
Vision Statement for Multiple Myeloma: Future Directions

Kenneth C. Anderson

Abstract

There has been great progress in the management and patient outcome in multiple myeloma due to the use of novel agents including immunomodulatory drugs and proteasome inhibitors; nonetheless, novel agents remain an urgent need. The three promising Achilles heels or vulnerabilities to be targeted in novel therapies include: protein degradation by the ubiquitin proteasome or aggresome pathways; restoring autologous antimyeloma immunity; and targeting aberrant biology resulting from constitutive and ongoing DNA damage in tumour cells. Scientifically based therapies targeting these vulnerabilities used early in the disease course, ie smouldering multiple myeloma, have the potential to significantly alter the natural history and transform myeloma into a chronic and potentially curable disease.

Keywords

Multiple myeloma · Targetted therapies · Immune therapies · Protein degradation

1 Introduction

Advances in biology, genomics, epigenetics, and immunity have transformed our understanding of the etiology and pathogenesis of multiple myeloma, allowing for delineation of those mechanisms both intrinsic to the tumor cell and in the host

K.C. Anderson (✉)

Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute,
Harvard Medical School, Boston, USA
e-mail: kenneth_anderson@dfci.harvard.edu

whereby monoclonal gammopathy of undetermined significance progresses to smoldering multiple myeloma and to active myeloma. Within myeloma, an unprecedented level of genetic heterogeneity and genomic instability has been defined, as well as clonal evolution underlying progression of disease [6, 33, 36]. The parallel development of in vitro and in vivo models of myeloma in its bone marrow milieu has facilitated the identification of mechanisms mediating myeloma cell homing to the bone marrow, growth, survival, and drug resistance, as well as egress to extramedullary sites [26, 28]. Taken together, these advances have allowed for the identification and targeting of Achilles heels or vulnerabilities in myeloma, directly leading to a transformation in therapeutic efficacy and patient outcome [4, 5, 12]. In the future, we will treat earlier in the disease course, at a time when patients are asymptomatic, to prevent the development of active disease using well-tolerated drug combination therapies targeting these Achilles heels. Myeloma will then be transformed to a chronic illness and ultimate cure.

2 Excess Protein Production

The first example of an Achilles heal in myeloma is due to their synthesis of excess monoclonal protein, which can either be degraded via the proteasomal or aggresomal cascade or secreted [25]. The development of the proteasome inhibitor Bortezomib demonstrated that primarily targeting the constitutive chymotryptic activity could achieve clinical responses in relapsed refractory myeloma, and it is now a standard component of initial and maintenance treatments. Furthermore, delineation of its mechanism of action has shown that it targets the tumor cell, tumor-host interaction, as well as bone marrow milieu and accessory cells [24]. Importantly, preclinical studies have informed the rational use of combination therapies, such as bortezomib with lenalidomide to trigger both intrinsic and extrinsic apoptotic signaling [38].

Bortezomib has already provided the framework for the development of second generation proteasome inhibitors carfilzomib [45, 46, 49], ixazomib [10, 30, 39], and marizomib [7, 9, 15], and also led to ongoing current efforts to target the ubiquitin proteasome cascade upstream of the proteasome with inhibitors of deubiquitylating enzymes [11, 48] or of the proteasome ubiquitin receptor to overcome proteasome inhibitor resistance. These preclinical and clinical studies have validated targeting the ubiquitin proteasome cascade for therapeutic application in myeloma.

When the proteasomal degradation pathway is inhibited, there is a compensatory upregulation of the aggresomal degradation pathway [25]. The latter can be blocked by either pan histone deacetylase inhibitors [17, 43] or by histone deacetylase six selective inhibitors [44], since the ubiquitinated misfolded protein binds to histone deacetylase 6, which in turn binds to the dynein tubulin carrier complex, thereby shuttling the protein load to the aggresome for its degradation. Already broad class I/II histone deacetylase inhibitors vorinostat [17] and panobinostat [43] have been combined with bortezomib to block the aggresomal and proteasomal degradation of protein, respectively. While the response rates and progression free survival are

prolonged with combination therapy, side effects of the broad acting histone deacetylase inhibitors preclude their use for long-term benefit. Ricolinostat is a histone deacetylase 6 selective inhibitor with a more favorable tolerability profile [44] and therefore can be readily combined with proteasome inhibitors to allow for long-term blockade of both aggresomal and proteasomal degradation pathways.

