Editorial

Cancer drug resistance in multiple myeloma

Fatih M. Uckun* 1,2

1Departments of Oncology and Developmental Therapeutics, Ares Pharmaceuticals, St. Paul, MN 55110, USA.
2Departments of Translational Oncology, Reven Pharmaceuticals, Westminster, CO 80234, USA.

Correspondence to: Prof. Dr. Fatih M. Uckun, Departments of Oncology and Developmental Therapeutics, Ares Pharmaceuticals, 12590 Ethan Ave. North, St. Paul, MN 55110, USA. E-mail: fatih.uckun@aresmit.com

How to cite this article: Uckun FM. Cancer drug resistance in multiple myeloma. Cancer Drug Resist 2022;5:271-6. https://dx.doi.org/10.20517/cdr.2022.32

Received: 3 Mar 2022 Accepted: 9 Mar 2022 Published: 25 Mar 2022

Academic Editor: Godefridus J. Peters Copy Editor: Xi-Jun Chen Production Editor: Xi-Jun Chen

INTRODUCTION

Multiple myeloma (MM) is the second most common hematologic malignancy after non-Hodgkin’s lymphoma. Intrinsic and acquired drug resistance of cancer cells to standard drugs is a major obstacle for a more successful survival outcome of MM patients treated on contemporary clinical protocols. The primary purpose of this special issue on “Drug Targets and Resistance Mechanisms in Multiple Myeloma” was to collect new and transformative information regarding new insights about the mechanisms of drug resistance in MM and the role of the tumor microenvironment in treatment failures.

MAIN TEXT

Overcoming inherent and acquired drug resistance of MM cells, especially in the context of the immunosuppressive tumor microenvironment (TME), remains a major challenge to effective therapy of high-risk or relapsed/refractory (R/R) MM[1-15]. Amplified expression of drug transporters P-glycoprotein (P-gp/ABCB1) and multidrug-resistance-associated protein 1 (MRP1/ABCC1) have been implicated in the resistance of MM cells to drugs that are known substrates for these proteins, such as melphalan, dexamethasone, and anthracyclines [Table 1][16-18]. Some studies have indicated that abundant expression levels of the lung resistance protein (LRP), another drug transporter protein, may also confer resistance to chemotherapy drugs and proteasome inhibitors (PIs) in MM[16-18]. It remains to be seen if a potent and safe inhibitor of these drug transporters can be identified and clinically leveraged to overcome drug resistance in
Table 1. Possible Mechanisms of Cancer Drug Resistance in Multiple Myeloma

| Therapeutics | Resistance Mechanism |
|--------------|----------------------|
| IMiD         | Mutations of proteins in CRBN-IK axis associated with deficient expression |
| PI           | Impaired binding to PSMB5 due to mutations; MIF overexpression; LRP abundance; epigenetic reprogramming; DNA hypermethylation in an active intronic CRBN enhancer |
| Chemo        | Amplified expression of P-gp/ABCB1 and MRPI/ABCC1 |
| MoAb         | Low expression level of target antigen; upregulation of the complement inhibitors CD55 and CD59 |
| DEX          | GR mutations and deficiency; amplified expression of P-gp/ABCB1 and MRPI/ABCC1 |

DEX: Dexamethasone; IMiD: immuno-modulatory drug; PI: proteasome inhibitor; Chemo: chemotherapy drugs; MIF: migration inhibitory factor; LRP: lung resistance protein; P-gp: P-glycoprotein; MRPI: multidrug-resistance-associated protein 1.

MM. Several humoral and cellular components of the TME facilitate the immune evasion and subsequent expansion of drug-resistant MM clones, such as myeloid-derived suppressor cells (MDSCs), regulatory T-cells, and MM-derived cytokines including TGF-β, and IL-6, and IL-10 [4]. MYC and hepatocyte growth factor/c-MET signaling networks have also been identified as potential contributors to cancer drug resistance in MM[15]. Patients with triple-class-refractory MM whose cells exhibit triple-class resistance to PIs, immunomodulatory drugs (IMiDs), and monoclonal antibodies (MoAb) have an OS of < 6 months emphasizing the urgency of this unmet medical need[19-20].

