New Strategies in the Treatment of Multiple Myeloma

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Running Title: New Strategies in myeloma
Abstract

Multiple myeloma (MM) is the second most common hematologic malignancy affecting terminally differentiated plasma cells. Although high-dose chemotherapy and autologous stem cell transplantation improved survival in younger patients, the natural history of MM has been changed with the availability of five new agents approved in last 10 years (thalidomide, bortezomib, lenalidomide, liposomal doxorubicin and carfilzomib). Despite this significant improvement in overall outcome, MM remains incurable in majority of patients prompting continued search for additional therapeutic options. Extensive molecular and genomic characterization of MM cells in its bone marrow milieu, which affects myeloma cell growth and survival, has provided number of novel drugable targets and pathways. Perturbation of protein catabolism at multiple levels has become an important target in MM. Similarly with improvements in monoclonal antibody generation and vaccine development along with identification of number of cell surface and cellular targets have led to development of various strategies including antibodies and antibody-drug conjugates which are under investigation both preclinically as well as in early clinical studies. We propose that eventually, molecularly-informed multi-agent combination therapies will be required to eliminate the MM cell clone for a long-term disease control.
Background
Multiple myeloma (MM) is characterized by excess bone marrow (BM) plasma cells in association with monoclonal protein in the blood and/or urine, often associated with bone destruction, anemia, hypercalcemia and renal dysfunction. It affected 21,700 new individuals in the United States in 2012, with a prevalence of 71,213 total patients, and 10,710 patients died from the disease. Fifty years ago the advent of melphalan and prednisone extended patient median survival to 2-3 years, and high dose therapy followed by stem cell rescue has prolonged median survival to 4-5 years. Increasing awareness of the role of the BM in supporting growth, survival, and drug resistance of MM cells, along with concomitant development of novel agents to overcome cell adhesion mediated drug resistance to conventional therapies, has transformed the treatment paradigm in MM. Specifically, proteasome inhibitor bortezomib and immunomodulatory drugs thalidomide and lenalidomide have formed the framework for multiple new treatment options for newly diagnosed and relapsed/refractory MM, as well as maintenance therapy. Most importantly, median survival has increased to greater than seven years as a direct result. (1) Parallel advances in the genomics of MM has defined additional disease heterogeneity and complexity, as well as provided the rationale for personalized single agent and combination therapies.

On the Horizon
Going forward, the major translational research focus in MM is in four main areas: development of novel agents targeting the MM cell in the BM microenvironment; development of immune (vaccine and adoptive immunotherapy) strategies; development of rationally-based combination therapies; as well as utilization of genomics for improved classification and personalized therapy.

Targeting protein catabolism
Normal cellular homeostasis is maintained by a balanced regulation of protein synthesis and degradation. The ubiquitin proteasome system (UPS) is a non-lysosomal intracellular protein degradation pathway mediated via proteasome holoenzymes, ubiquitin ligases, and deubiquitylating enzymes (DUBs) (2). Deregulation of the UPS pathway is linked to the pathogenesis of various human diseases including MM; therefore, inhibitors of UPS pathways either at the level of proteasomal or ubiquitylating/deubiquitylating enzymes offers great promise as a novel therapeutic strategy (Fig 1). We and others have characterized targeting the UPS using our in vitro and in vivo models of the MM cell in the BM milieu, specifically elucidating the
molecular and cellular mechanisms whereby proteasome inhibitors target tumor cells, host tumor interactions, and the BM microenvironment to overcome conventional drug resistance. Our preclinical and clinical studies led to the FDA approval of bortezomib for relapsed/refractory and newly diagnosed MM. Although bortezomib represents a major advance, not all patients respond, and those that respond relapse. More recent studies have therefore defined mechanisms of resistance to proteasome inhibitors and strategies to overcome it, including second-generation proteasome inhibitors and scientifically-informed combination therapies.