3 The Host Immunosuppressive Environment

A second Achilles heal in myeloma is the immunosuppressive environment in the host. In this case, targeting the vulnerability consists of strategies to restore host anti-myeloma immunity. There are five strategies, which when combined will markedly improve patient outcome: immunomodulatory drugs, monoclonal antibodies, checkpoint inhibitors, vaccines, and cellular therapies.

Lenalidomide and other immunomodulatory drugs target cereblon [29, 35] and trigger the degradation of alios and ikaros gene products, thereby upregulating transcription of interleukin 2 and interferon gamma genes [18]. They upregulate cytolytic T cell, natural killer cell, and natural killer cell-T cell anti-MM immunity, while at the same time inhibiting aberrant increased regulatory T cell function in myeloma [20, 23]. Lenalidomide is now incorporated into initial, salvage, and maintenance therapies worldwide.

The search for therapeutic monoclonal antibodies in myeloma has been ongoing for decades, and is now coming to fruition. For example, elotuzumab targets SLAMF-7 on the multiple myeloma surface, mediating complement dependent and antibody dependent cellular cytotoxicity [47]. This antibody also targets natural killer cells and enhances their activity. Although single agent clinical trials of elotuzumab saturated SLAMF-7 sites on tumor cells, only stable disease and no clinical responses were observed. Importantly, preclinical studies showed that lenalidomide augments antibody dependent cellular cytotoxicity [47], and combination lenalidomide elotuzumab therapy of relapsed myeloma has markedly prolonged progression free survival in patients with relapsed myeloma [34, 40], providing the basis for its regulatory approval.

The second antibody example is anti-CD38 monoclonal antibodies daratumumab [16, 31] and SAR650984 [27]. CD38 was originally described as T 10 antigen expressed on activated T, B, natural killer, myeloid, and monocytoic cells, as well as endothelial cells and hematopoietic progenitor cells. Due to its broad expression, it was not developed therapeutically based on fears that there may not be an acceptable therapeutic window or index. Remarkably, anti-CD38 monoclonal antibody daratumumab achieves responses as a single agent in relapsed refractory myeloma; and as with elotuzumab, the combination of daratumumab with lenalidomide markedly augments clinical response.

Checkpoint inhibitors are the third immune targeted treatment approach in myeloma. Myeloma cells express PD-L1, as do plasmacytoid dendritic cells [8, 37] and myeloid-derived suppressor cells [21, 22] which both promote myeloma cell growth and drug resistance as well as downregulate host immune response. T,

natural killer, and natural killer-T cells in myeloma express PD-1. Checkpoint blockade with anti-PD-L1 monoclonal antibody may therefore have broader effects than anti-PD-1 monoclonal antibody. Recent preclinical data shows that lenalidomide downregulates PD-L1 on myeloma cells, plasmacytoid dendritic cells, and myeloid derived suppressor cells; as well as downregulates PD-1 expression on immune effector T, natural killer, and T-natural killer cells [22]. Importantly, the combination of checkpoint inhibitors and lenalidomide markedly augments cytolytic response, another example of combination immune therapies.

The fourth example of immune therapies is vaccines. In myeloma two examples are peptide-based vaccines being evaluated to prevent progression of patients with smoldering multiple myeloma to active myeloma [1–3]; and myeloma-dendritic cell-based vaccines now in clinical trials to treat minimal residual disease post autologous stem cell transplant and improve patient outcome [41, 42]. In both cases, vaccines have achieved immune responses in patients against their own myeloma cells. The addition of lenalidomide in preclinical studies can augment this response [22], and the combination of vaccine with lenalidomide strategy is currently under evaluation in both settings. Moreover, checkpoint inhibitor therapy can similarly augment response to vaccination [3], setting the stage for combination vaccine, lenalidomide, and checkpoint inhibitor clinical trials, with the goal of achieving central and effector memory cell autologous anti-myeloma immunity.

Finally, adoptive cellular therapies represent a fifth immune strategy, exemplified by CART cells. The strategy of genetically activating host T cells to target tumor specific antigens, expanding them *ex vivo*, and transfusing them back to the patient has already achieved remarkable responses in leukemias and lymphomas. In myeloma, the optimal antigens are not defined; BCMA, SLAMF-7, and CD19 are among those under evaluation. A single patient with high-risk relapsed myeloma refractory to all known therapies has recently achieved a molecular complete response after CD19 CART therapy [19]. As a further example of combination therapy, she is receiving lenalidomide to prevent T cell exhaustion.

Thus the second Achilles heal in patients with myeloma is immunosuppression, which can be overcome by these and other related strategies. The ability in particular to achieve memory cell immunity in patients against their own myeloma is very promising, given the ability of host immunity to potently, selectively, and adaptively target ongoing genomic evolution underlying myeloma progression.