IMiDs such as thalidomide, lenalidomide, and pomalidomide trigger cereblon (CRBN)-mediated ubiquitination and degradation of important regulatory proteins that contribute to the expansion of drug-resistant clones, including the transcription factor Ikaros[18]. They also augment the proliferation and effector function of cytotoxic T-cells (CTLs) and natural killer (NK) cells while inhibiting immunosuppressive T-regs. Unfortunately, deficient expression of the target CRBN, as reported for MM cells with certain mutations of the cereblon gene or DNA hypermethylation in an active intronic CRBN enhancer, occurs in almost one-third of the patients with R/R MM and causes resistance to the IMiDs [Table 1][21,22]. CRBN-independent resistance to IMiDs has also been reported[1,4]. Ongoing research will explore if the clinical benefit of IMiDs could be augmented by using them in combination with CRBN E3-ligase modulators (e.g., iberdomide) to accelerate the degradation of Ikaros transcription factor proteins IKZF1/IKZF3[1,4].

In contemporary induction protocols for MM, IMiDs are often combined with PIs such as bortezomib and Carfilzomib[5,20]. PIs trigger apoptotic death of MM cells by contributing to an exaggerated unfolded protein response (UPR) pathway and ER stress[1,4]. They further impair the survival-promoting interactions between MM cells and stromal elements in the bone marrow microenvironment, and they promote the immunogenic death of damaged MM cells[1,4]. Impaired binding of PIs to the target proteasome β5 subunit (PSMB5) has been associated with PI resistance and can occur due to mutations of the encoding gene that cause conformational alterations at the binding region [Table 1][23,24]. MicroRNAs (miRNAs) play important roles in mRNA silencing and regulation of gene expression in MM cells[25]. CD47 antigen is overexpressed in MM, likely due to miR155 down-regulation, and its abundance was associated with a poor prognosis[26-28]. Recent studies have implicated CD47 in PI resistance of MM cells[28]. In view of the promising early clinical experience in patients with myeloid malignancies, evaluation of the anti-CD47 MoAb Magrolimab in R/R MM patients would also seem warranted[4]. Notably, CD47-targeting with synthetic micro-RNA miR-155 overcame bortezomib resistance and induced phagocytosis as well as apoptosis of MM cells by causing loss of CD47[28]. Likewise, another micro-RNA, miR-218, is decreased in MM and synthetic miR-218 may help overcome PI resistance[29]. In the future, nanoformulations of synthetic miR155 and miR-218 could be used for the resensitization of resistant MM cells to PI. Another emerging new strategy to overcome PI resistance...
involves the targeting of the macrophage migration inhibitory factor, which has been shown to render MM cells resistant to PI-induced apoptosis[30]. Clinical biomarker studies have demonstrated that the high-level expression of this target is associated with poor prognosis and survival in MM[30].

BCL-2 is a predominant anti-apoptotic protein in B-lineage lymphoid malignancies, including MM. Venetoclax is a BCL-2 homology 3 (BH3)-mimetic that disrupts the association of the proapoptotic BH3-only proteins such as BIM and BID with BCL-2[31]. BCL-2 inhibition by Venetoclax could theoretically damage chemotherapy-resistant MM cells by inhibiting the amino acid metabolism and reducing oxidative phosphorylation like its effects on leukemic cell populations[1,32,33]. Venetoclax exhibited meaningful single-agent activity in R/R MM patients, especially those with a t(11;14) translocation[34]. A combination of Venetoclax plus Bortezomib and dexamethasone was more effective than placebo plus bortezomib and dexamethasone in patients with R/R MM, albeit with higher toxicity due to infections[35]. Besides BCL-2, MCL-1 is also an important survival-promoting anti-apoptotic protein for MM cells, and inhibitors of MCL-1 such as AMG-176 and MIK665 have been developed as potential anti-MM drugs that could be combined with other apoptosis-promoting anti-MM drug candidates including Venetoclax[36].