**Novel proteasome inhibitors:** Second generation proteasome inhibitors differ qualitatively and quantitatively from bortezomib in their pattern of proteasome inhibition, and can overcome bortezomib resistance in preclinical models. Carfilzomib, a recently approved agent for relapsed MM, is an epoxyketone which irreversibly and covalently binds to the chymotrypsic site of the proteasome, resulting in increased extent and duration of inhibition compared to bortezomib (3, 4). In relapsed and bortezomib refractory MM, Phase I/II clinical trials have demonstrated 20% single agent responses lasting 8 months, with prolongation of survival to 15 months and lack of neuropathy (5-7). In bortezomib naïve patients, response rates are at least doubled, and combination trials of carfilzomib with lenalidomide and dexamethasone demonstrate remarkable extent and frequency of response both in relapsed and in newly diagnosed MM. Another second generation proteasome inhibitor Marizomib blocks chymotryptic-, tryptic-, and caspase-like proteasome activities and overcomes bortezomib resistance in preclinical models. Ongoing clinical studies have defined the dose and schedule and early signs of efficacy (8). MLN 9708 is an oral boron-containing proteasome inhibitor which has a shorter proteasome dissociation half-life than bortezomib, with improved pharmacokinetics and anti-tumor activity both in vitro and in vivo (9, 10). Already MLN9708 has shown single agent clinical activity in relapsed refractory MM, as well as high response rates when combined with lenalidomide and dexamethasone in an all oral regimen to treat newly diagnosed MM.

**Deubiquitylating enzymes (DUB) inhibitors:** Bortezomib has validated targeting protein homeostasis as an effective therapeutic strategy in MM. More recent efforts have focused on discovery and development of small molecule inhibitors of DUBs, another major component of UPS (2). Our studies show increased expression and activity of the DUB USP7 in MM cells versus normal plasma cells, and that its inhibition by P5091 triggers ubiquitylation and degradation of HDM2, thereby activating p53 and p21 signaling and triggering apoptosis. Importantly, blocking UPS in this manner upstream of the proteasome can overcome
bortezomib resistance.

**Inhibitors of aggresome pathway:** Recent studies have identified the aggresome pathway as an alternative system for polyubiquitylated protein degradation, and shown that HDAC6 binds to both polyubiquitylated proteins and dynein motors, thereby acting to shuttle protein complexes to aggresomes (11). We have led both preclinical studies and clinical trials combining broad type 1,2 HDAC inhibitors vorinostat or panobinostat to block aggresomal pathway with proteasome inhibitor bortezomib to overcome bortezomib resistance (12, 13). In an international phase III clinical trial, the combination of vorinostat and bortezomib was superior to bortezomib and placebo in relapsed and refractory MM, with ORR 54% versus 41%, respectively (P<0.0001). The progression free survival (PFS) and time to progression (TTP) were prolonged in the combination arm compared to the bortezomib alone cohort, with PFS hazard ratio reduction of 23% (P=0.01). However, the actual PFS difference was only 7.63 months versus 6.83 months, due at least in part to the side effect profile of diarrhea, fatigue, and thrombocytopenia attendant to combined therapy. A clinical grade prototype selective HDAC6 inhibitor ACY 1215 has rapidly translated from the bench to the bedside and is now under evaluation as a single agent, as well as in combination with bortezomib to achieve dual blockade or proteasomal and aggresomal protein degradation, with a more favorable therapeutic index (14).

**Immune manipulations**

Immune dysfunction with decreased humoral and cellular responses and related risk of infection is a hallmark of MM. This suppressed immune function permits continued growth of tumor cells. Dysregulation of various components of T helper cells has recently been described including: decreased TH1 responses with interferon-γ production; increased suppressor responses by TH2 cells, as well as dysfunctional T regulatory cells (15); and increased TH17 cells with associated cytokines (IL-17, IL-21, IL-22, and IL-23), which both promote tumor cell growth and bone disease and suppress immune function (16). Similarly, plasmacytoid dendritic cells are abnormal in MM, since they do not trigger normal effector cell function, as well as promote tumor cell growth and drug resistance (17). Strategies to overcome these mechanisms of immune suppression for clinical application include anti-IL17 MAb, anti-IL6 MAb, anti-PD1 MAb, CpG oligonucleotides, and immunomodulatory agents (18).

**Immunomodulatory agents**—Thalidomide, lenalidomide, and pomalidomide are
immunomodulatory agents which directly target MM cells, abrogate binding of MM cells in BM, inhibit constitutive and MM cell binding-induced transcription and secretion of cytokines, inhibit angiogenesis, and modulate T, NK, NKT and dendritic cell function (19-24). Thalidomide and lenalidomide have been incorporated into the treatment paradigm of newly diagnosed and relapsed MM, as well as maintenance therapy. Pomalidamide, the more potent drug in this class, has shown promising results in Phase I and II studies, and was recently approved for relapsed MM. (25-28). Pomalidomide with low dose dexamethasone, has achieved 30-40% durable responses even in patients whose MM is resistant to both lenalidomide and bortezomib, and is currently under evaluation in combination clinical trials with proteasome inhibitors.