4 Genomic Abnormalities

The third Achilles heal in myeloma is predicated upon genomic analyses [6, 32, 33, 36]. To date, profiling of myeloma genomics and epigenomics has revealed a very heterogeneous and complex baseline status, with many abnormalities and multiple clones even at diagnosis. Moreover, further genomic and epigenomic changes and clonal evolution underlie relapse of disease. Ongoing attempts are targeting abnormalities with targeted single or combination agents; however, the lack of predominant abnormalities in myeloma, coupled with the genomic instability and

evolution, represents a major obstacle to these approaches. However, genomic and epigenomic patient profiling analyses can identify those critical pathways which can then be targeted to abrogate aberrant biology.

The first example stems from our recent genomic study showing that a subset of patients with myeloma, leukemia, and lymphoma has decreased copy number and expression of YAP-1 [13]. In myeloma cells with constitutive genomic instability and DNA damage, a DNA damage response is initiated in which ABL-1 binds to nuclear YAP-1, thereby triggering p73-mediated apoptosis of damaged cells in a p53-independent process. Restoration of YAP-1 in vitro or in vivo can restore this apoptotic signaling and response. Importantly, YAP-1 expression is inhibited in these tumor cells by increased expression of STK4; and conversely, genetic depletion of STK4 can upregulate YAP-1 and related p73-mediated apoptosis. Efforts are ongoing at present to develop therapeutic STK4 inhibitors to treat this subset of patients.

A second example of a genomically-based Achilles heal is in those patient whose myeloma expresses very high levels of c-Myc [14]. In this patient subset, there are two processes that represent vulnerabilities to be targeted. First, there is a DNA damage response ongoing which can be targeted, i.e., with ATR inhibitors. Second, there is an abundance of reactive oxygen species, which can be further increased pharmacologically. We have shown that either inhibiting ATR or augmenting reactive oxygen species can trigger apoptosis in this subset of myeloma, and that the combination induces synergistic cytotoxicity.

These examples therefore utilize genomic studies to define critical pathways for therapeutic targeting.

5 Summary and Future Directions

There has been a paradigm shift in the treatment and outcome of myeloma based upon improved understanding of the biology of the myeloma cell in the host bone marrow microenvironment. Already increasing genomic and epigenomic understanding in myeloma has identified Achilles heals to target therapeutically. Importantly, multiple strategies for restoring host anti-myeloma immunity represent overcoming an additional Achilles heal in the host. Ultimately, combination targeted and immune therapies used early in the disease course offer the real potential for long-term disease-free survival and cure.

References

1. Bae J, Smith R, Daley J et al (2012) Myeloma-specific multiple peptides able to generate cytotoxic T lymphocytes: a potential therapeutic application in multiple myeloma and other plasma cell disorders. *Clin Cancer Res* 17:4850–4860
2. Bae J, Rao P, Voskertchian A et al (2015) A multipeptide of XBP-1, CD138, and CS1 peptides induces myeloma-specific cytotoxic T lymphocytes in T cells of smoldering myeloma patients. *Leukemia* 29:218–229

