancy. MM is a highly heterogeneous disease and can be classified into a spectrum of subgroups based on their molecular and cytogenetic abnormalities. In the past decade, novel therapies, especially, the first-in-class proteasome inhibitor bortezomib, have been revolutionary for the treatment of MM patients. Despite these remarkable achievements, myeloma remains incurable with a high frequency of patients suffering from a relapse, due to drug resistance. Mutation in the proteasome β5-subunit (PSMB5) was found in a bortezomib-resistant cell line generated *via* long-term coculture with increasing concentrations of bortezomib in 2008, but their actual implication in drug resistance in the clinic has not been reported until recently. A recent study discovered four resistance-inducing PSMB5 mutations from a relapsed MM patient receiving prolonged bortezomib treatment. Analysis of the dynamic clonal evolution revealed that two subclones existed at the onset of disease, while the other two subclones were induced. Protein structural modeling and functional assays demonstrated that all four mutations impaired the binding of bortezomib to the 20S proteasome, conferring different degrees of resistance. The authors further demonstrated two potential approaches to overcome drug resistance by using combination therapy for targeting proteolysis machinery independent of the 20S proteasome.

Key words: Multiple myeloma; Proteasome inhibitor; Bortezomib; Proteasome β5-subunit; Drug resistance; Clonal evolution; Combination therapy

Core tip: Multiple myeloma (MM) is the second common hematological malignancy. An array of new treatments has been approved over the last decade. Hence, the survival of MM patients has improved steadily. Among these new drugs, the first-in-class proteasome inhibitor bortezomib has been revolutionary for targeted therapy. Now bortezomib is the backbone for treating MM. However, emerging drug resistance poses a major challenge for clinicians to use proteasome inhibitors. In this editorial, we discuss proteasome β5-subunit mutations as a novel resistant mechanism to bortezomib and its implication in tracking clonal evolution and suggest potential strategies to overcome drug resistance.

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INTRODUCTION

Multiple myeloma (MM) is the second most common hematological malignancy with approximate 138000 cases worldwide in 2016[1], so it is a significant social and economic burden globally. MM is characterized by uncontrolled proliferation of clonal antibody-secreting plasma cells in bone marrow. The aberrant accumulation of monoclonal proteins in blood and urine causes organ damage, summarized as calcium elevation, renal complications, anemia, and bone lesions[2]. MM is a highly heterogeneous disease and can be classified into a spectrum of subgroups based on their molecular and cytogenetic abnormalities[3]. According to primary genetic events, MM can be divided into hyperdiploid (HD) and non-hyperdiploid (NHD). There are several subgroups within NHD, such as t(11;14)(q13;q32) and CCND3, t(4;14)(p16;q32) and MMSET, FGFR3, t(14;16)(q32;q23), and other MAF translocations. These molecular cytogenetic subgroups and their associated prognosis are summarized in Table 1.

This heterogeneity is one of the factors contributing to the limited effect of chemotherapy (melphalan, cyclophosphamide, and doxorubicin) in general. In the last 12 years, significant progress has been made in the novel therapies for the treatment of MM patients[10]. These new agents, including proteasome inhibitors, immunomodulatory drugs (IMiDs), histone deacetylase (HDAC) inhibitors, and monoclonal antibodies, have significantly improved the survival of standard risk MM patients[11]. Especially, the first-in-class proteasome inhibitor bortezomib has been revolutionary for targeted therapy for MM[12]. Despite remarkable achievements in the past decade, myeloma remains incurable with a high frequency of patients suffering from a relapse, due to primary (inherent) and secondary (acquired) drug resistance[13]. Diversified molecular mechanisms underlying the resistance to proteasome inhibitor have been unveiled, including overexpression of a superfamily of ATP-binding cassette transporters (MDR, MRP1, *etc*.), enhanced aggresomal protein pathway, overexpression of heat shock proteins, bone marrow microenvironment, and appearance of mutations in proteasome subunits[14]. Although mutation in the proteasome β5-subunit (PSMB5) was found in a bortezomib-resistant cell line generated *via* long-term coculture with increasing concentrations of bortezomib in 2008[15], PSMB5 mutation has never been identified in relapsed or refractory MM patients until recently.