**Monoclonal Antibodies:** Monoclonal antibody (MAb)-based therapies function by: stimulating antibody dependent cellular cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC) mediated by NK or T cells; blocking growth or survival signaling molecules by inhibiting ligand or its binding to receptors; stimulating apoptosis signaling cascades; and/or specifically delivering chemotherapeutic agents or toxins to MM cells (29). Numerous MAb-based strategies have been preclinically and clinically evaluated in MM. One of the most promising MAbs is Elotuzumab targeting CS1, an antigen highly and uniformly expressed at the gene and protein level in patient MM cells(30). Elotuzumab mediates ADCC in preclinical models, and a derived clinical trial of single agent Elotuzumab in relapsed refractory MM achieved stable disease. Importantly, our laboratory studies showed that ADCC activity of Elotuzumab against MM cells was enhanced by lenalidomide, which in turn translated to Phase I/II trials of lenalidomide, Elotuzumab and dexamethasone. Remarkably, this combination achieved 82% response in relapsed MM and after a median follow up of 16.4 months, the median time to progression was not reached (31), providing the framework for an ongoing Phase III trial of lenalidomide, Elotuzumab and dexamethasone versus lenalidomide and dexamethasone in relapsed MM.

A number of other MAbs targeting MM cells or its BM environment have progressed to phase I/II studies. These include Daratumumab, a humanized MAb targeting CD38 which induces ADCC and CDC, modulates enzymatic activation, and induces apoptosis by crosslinking CD38 (32). A preliminary Phase I/II investigation of this MAb in heavily pretreated MM demonstrated clinical benefit in 18 of 29 patients, including 5 partial responses. BT062, an anti-CD138 MAb conjugated to mytansaponoid DM4, selectively triggers apoptosis in MM cells in preclinical models (33). In Phase I/II trials, preliminary evidence of clinical benefit has been observed. MAbs targeting cytokines including Siltuximab targeting IL-6 (34), BHQ880 targeting DKK1 (35), Tabalumab targeting BAFF (36), and Denosumab, a fully human monoclonal antibody that
inhibits RANK Ligand (37) also have promise as a treatment for both MM and/or related bone disease. Combination of Tabalumab and bortezomib has show interesting activity in Phase I/II study. The stage of clinical development of additional MAbs in MM is shown in Table 1.

**Vaccination strategies:** Based on the success of allogeneic transplantation in achieving long-term disease free survival as well as graft-versus-MM responses following donor lymphocyte infusions, other immunotherapeutic approaches are being evaluated to treat MM. An emerging focus has been to augment autologous anti-MM immune responses using both dendritic cell (DC)-based (38), as well protein and peptide-based, vaccination approaches. A DC/MM cell fusion vaccination has demonstrated induction of humoral and cellular immune response in patients post-transplant (39); its clinical benefit will be evaluated in a clinical trial. Anti-PD-1 MAb is similarly in clinical trials to restore immune function and prolong clinical response post-transplant. To overcome the complexity of cell-based vaccination as well as the need to produce individual patient-specific vaccines, tumor-associated antigen (TAA)-specific protein or peptide-based vaccinations are also being investigated in MM. One of the best studied target antigens is idiotype protein (Id), the immunoglobulin produced by MM cells. Although clinically meaningful immunologic responses and anti-tumor effects after Id vaccination have been reported in lymphoma, direct evidence of clinical benefit in MM is lacking (18). Other MM-associated antigen targets for vaccines include Sp17, MAGE-1, NY-ESO, Xbp-1, CD138, DKK-1 and CS1, which are commonly tested first in the context of HLA-A2+ patients (40-46). Moreover, peptide cocktails from several antigens have been pooled for vaccination to expand breadth and potency of response (47). The task ahead is to evaluate these vaccine approaches in appropriate clinical settings, ie early in the disease course or in the setting of minimal residual disease, and to couple them with strategies to overcome mechanisms of immunoparesis (19) in order to induce more robust clinically significant immune responses.