A recent prospective clinical study employed longitudinal single-cell RNA-sequencing (scRNA-seq) to study the mechanism and dynamics of drug resistance in MM[37]. An enzyme of the UPR pathway, peptidylprolyl isomerase A, was identified as a new molecular target demonstrating the clinical potential of this new strategy in identifying clinically relevant new therapeutic targets for overcoming cancer drug resistance in MM[37]. Another important strategy for further identification of new molecular targets contributing to cancer drug resistance in MM is deep measurable residual disease (MRD) profiling, which is based on the characterization of MRD clones using flow cytometry in combination with whole-exome sequencing[38].

Precision medicines as well as biotherapeutic agents, including therapeutic monoclonal antibodies such as the anti-CD38 MoAb Daratumumab and isatuximab, and the anti-signaling lymphocyte activation marker F7, antibody elotuzumab, antibody-drug conjugates, and bispecific antibodies (BiAb) have been developed to damage drug-resistant MM clones as well as alter the immunosuppressive bone marrow microenvironment with some very promising clinical data regarding their clinical impact potential[1,4,39]. T-cell redirecting BiAb and bispecific T-cell engagers (BiTES) targeting CD38, the orphan G protein-coupled receptor GPRC5D, and the B-cell maturation antigen (BCMA)/CD269 on MM cells and CD3 antigen on T-cells facilitate the CTL-mediated destruction of drug-resistant MM cells in cytolytic synapses[4,40]. They showed promising single-agent activity in early clinical trials of R/R MM patients, and risk mitigation strategies have been identified for their potentially serious side effects such as cytokine release syndrome and neurotoxicity[4,40]. BCMA-targeting cellular immunotherapy platforms using chimeric antigen receptor (CAR)-T cells or NK cells have also been developed with documented objective clinical responses in single-agent trials[1,4,6-9,40].

Another area of active clinical research to improve the outcome of cancer drug-resistant MM is related to efforts for overcoming the immunosuppressive TME[4,40]. BiAb and anti-CD38 MoAb are capable of dual targeting of both MM cells and immunosuppressive elements of the TME such as the MDSC, and are being explored as potential therapeutic platforms[40].

Each of the new modalities designed to mitigate or overcome cancer drug resistance in MM has faced inherent and acquired resistance mechanisms[21]. For example, soluble BCMA renders MM cells resistant to the cytolytic actions of BCMA-directed BiAb/BiTES and CAR-T cells by serving as a competing target for
these biotherapeutic platforms. It remains to be seen if this resistance can be overcome by using a $\gamma$-secretase inhibitor to reduce the $\gamma$-secretase mediated production of soluble BCMA. It will be important to develop multi-modality combination regimens to minimize the risk of escape by drug-resistant MM clones as well as the emergence of MM clones refractory to the new agents with promising activity\textsuperscript{1,4,13,20,21,35,40-45}. The timely definition of optimal strategies for overcoming the cancer drug resistance in MM will require randomized adaptive clinical trials with multiple parallel cohorts, each evaluating a promising new treatment strategy.

DECLARATIONS

Authors’ contributions
The author contributed solely to the article.

Availability of data and materials
Not applicable.

Financial support and sponsorship
None.

Conflicts of interest
Author Fatih M. Uckun was employed by Ares Pharmaceuticals, and he was a consultant for Reven Pharmaceuticals. The author declares that this study did not receive any funding from any sponsor or commercial entity. No person other than the author was involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication. The author declares no other competing interests.

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Copyright
© The Author(s) 2022.