STUDY ANALYSIS

In a recent study by Barrio *et al*[16], four PSMB5 mutations from a MM patient receiving prolonged bortezomib treatment have been discovered and functionally validated. These investigators performed targeted deep-sequencing of 88 MM-related genes (M^3P panel) on paired tumor-germline samples from 161 multi-refractory MM patients. They reported four subclonal mutations in PSMB5 gene: c.235G>A (p.A20T), c.256G>C (p.A27P), c.312G>C (p.M45I), and c.365G>A (p.C63Y) (protein positions

Table 1 Molecular cytogenetic classification of multiple myeloma and prognosis

Chromosomes affected (gene)	Ploidy	Prognosis	Ref.
t (11;14) (*CCND3*)	NH	Good	[4]
t (14;16) (*c-MAF*)	NH	Poor	[5]
t (4;14) (*FGFR3* and *NSD2*)	NH/H	Poor	[6,7]
Other IgH	NH/H	Poor	[8]
Hyperdiploidy	H	Good	[9]

IgH: Immunoglobulin heavy chain; H: Hyperdiploidy; NH: Non-hyperdiploidy.

refer to the cleaved mature protein). These mutations were further confirmed by whole exome sequencing. Interestingly, these subclonal lines were still sensitive to the combination of pomalidomide and elotuzumab as analysis of clonal evolution at different time points (TP) revealed that two subclonal lines (C63Y and A27P) become undetectable at TP4 and the remaining M45I and A20T also disappeared at TP5 (5 months later than TP4). Tracing back the samples available at TP1 (diagnosis) and TP2 (first relapse) confirmed the pre-existence of two of the variants, c.235G>A and c.365G>A, at these two earlier TPs. The illustration of the temporal order of clonal evolutionary trajectory in this patient adds to our growing understanding of MM evolution and therapeutic resistance. The co-existence of emergent new subclones after selection pressure (bortezomib treatment) on the original subclones confirms the "Big Bang" model of cancer evolution in a branching rather than in a "step-wise" linear progression[17,18]. Furthermore, the eradication of all these four subclones after a combination regime including the second-generation IMiD pomalidomide and the immunostimulatory monoclonal antibody elotuzumab underpins the importance of developing novel drugs for relapsed MM patients.

Notably, all four mutations occurred within a highly conserved region in exon 2, and protein structural analysis demonstrated that the mutations are located either within the S1 pocket (A20T, A27P, and M45I) or in proximity to the substrate-binding channel (C63Y). The authors performed *in vitro* functional assays and all the mutants impaired the binding of bortezomib to the proteasome, reduced catalytic proteasome activity, and conferred resistance to bortezomib and other proteasome inhibitors to varying degrees. Importantly, these PSMB5 mutant lines remain sensitive to p97/VCP AAA ATPase inhibitor, CB5083, which blocks proteolysis machinery independent of 20S proteasome. These results highlight another approach to overcome drug resistance to proteasome inhibitors by using p97/VCP inhibitors.

In conclusion, this study not only validated the importance of PSMB5 in mediating drug resistance to proteasome inhibitors, but also deciphered the dynamic and temporal effect of clonal evolution in the development of resistance and deepened our understanding of the relationship between clonal evolution and drug resistance in MM cells.

CONCLUSION

Drug resistance has been implicated in 90% of MM-related deaths, which poses a daunting challenge in the management of MM. The combination of the second-generation IMiD and antibody therapy or novel agents targeting proteasome-independent proteolysis machinery can override the resistance to proteasome inhibitors. These approaches hold promise to further improve the survival of relapsed and refractory MM patients. However, we have to wait for well-designed clinical trials to validate its efficacy and evaluate the toxicity. In addition, prospective biomarkers for prediction of drug resistance are absent. Owing to the heterogeneity of MM and various mechanisms involved in resistance, it is unlikely that one biomarker fits all MM. Nevertheless, screening PSMB5 mutations at diagnosis, during the treatment, and subsequent follow-ups should be useful in monitoring drug resistance to proteasome inhibitors. Furthermore, some important questions remain unanswered, for example, whether mutations in other 20S proteasome subunits, like PSMA5, exist. Finally, single-cell sequencing technology is particularly useful in tracking clonal evolution, providing opportunities to characterize MM subclones in unprecedented detail. We now have a better chance to conquer drug resistance and significantly further improve the outcome of MM patients.