**Promising Novel Targets**

**BET Bromodomains** Gene regulation is fundamentally governed by reversible, non-covalent assembly of macromolecules. The ε-N-acetylation of lysine residues on histone tails (Kac) is associated with an open chromatin architecture and transcriptional activation. Context-specific molecular recognition of acetyl-lysine is principally mediated by bromodomains. Therefore bromodomain-containing proteins are of substantial biological interest, both as components of transcription factor (TF) complexes and determinants of epigenetic memory. The bromodomain
and extra-terminal (BET)-family (BRD2, BRD3, BRD4 and BRDT) is defined by a common domain architecture comprising two N-terminal bromodomains which share high level of sequence conservation, and a more divergent C-terminal recruitment domain. Recent research has established a compelling rationale for targeting bromodomains in cancer (48), in particular BRD4 in MM(49). BRD4 is a critical mediator of transcriptional elongation, recruiting the transcription elongation factor complex (P-TEFb). Knockdown of BRD4 in proliferating cells leads to G1 arrest and apoptosis, associated with decreased expression of genes important for mitotic progression and survival. The mechanistic link between transcriptional elongation, BRD4, and the c-Myc oncogenic transcription factor provided the rationale for BRD4 inhibition in MM(49). JQ1, the first chemically optimized potent and selective inhibitor of BET bromodomains, showed efficacy in preclinical models of MM(50). Specifically, JQ1 leads to depletion of the c-Myc oncoprotein and downregulation of the c-Myc transcriptional program, leading to cell cycle arrest and tumor cell senescence both in vitro and in vivo. Clinical trials of BRD4 inhibitors therefore represent a new potential therapeutic modality for MM.

**MMSET**

MMSET is a MM oncogene identified at the t(4;14) translocation breakpoint present in approximately 15% of MM(51). Microarray analysis showed that all patients harboring the t(4;14) rearrangement overexpressed MMSET(52). MMSET contains several potential functional motifs, including a SET (Suvar 3-9, Enhancer-of-zeste, Trithorax) domain with histone methyltransferase activity (HMT). Like other SET domain containing proteins, MMSET can methylate histones, thereby leading to changes in gene expression. Methylation of histone 3 lysine tail residue 36 (H3K36) is associated with activation of gene transcription in MM(53, 54). Overexpression of MMSET in MM cells has profound effects on gene expression and cell growth, which requires the enzymatic function of the SET domain. Since MMSET plays a critical role in pathogenesis of t(4;14) MM, it represents a novel therapeutic target amenable to blockade with small molecules.

**BTK**

Bruton's tyrosine kinase (Btk), a nonreceptor tyrosine kinase, plays a key role in normal B cell function through activation of B-cell antigen receptor (BCR) signaling pathway. Btk also plays a major role in osteoclastogenesis and osteoclast (OC) maturation by modulating the activity of NFATc1, the major transcriptional factor activated following RANKL stimulation. Its potential role in the MM cell and its microenvironment has therefore recently been evaluated. Btk knockdown confirmed the role of Btk activation in the BM milieu in promoting MM cell growth, survival, and interaction with other BM stromal components, as well as MM-induced...
bone lysis(55). Importantly, an oral and selective Btk inhibitor PCI-32765 blocked RANKL/M-CSF-induced phosphorylation of Btk and downstream PLCγ2 in OC, thereby abrogating TRAP5b and bone resorption activity, as well as decreasing secretion of multiple cytokines and chemokines from OCs and BM stromal cells. It also blocked MM cell growth and survival triggered by IL-6 or coculture with BMSCs or OCs in vitro. In addition, in vivo activity of PCI-32765 against MM cells and MM cell-induced osteolysis has been shown in the SCID-hu model of human MM in mice. These functional sequelae of Btk activation mediating osteolysis and growth of MM cells have provided the basis for ongoing Phase I/II clinical trials of PCI-32765 in MM.

Synergistic Combination Therapies
The success rate of phase III randomized clinical trials in oncology has been very low, but in MM we have informed the design of combination clinical trials based upon additive or synergistic cytotoxicity, as well as on overcoming drug resistance, in preclinical models. For example, pegylated doxorubicin with bortezomib, based upon inhibition of DNA damage repair by bortezomib in preclinical studies, demonstrated efficacy in a phase III trial and is now FDA approved. Enhanced efficacy of immunomodulatory drugs thalidomide and lenalidomide with corticosteroids in preclinical models provided the framework for their clinical evaluation and ultimate FDA approval in combination. Recent studies have validated a number of targets whose inhibition can sensitize or overcome resistance to bortezomib in vitro, including inhibitors of histone deacetylases (HDACs) (56, 57), Aurora kinase A (58), Akt(59), heat shock protein (hsp) 90(60, 61), B cell activating factor (BAFF) (36, 62), and cyclin dependent kinase (CDK) 5(63), and combination clinical trials are ongoing. Perhaps the most active combination to date is that of lenalidomide, bortezomib, and dexamethasone, which preclinically triggers dual apoptotic signaling and clinically can achieve responses in nearly two thirds of patients whose MM is resistant to either lenalidomide or bortezomib alone (64). Importantly, this combination as initial therapy in a phase II study has reported 100% overall response, with three quarters very good partial responses and nearly half complete responses, including molecular complete responses (65). Indeed we are presently evaluating the role of high dose melphalan and stem cell transplantation in the context of this unprecedented extent and frequency of response. These studies demonstrate rapid translation of preclinical leads from the bench to the bedside and clinical trials, which have improved the practice of medicine in MM.