REFERENCES
1. Uckun FM, Qazi S, Demirer T, Champlin RE. Contemporary patient-tailored treatment strategies against high risk and relapsed or refractory multiple myeloma. EBioMedicine 2019;39:612-20. DOI PubMed PMC
2. Minnie SA, Hill GR. Immunotherapy of multiple myeloma. J Clin Invest 2020;130:1565-75. DOI PubMed PMC
3. Martínez-martín S, Soucek L. MYC inhibitors in multiple myeloma. Cancer Drug Resist 2021;4:842-65. DOI PubMed PMC
4. Uckun FM. Overcoming the Immunosuppressive tumor microenvironment in multiple myeloma. Cancers (Basel) 2021;13:2018. DOI PubMed PMC
5. Voorhees PM, Kaufman JL, Laubach J, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. Blood 2020;136:936-45. DOI PubMed PMC
6. Topp MS, Duell J, Zugmaier G, et al. Anti-B-cell maturation antigen BiTE molecule AMG 420 induces responses in multiple myeloma. J Clin Oncol 2020;38:775-83. DOI PubMed
7. Fayon M, Martinez-Cingolani C, Abecassis A, et al. Bi38-3 is a novel CD38/CD3 bispecific T-cell engager with low toxicity for the treatment of multiple myeloma. Haematologica 2021;106:1193-7. DOI PubMed PMC
8. Alhallak K, Sun J, Jeske A, et al. Bispecific T cell engagers for the treatment of multiple myeloma: achievements and challenges. Cancers (Basel) 2021;13:2853. DOI PubMed PMC
9. Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Lancet 2021;398:318-24. DOI PubMed
10. Usmani SZ, Garfall AL, van de Donk NWCI, et al. Tecclistamab, a B-cell maturation antigen × CD3 bispecific antibody, in patients
with relapsed or refractory multiple myeloma (MajesTEC-1): a multicentre, open-label, single-arm, phase 1 study. *Lancet* 2021;398:665-74. DOI: PubMed

11. Berdeja JG, Krishnan AY, Orioli A, et al. Updated results of a phase 1, first-in-human study of talquetamab, a G protein-coupled receptor family C group S member D (GPRC5D) × CD3 bispecific antibody, in relapsed/refractory multiple myeloma (MM). *J Clin Oncol* 2021;39:8008. DOI: PubMed

12. Gozzetti A, Ciofﬁni S, Sicuranza A, et al. Drug resistance and minimal residual disease in multiple myeloma. *Cancer Drug Resist* 2022;5:171-83. DOI: PubMed

13. Moscini M, Ho M, Bianchi G. Overcoming drug resistance by targeting protein homeostasis in multiple myeloma. *Cancer Drug Resist* 2021;4:1028-46. DOI: PubMed PMC

14. Black H, Glavey S. Gene expression proﬁling as a prognostic tool in multiple myeloma. *Cancer Drug Resist* 2021;4:1008-18. DOI: PubMed

15. Giannoni P, de Totero D. The HGF/c-MET axis as a potential target to overcome survival signals and improve therapeutic efﬁcacy in multiple myeloma. *Cancer Drug Resist* 2021;4:923-33. DOI: PubMed

16. Pinto V, Bergantim R, Caires HR, Seca H, Guimarães JE, Vasconcelos MH. Multiple myeloma: available therapies and causes of drug resistance. *Cancers (Basel)* 2020;12:407. DOI: PubMed PMC

17. Mynott RL, Wallington-Beddoe CT. Drug and solute transporters in mediating resistance to novel therapeutics in multiple myeloma. *ACS Pharmacol Transl Sci* 2021;4:1050-65. DOI: PubMed PMC

18. Mynott RL, Wallington-Beddoe CT. Inhibition of P-glycoprotein does not increase the efﬁcacy of proteasome inhibitors in multiple myeloma cells. *ACS Pharmacol Transl Sci* 2021;4:713-29. DOI: PubMed PMC

19. Gandhi UH, Cornell RF, Lakshman A, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia* 2019;33:2666-75. DOI: PubMed PMC

20. Moreau P, Kumar SK, San Miguel J, et al. Treatment of relapsed and refractory multiple myeloma: recommendations from the International Myeloma Working Group. *Lancet Oncol* 2021;22:e105-18. DOI: PubMed

21. Davis LN, Sherbenou DW. Emerging therapeutic strategies to overcome drug resistance in multiple myeloma. *Cancers (Basel)* 2021;13:1686. DOI: PubMed PMC