REFERENCES

1 **Cowan AJ**, Allen C, Barac A, Basaleem H, Bensenor I, Curado MP, Foreman K, Gupta R, Harvey J, Hosgood HD, Jakovljevic M, Khader Y, Linn S, Lad D, Mantovani L, Nong VM, Mokdad A, Naghavi M, Postma M, Roshandel G, Shackelford K, Sisay M, Nguyen CT, Tran TT, Xuan BT, Ukwaja KN, Vollset SE, Weiderpass E, Libby EN, Fitzmaurice C. Global Burden of Multiple Myeloma: A Systematic Analysis for the Global Burden of Disease Study 2016. *JAMA Oncol* 2018; **4**: 1221-1227 [PMID: 29800065 DOI: 10.1001/jamaoncol.2018.2128]

2 **Kyle RA**, Rajkumar SV. Multiple myeloma. *Blood* 2008; **111**: 2962-2972 [PMID: 18332230 DOI: 10.1182/blood-2007-10-078022]

3 **Chng WJ**, Glebov O, Bergsagel PL, Kuehl WM. Genetic events in the pathogenesis of multiple myeloma. *Best Pract Res Clin Haematol* 2007; **20**: 571-596 [PMID: 18070707 DOI: 10.1016/j.beha.2007.08.004]

4 **Fonseca R**, Blood EA, Oken MM, Kyle RA, Dewald GW, Bailey RJ, Van Wier SA, Henderson KJ, Hoyer JD, Harrington D, Kay NE, Van Ness B, Greipp PR. Myeloma and the t(11;14)(q13;q32); evidence for a biologically defined unique subset of patients. *Blood* 2002; **99**: 3735-3741 [PMID: 11986230 DOI: 10.1182/blood.V99.10.3735]

5 **Narita T**, Inagaki A, Kobayashi T, Kuroda Y, Fukushima T, Nezu M, Fuchida S, Sakai H, Sekiguchi N, Sugiura I, Maeda Y, Takamatsu H, Tsukamoto N, Maruyama D, Kubota Y, Kojima M, Sunami K, Ono T, Ri M, Tobinai K, Iida S. t(14;16)-positive multiple myeloma shows negativity for CD56 expression and unfavorable outcome even in the era of novel drugs. *Blood Cancer J* 2015; **5**: e285 [PMID: 25723856 DOI: 10.1038/bcj.2015.6]

6 **Chesi M**, Nardini E, Lim RS, Smith KD, Kuehl WM, Bergsagel PL. The t(4;14) translocation in myeloma dysregulates both FGFR3 and a novel gene, MMSET, resulting in IgH/MMSET hybrid transcripts. *Blood* 1998; **92**: 3025-3034 [PMID: 9787135 DOI: 10.1016/S0006-355X(99)80021-3]

7 **Kalff A**, Spencer A. The t(4;14) translocation and FGFR3 overexpression in multiple myeloma: prognostic implications and current clinical strategies. *Blood Cancer J* 2012; **2**: e89 [PMID: 22961061 DOI: 10.1038/bcj.2012.37]

8 **Cleynen A**, Szalat R, Kemal Samur M, Robiou du Pont S, Buisson L, Boyle E, Chretien ML, Anderson K, Minvielle S, Moreau P, Attal M, Parmigiani G, Corre J, Munshi N, Avet-Loiseau H. Expressed fusion gene landscape and its impact in multiple myeloma. *Nat Commun* 2017; **8**: 1893 [PMID: 29196615 DOI: 10.1038/s41467-017-00638-w]