3. Bae J, Keskin D, Cowens K et al (in press) Lenalidomide polarizes Th1 specific anti-tumor response and expands XBP-1 antigen-specific central memory CD3 + CD8 + T cells against various solid tumors. *Leukemia*
4. Bianchi G, Richardson PR, Anderson KC (2014) Best treatment strategies in high-risk multiple myeloma: navigating a gray area. *J Clin Oncol* 32:2125–2132
5. Bianchi G, Richardson PG, Anderson KC (2015) Promising therapies in multiple myeloma. *Blood* 16:300–310
6. Bolli N, Avet-Loiseau H, Wedge DC et al (2014) Heterogeneity of somatic mutations, clonal architecture and genomic evolution in multiple myeloma. *Nat Commun* 5:2997
7. Chauhan D, Catley L, Li G et al (2005) A novel orally active proteasome inhibitor induces apoptosis in multiple myeloma cells with mechanisms distinct from Bortezomib. *Cancer Cell* 8:407–419
8. Chauhan D, Singh AV, Brahmandam M et al (2009) Functional interaction of plasmacytoid dendritic cells with multiple myeloma cells: a novel therapeutic target. *Cancer Cell* 16:309–323
9. Chauhan D, Singh A, Richardson P et al (2009) Combination of novel proteasome inhibitor NPI-0052 and lenalidomide trigger in vivo synergistic cytotoxicity in multiple myeloma. *Blood* 115:834–845
10. Chauhan D, Tian Z, Zhou B et al (2011) In vitro and in vivo selective antitumor activity of a novel orally bioavailable proteasome inhibitor MLN9708 against multiple myeloma cells. *Clin Cancer Res* 17:5311–5321
11. Chauhan D, Tian Z, Nicolson B et al (2012) A novel small molecule inhibitor of ubiquitin-specific protease-7 induces apoptosis in multiple myeloma cells and overcomes bortezomib resistance. *Cancer Cell* 22:345–358
12. Cottini F, Anderson KC (2015) Novel therapeutic targets in multiple myeloma. *Clin Adv Hematol Oncol* 13:236–248
13. Cottini F, Hideshima T, Xu C et al (2014) Rescue of YAP1 triggers DNA damage-induced apoptosis in hematological cancers. *Nat Med* 20:599–606
14. Cottini F, Hideshima T, Suzuki R et al (2015) Synthetic lethal approaches exploiting DNA damage in aggressive myeloma. *Cancer Discov* 5:972–87
15. Das DS, Ray A, Song Y et al (2015) Synergistic anti-myeloma activity of a proteasome inhibitor marizomib and immunomodulatory drug pomalidomide. *Br J Haematol* 171:798–812
16. de Weers M, Yu-Tzu Tai, van der Veer MS et al (2011) Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. *J Immunol* 186:1840–1848
17. Dimopoulos M, Jagannath S, Yoon S-Y et al (2013) Vantage 088: an international, multicenter, randomized double-blind study of vorinostat (MK-0683) or placebo in combination with bortezomib in patients with multiple myeloma. *Lancet Oncol* 14:1129–1140
18. Gandhi AK, Kang J, Havens CG et al (2014) Immunomodulatory agents lenalidomide and pomalidomide co-stimulate T cells by inducing degradation of T cell repressors Ikaros and Aiolos via modulation of the E3 ubiquitin ligase complex CRL4(CRBN.). *Br J Haematol* 164:811–821
19. Garfall AL, Maus MV, Hwang WT et al (2015) Chimeric antigen receptor T cells against CD19 for multiple myeloma. *N Engl J Med* 373:1040–1047
20. Gorgun G, Calabrese E, Soydan E et al (2010) Immunomodulatory effects of lenalidomide and pomalidomide on interaction of tumor and bone marrow accessory cells in multiple myeloma. *Blood* 116:3227–3237
21. Gorgun G, Whitehill G, Anderson JL et al (2012) Tumor promoting immune suppressive myeloid derived suppressor cells in multiple myeloma microenvironment. *Blood* 121:2975–2987
22. Gorgun G, Samur MK, Cowens KB et al (2015) Lenalidomide enhances immune checkpoint blockade induced immune response in multiple myeloma. *Clin Cancer Res* 21:4607–18