22. Haertle T, Barrio S, Munawar U, et al. Cerebrom enhancer methylation and IMiD resistance in multiple myeloma. *Blood* 2021;138:1721-6. DOI: PubMed PMC

23. Wallington-Beddoe CT, Sobieraj-Teague M, Kuss BJ, Pitson SM. Resistance to proteasome inhibitors and other targeted therapies in myeloma. *Br J Haematol* 2018;182:11-28. DOI: PubMed PMC

24. Barrio S, Stühmer T, Da-Viá M, et al. Spectrum and functional validation of PSMB5 mutations in multiple myeloma. *Leukemia* 2019;33:447-56. DOI: PubMed

25. Pula A, Robak P, Robak T. MicroRNA in multiple myeloma - a role in pathogenesis and prognostic signiﬁcance. *Curr Med Chem* 2021;28:6753-72. DOI: PubMed

26. Muz B, Kudono HD, King I, et al. Targeting CD47 As a novel therapeutic strategy in multiple myeloma. *Blood* 2017;130:3099. DOI: PubMed

27. Kim D, Wang J, Willingham SB, Martin R, Wernig G, Weissman IL. Anti-CD47 antibodies promote phagocytosis and inhibit the growth of human myeloma cells. *Leukemia* 2012;26:2538-45. DOI: PubMed

28. Rastgou N, Wu J, Liu A, et al. Targeting CD47/TNFAIP8 by miR-155 overcomes drug resistance and inhibits tumor growth through induction of phagocytosis and apoptosis in multiple myeloma. *Haematologica* 2020;105:2813-23. DOI: PubMed PMC

29. Chen H, Cao W, Chen J, et al. miR-218 contributes to drug resistance in multiple myeloma via targeting LRRC28. *J Cell Biochem* 2021;122:305-14. DOI: PubMed

30. Wang Q, Zhao D, Xian M, et al. MIF as a biomarker and therapeutic target for overcoming resistance to proteasome inhibitors in human myeloma. *Blood* 2020;136:2557-73. DOI: PubMed PMC

31. Bajpai R, Matulis SM, Wei C, et al. Targeting glutamine metabolism in multiple myeloma enhances BIM binding to BCL-2 eliciting synthetic lethality to venetoclax. *Oncogene* 2016;35:3995-64. DOI: PubMed PMC

32. Lagadinou ED, Sach A, Callahan K, et al. BCL-2 inhibition targets oxidative phosphorylation and selectively eradicates quiescent human leukemia stem cells. *Cell Stem Cell* 2013;12:329-41. DOI: PubMed PMC

33. Jones CL, Stevens BM, D’Alessandro A, et al. Inhibition of amino acid metabolism selectively targets human leukemia stem cells. *Cancer Cell* 2018;34:713-29. DOI: PubMed PMC

34. Mynott RL, Wallington-Beddoe CT. Drug and solute transporters in mediating resistance to novel therapeutics in multiple myeloma. *ACS Pharmacol Transl Sci* 2021;4:1050-65. DOI: PubMed PMC

35. Mynott RL, Wallington-Beddoe CT. Inhibition of P-glycoprotein does not increase the efficacy of proteasome inhibitors in multiple myeloma cells. *ACS Pharmacol Transl Sci* 2021;4:713-29. DOI: PubMed PMC

36. Gandhi UH, Cornell RF, Lakshman A, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia* 2019;33:2666-75. DOI: PubMed PMC

37. Moreau P, Kumar SK, San Miguel J, et al. Treatment of relapsed and refractory multiple myeloma: recommendations from the International Myeloma Working Group. *Lancet Oncol* 2021;22:e105-18. DOI: PubMed

38. Davis LN, Sherbenou DW. Emerging therapeutic strategies to overcome drug resistance in multiple myeloma. *Cancers (Basel)* 2021;13:1686. DOI: PubMed PMC

39. Haertle T, Barrio S, Munawar U, et al. Cerebrom enhancer methylation and IMiD resistance in multiple myeloma. *Blood* 2021;138:1721-6. DOI: PubMed PMC

