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Cancer Drug Resistance

Editorial

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Cancer drug resistance in multiple myeloma

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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 MRP1/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 MRP1/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; MRP1: 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 γ-secretase inhibitor to reduce the γ-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[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.

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Conflicts of interest

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Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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