23. Hideshima T, Chauhan D, Shima Y et al (2000) Thalidomide and its analogues overcome drug resistance of human multiple myeloma cells to conventional therapy. *Blood* 96:2943–2950
24. Hideshima T, Richardson P, Chauhan D et al (2001) The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. *Cancer Res* 61:3071–3076
25. Hideshima T, Bradner J, Wong J et al (2005) Small molecule inhibition of proteasome and aggresome function induces synergistic anti-tumor activity in multiple myeloma. *Proc Natl Acad Sci* 102:8567–8572
26. Hideshima T, Mitsiades C, Tonon G et al (2007) Understanding multiple myeloma pathogenesis and the role of bone marrow microenvironment to identify new therapeutic targets. *Nat Rev Cancer* 7:585–598
27. Jiang H, Acharya C, An G et al (2016) SAR650984 directly induces multiple myeloma cell death via lysosomal-associated and apoptotic pathways, which is further enhanced by pomalidomide. *Leukemia* 30:399–408
28. Kawano Y, Moschetta M, Manier S et al (2015) Targeting the bone marrow microenvironment in multiple myeloma. *Immunol Rev* 263:160–172
29. Kronke J, Udeshi ND, Narla A et al (2014) Lenalidomide causes selective degradation of IKZF1 and IKZF3 in multiple myeloma cells. *Science* 343:301–305
30. Kumar SK, Bensinger WI, Zimmerman TM et al (2014) Phase I study of weekly dosing with the investigational oral proteasome inhibitor ixazomib in relapsed/refractory multiple myeloma. *Blood* 124:1047–1055
31. Laubach JP, Tai YT, Richardson PG, Anderson KC (2014) Daratumumab granted breakthrough drug status. *Expert Opin Investig Drugs* 23:445–452
32. Lichter DI, Danaee H, Pickard MD et al (2012) Sequence analysis of β -subunit genes of the 20S proteasome in patients with relapsed multiple myeloma treated with bortezomib or dexamethasone. *Blood* 120:4513–4516
33. Lohr JG, Stojanov P, Carter SL et al (2014) Widespread genetic heterogeneity in multiple myeloma: implications for targeted therapy. *Cancer Cell* 25:1–10
34. Lonial S, Dimopoulos Palumbo A et al (2015) Elotuzumab therapy for relapsed or refractory multiple myeloma. *N Engl J Med* 373:621–631
35. Lu G, Middleton RE, Sun H et al (2014) The myeloma drug lenalidomide promotes the cereblon-dependent destruction of Ikaros proteins. *Science* 343(6168):305–309
36. Rashid N, Sperling A, Bolli N, Wedge D, Van Loo P, Tai Y-T, Shamma M, Fulciniti M, Smur M, Richardson P, Magrangeas F, Minvielle S, Futreal P, Anderson K, Avet-Loiseau H, Campbell P, Parmigiani G, Munshi N (2014) Differential and limited expression of mutant alleles in multiple myeloma. *Blood* 124:3110–3117
37. Ray A, Das DS, Song Y, Richardson P, Chauhan D, Anderson KC (2015) Targeting PD1-PDL1 in immune checkpoint in plasmacytoid dendritic cell interactions with T cells, natural killer cells, and multiple myeloma cells. *Leukemia* 29: 1441–1444
38. Richardson PG, Weller E, Lonial S et al (2010) Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly-diagnosed multiple myeloma. *Blood* 116:679–686
39. Richardson PG, Moreau P, Laubach JP et al (2015) The investigational proteasome inhibitor ixazomib for the treatment of multiple myeloma. *Future Oncol* 11:1153–1168
40. Richardson PG, Jagannath S, Moreau P et al (2015) Elotuzumab in combination with lenalidomide and dexamethasone in patients with relapsed multiple myeloma: final results from the 1703 phase 1b/2, open-label, randomized study. *Lancet Oncol* 2:e516–27
41. Rosenblatt J, Vasir B, Uhl L et al (2011) Vaccination with DC/tumor fusion cells results in cellular and humoral anti-tumor immune responses in patients with multiple myeloma. *Blood* 117:393–402
42. Rosenblatt J, Avivi I, Vasir B et al (2013) Vaccination with dendritic cell/tumor fusions following autologous stem cell transplant induces immunologic and clinical responses in multiple myeloma patients. *Clin Cancer Res* 19:3640–3648

43. San Miguel JF, Richardson PG, Gunther A et al (2013) A Phase Ib study of panobinostat and bortezomib in relapsed or relapsed and refractory multiple myeloma. *J Clin Oncol* 31:3696–3703
44. Santo A, Hideshima T, Li-Jen Kung A et al (2012) Preclinical activity, pharmacodynamic and pharmacokinetic properties of a selective HDAC6 inhibitor, ACY-1215, in combination with bortezomib in multiple myeloma. *Blood* 119:2579–2589
45. Siegel DS, Martin T, Wang M et al (2012) A phase 2 study of single-agent carfilzomib in patients with relapsed and refractory multiple myeloma. *Blood* 120:2817–2825
46. Stewart AK, Rajkumar SV, Dimopoulos MA et al (2015) Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med* 372:142–152
47. Tai Y-T, Dillon M, Song W et al (2008) Anti-CS-1 humanized monoclonal antibody HuLuc63 inhibits myeloma cell adhesion and induces antibody-dependent cellular cytotoxicity in the bone marrow milieu. *Blood* 112:1329–1337
48. Ze Tian, D’Arcy P, Wang X et al (2014) A novel small molecule inhibitor of deubiquitylating enzyme USP14 and UCHL5 induces apoptosis in myeloma cells and overcomes bortezomib resistance. *Blood* 123:706–716
49. Vij R, Wang M, Kaufman JL et al (2012) An open-label, single-arm, phase 2 (PX-171-004) study of single-agent carfilzomib in bortezomib-naïve patients with relapsed and/or refractory multiple myeloma. *Blood* 119:5661–5670

Plasma Cell Dyscrasias

Roccaro, A.M.; Ghobrial, I.M. (Eds.)

2016, VI, 361 p. 9 illus., 7 illus. in color., Hardcover

ISBN: 978-3-319-40318-2