9 **Chretien ML**, Corre J, Lauwers-Cances V, Magrangeas F, Cleynen A, Yon E, Hulin C, Leleu X, Orsini-Piocelle F, Blade JS, Sohn C, Karlin L, Delbrel X, Hebraud B, Roussel M, Marit G, Garderet L, Mohty M, Rodon P, Voillat L, Royer B, Jaccard A, Belhadj K, Fontan J, Caillot D, Stoppa AM, Attal M, Facon T, Moreau P, Minvielle S, Avet-Loiseau H. Understanding the role of hyperdiploidy in myeloma prognosis: which trisomies really matter? *Blood* 2015; **126**: 2713-2719 [PMID: 26516228 DOI: 10.1182/blood-2015-06-650242]

10 **Ria R**, Reale A, Vacca A. Novel agents and new therapeutic approaches for treatment of multiple myeloma. *World J Methodol* 2014; **4**: 73-90 [PMID: 25332907 DOI: 10.5662/wjm.v4.i2.73]

11 **Larocca A**, Mina R, Gay F, Bringhen S, Boccadoro M. Emerging drugs and combinations to treat multiple myeloma. *Oncotarget* 2017; **8**: 60656-60672 [PMID: 28948001 DOI: 10.18632/oncotarget.19269]

12 **Grosicki S**, Barchnicka A, Jurczyszyn A, Grosicka A. Bortezomib for the treatment of multiple myeloma. *Expert Rev Hematol* 2014; **7**: 173-185 [PMID: 24617331 DOI: 10.1586/17474086.2014.899144]

13 **Robak P**, Drozdz I, Szemraj J, Robak T. Drug resistance in multiple myeloma. *Cancer Treat Rev* 2018; **70**: 199-208 [PMID: 30245231 DOI: 10.1016/j.ctrv.2018.09.001]

14 **Manasanch EE**, Orlowski RZ. Proteasome inhibitors in cancer therapy. *Nat Rev Clin Oncol* 2017; **14**: 417-433 [PMID: 28117417 DOI: 10.1038/nrclinonc.2016.206]

15 **Oerlemans R**, Franke NE, Assaraf YG, Cloos J, van Zantwijk I, Berkers CR, Scheffer GL, Debipersad K, Vojtekova K, Lemos C, van der Heijden JW, Ylstra B, Peters GJ, Kaspers GL, Dijkmans BA, Scheper RJ, Jansen G. Molecular basis of bortezomib resistance: proteasome subunit beta5 (PSMB5) gene mutation and overexpression of PSMB5 protein. *Blood* 2008; **112**: 2489-2499 [PMID: 18565852 DOI: 10.1182/blood-2007-08-104950]

16 **Barrio S**, Stühmer T, Da-Viá M, Barrio-Garcia C, Lehners N, Besse A, Cuenca I, Garitano-Trojaola A, Fink S, Leich E, Chatterjee M, Driessen C, Martinez-Lopez J, Rosenwald A, Beckmann R, Bargou RC, Braggio E, Stewart AK, Raab MS, Einsele H, Kortüm KM. Spectrum and functional validation of PSMB5 mutations in multiple myeloma. *Leukemia* 2019; **33**: 447-456 [PMID: 30026573 DOI: 10.1038/s41375-018-0216-8]

17 **Sottoriva A**, Kang H, Ma Z, Graham TA, Salomon MP, Zhao J, Marjoram P, Siegmund K, Press MF, Shibata D, Curtis C. A Big Bang model of human colorectal tumor growth. *Nat Genet* 2015; **47**: 209-216 [PMID: 25665006 DOI: 10.1038/ng.3214]

18 **Keats JJ**, Chesi M, Egan JB, Garbitt VM, Palmer SE, Braggio E, Van Wier S, Blackburn PR, Baker AS, Dispenzieri A, Kumar S, Rajkumar SV, Carpten JD, Barrett M, Fonseca R, Stewart AK, Bergsagel PL. Clonal competition with alternating dominance in multiple myeloma. *Blood* 2012; **120**: 1067-1076 [PMID: 22498740 DOI: 10.1182/blood-2012-01-405985]

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