40. Wallington-Beddoe CT, Sobieraj-Teague M, Kuss BJ, Pitson SM. Resistance to proteasome inhibitors and other targeted therapies in myeloma. *Br J Haematol* 2018;182:11-28. DOI: PubMed PMC

41. Barrio S, Stühmer T, Da-Viá M, et al. Spectrum and functional validation of PSMB5 mutations in multiple myeloma. *Leukemia* 2019;33:447-56. DOI: PubMed

42. Pula A, Robak P, Robak T. MicroRNA in multiple myeloma - a role in pathogenesis and prognostic signiﬁcance. *Curr Med Chem* 2021;28:6753-72. DOI: PubMed

43. Muz B, Kudono HD, King I, et al. Targeting CD47 As a novel therapeutic strategy in multiple myeloma. *Blood* 2017;130:3099. DOI: PubMed

44. Kim D, Wang J, Willingham SB, Martin R, Wernig G, Weissman IL. Anti-CD47 antibodies promote phagocytosis and inhibit the growth of human myeloma cells. *Leukemia* 2012;26:2538-45. DOI: PubMed

45. Rastgou N, Wu J, Liu A, et al. Targeting CD47/TNFAIP8 by miR-155 overcomes drug resistance and inhibits tumor growth through induction of phagocytosis and apoptosis in multiple myeloma. *Haematologica* 2020;105:2813-23. DOI: PubMed PMC

46. Chen H, Cao W, Chen J, et al. miR-218 contributes to drug resistance in multiple myeloma via targeting LRRC28. *J Cell Biochem* 2021;122:305-14. DOI: PubMed

47. Wang Q, Zhao D, Xian M, et al. MIF as a biomarker and therapeutic target for overcoming resistance to proteasome inhibitors in human myeloma. *Blood* 2020;136:2557-73. DOI: PubMed PMC

48. Bajpai R, Matulis SM, Wei C, et al. Targeting glutamine metabolism in multiple myeloma enhances BIM binding to BCL-2 eliciting synthetic lethality to venetoclax. *Oncogene* 2016;35:3995-64. DOI: PubMed PMC

49. Lagadinou ED, Sach A, Callahan K, et al. BCL-2 inhibition targets oxidative phosphorylation and selectively eradicates quiescent human leukemia stem cells. *Cell Stem Cell* 2013;12:329-41. DOI: PubMed PMC

50. Jones CL, Stevens BM, D’Alessandro A, et al. Inhibition of amino acid metabolism selectively targets human leukemia stem cells. *Cancer Cell* 2018;34:713-29. DOI: PubMed PMC
resistant multiple myeloma. *Front Oncol* 2021;11:760382. DOI PubMed PMC

41. Fontana F, Scott MJ, Allen JS, et al. VLA4-targeted nanoparticles hijack cell adhesion-mediated drug resistance to target refractory myeloma cells and prolong survival. *Clin Cancer Res* 2021;27:1974-86. DOI PubMed PMC

42. Byrgazov K, Kraus M, Besse A, et al. Up-regulation of multidrug resistance protein MDR1/ABCB1 in carfilzomib-resistant multiple myeloma differentially affects efficacy of anti-myeloma drugs. *Leuk Res* 2021;101:106499. DOI PubMed

43. Chari A, Vogl DT, Gavriatopoulou M, et al. Oral Selinexor-dexamethasone for triple-class refractory multiple myeloma. *N Engl J Med* 2019;381:727-38. DOI PubMed

44. Innao V, Rizzo V, Allegra AG, Musolino C, Allegra A. Promising anti-mitochondrial agents for overcoming acquired drug resistance in multiple myeloma. *Cells* 2021;10:439. DOI PubMed PMC

45. Federico C, Alhallak K, Sun J, et al. Tumor microenvironment-targeted nanoparticles loaded with bortezomib and ROCK inhibitor improve efficacy in multiple myeloma. *Nat Commun* 2020;11:6037. DOI PubMed PMC