Development of personalized medicine in MM
Comprehensive oncogenomic analysis has identified numerous complex genetic and epigenetic alterations in MM. Some of these recurrent and highly focal amplifications/deletions in the MM genome have now been identified at an early stage of plasma cell disorder(66), including monoclonal gammopathy of undetermined significance and smoldering MM, with further evolution associated with progression to active MM. (67) Importantly, an integrated analyses of genomic data has identified candidates resident within regions of genomic alterations predicted to be involved in MM pathogenesis and progression. The biological behavior and clinical outcome in MM is dependent on these molecular determinants, which are also attractive therapeutic targets. Although FISH-identified t(4;14), t(14;16), and del17p13 have been considered to portend poor prognosis(68), more recent SNP array analysis in 192 uniformly-treated patients identified amp(1q23.3), amp(5q31.3), and del(12p13.31) as the most powerful independent adverse prognostic markers (P < .0001) (69). The data obtained from extensive analysis of patient samples with annotated clinical outcome have now provided insight into molecular mechanism of disease behavior, help develop sensitive prognostic models, identified novel therapeutic targets and provided the framework for the development of molecularly-based therapies and eventually help develop individualized therapy(70) to improve outcome with reduced toxicity. Importantly, our and other studies profiling DNA, mRNA, miRNA, and spliced RNA(67), as well as proteomics and whole genome sequencing(71), have demonstrated remarkable complexity in MM even at diagnosis, with further genomic evolution ultimately leading to relapse of disease. It therefore appears, as in the models of childhood acute lymphoblastic leukemia and other curable cancers or infectious diseases such as tuberculosis and human immunodeficiency virus, that combination therapies will be needed. Specifically, combination targeted therapy regimens directed at those genetic abnormalities present, as well as those known to confer development of resistance, will be needed from the outset to treat newly diagnosed MM. For example with a backbone of combination containing proteasome inhibitor, immunomodulatory agent and steroid, additional agents can be added based on patient specific genomic abnormalities such an activated Ras/Raf pathway, p53 abnormality, MMSET or specific HDAC upregulation. Then maintenance therapies, such as lenalidomide or newer agents under investigation, may prolong response. The parallel development of assays for minimal residual disease, including polymerase chain reaction for patient specific Ig gene rearrangements or utilizing multiparameter flow cytometry, can in turn inform the need for and duration of maintenance treatment strategies. Ultimately prolonged disease free survival and cure is on the horizon in MM.
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Conflict of Interest
Ownership Interest, Acetylon (KCA), scientific founder, Oncopep, consultant/advisory board, Celgene, Millennium, Onyx, Merck, (KCA, NCM) and Bristol-Myers Squibb (KCA)

Figure Legend

Figure 1: Schematic representation of the Ubiquitin Proteasome System. UPS function is mediated via a large number of indicated components, suggesting many potential sites of pharmacological intervention.
References


Table 1: Monoclonal antibody-based clinical studies in myeloma.

<table>
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<th>Target</th>
<th>Agent</th>
<th>Clinical Study Phase</th>
<th>Single Agent(S)/Combination(C)</th>
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<td>Tabalumab (mAb)</td>
<td>I/II</td>
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Figure 1:

Ubiquitin Proteasome System

- Inhibitors of E3 ubiquitin ligase
- Inhibitors of deubiquitylating enzymes
- E3 ubiquitin ligases
- Deubiquitylating enzymes
- Exogenous Ub
- Inhibitors of ubiquitin activation/transfer
- E1/E2 enzymes
- Proteasome inhibitors
- Inhibitors of Ub-substrate/proteasome interface
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