Published in final edited form as:
Hematology. 2012 April ; 17(0 1): S105–S108. doi:10.1179/102453312X13336169156131.

Novel therapeutics in multiple myeloma

A. Keith Stewart
Division of Hematology-Oncology, Mayo Clinic in Arizona, Scottsdale, AZ, USA

Abstract

Most myeloma patients still experience recurrent relapse and eventually become resistant and/or intolerant of effective agents such as corticosteroids, alkylating agents, immune modulators (lenalidomide and thalidomide) or proteasome inhibitors such as bortezomib. Once this happens average survivals are less than one year. Progress has been made for such patients, however, with the demonstration of clinical benefit of novel proteasome inhibitors (carfilzomib) and immune modulators (pomalidomide). Pomalidomide when used with dexamethasone has activity in 30–60% of patients depending on disease stage. Carfilzomib is an irreversible proteasome inhibitor with favorable toxicity profile (minimal neuropathy) and response rates of 17–54% depending on the disease stage treated. Novel targets are also being explored. Histone deacetylase inhibitors such as vorinostat and panobinostat are in phase II testing although results from a randomized trial combining vorinostat with bortezomib were disappointing. Other small molecules or monoclonal antibodies with novel targets such as kinase inhibitors(AKT, CDK5) and cell surface receptors (e.g. elotuzumab) are undergoing active investigation.

Keywords

Myeloma; Therapy; Carfilzomib; Vorinostat; Pomalidomide; Novel agents

Introduction

Much progress has been made in multiple myeloma (MM) therapy with dramatic improvements in survival in the past decade.[1] Unfortunately, most patients still experience recurrent relapse and eventually become resistant and/or intolerant of effective agents such as corticosteroids, alkylating agents, immune modulators (lenalidomide and thalidomide) or proteasome inhibitors such as bortezomib (BTZ). Once this happens, average survivals are less than 1 year.[2] This review will examine new therapeutic agents which are in clinical testing in relapsed patients with a view to describing their efficacy and toxicity. The review will cover not only new derivatives targeting known pathways but also therapies addressing novel targets. By way of background, over 200 new drugs have been shown to have efficacy in preclinical models but few drugs have survived the harsh spotlight of clinical experience.

Novel Immune Modulators (IMiDs)

Along with thalidomide and lenalidomide, the structurally related analog compound pomalidomide is the newest immunomodulatory drug in the clinic, and has single-agent activity in relapsed myeloma.[3] We and others have previously reported that pomalidomide and low-dose dexamethasone (pom/dex) is highly active in relapsed MM, with an overall

Correspondence to: A. K. Stewart, Division of Hematology-Oncology, Mayo Clinic in Arizona, 13400 East Shea Boulevard, Scottsdale, AZ, USA. stewart.keith@mayo.edu.

response rate in early relapse [partial response (PR) or better] of 63%.[4] Next, we treated a cohort of patients with lenalidomide refractory disease.[5] Among 34 patients enrolled, responses of ≥PR were seen in 31% of patients. The median time to response was 2 months and response duration was 9.1 months. In a more recent study, we have addressed dosing levels in two sequential phase II trials.[6] Our results show that the pomalidomide plus low-dose dexamethasone combination is significantly active in BTZ and lenalidomide refractory myeloma at two different dosing levels of pomalidomide (2 or 4 mg), but we did not observe any advantage with the higher dose.

Pomalidomide was given orally 2 or 4 mg daily with oral dexamethasone given 40 mg weekly. Thirty-five patients were enrolled in each cohort. Confirmed responses [≥ minor response (MR)] in the 2-mg cohort consisted of very good partial response in 5 (14%), PR in 4 (11%), and MR in 8 (23%) for an overall response rate of 49%. In the 4-mg cohort, confirmed responses (≥MR) consisted of complete response in 1 (3%), very good partial response in 3 (9%), PR in 6 (17%), and MR in 5 (14%) for an overall response rate of 43%. Overall survival at 6 months is 78% (95% confidence interval: 65–94) in the 2-mg cohort and 67% (95% confidence interval: 52–86) in the 4-mg cohort. Toxicity consisted primarily of myelosuppression with grade 3 or 4 neutropenia in 51% (2-mg cohort) and 66% (4-mg cohort). These data suggest no advantage for 4 mg over the 2 mg per day when administered on a 28-day schedule. Pomalidomide appears active and overcomes resistance in myeloma refractory to both lenalidomide and BTZ.

Novel Proteasome Inhibitors

The proteasome inhibitor, BTZ, is the first in its class to be approved for treatment of MM and mantle cell lymphoma. It is a boronic acid analog that is a covalent, slowly reversible inhibitor of the chymotrypsin-like activity of the proteasome. While demonstrating substantial activity in both newly diagnosed and relapsed myeloma, clinical use may be limited by resistance or dose-limiting toxicity, namely painful peripheral neuropathy. This has led to further investigation of additional proteasome inhibitor classes. More potent inhibitors of chymo-tryptic activity (e.g. CEP-18770, carfilzomib) can overcome BTZ resistance in preclinical and early clinical trials.[7–8] Marizonib (NPI-0052)[9,10] targets chymotryptic, tryptic-like, and caspase-like activities, and similarly as recently reported at the American Society of Hematology annual meeting shows early clinical efficacy with ~20% response rate when given twice weekly, although a novel central nervous system toxicity profile may be limiting." Oral derivatives of BTZ such as MLN9708[12] are now in trials and have shown some early clinical indicators of response in refractory patients.

The most advanced one of the second-generation proteasome inhibitors is carfilzomib (PR-171).[13] Carfilzomib is a novel second-generation proteasome inhibitor of the epoxyketone class that is structurally and mechanistically distinct from BTZ. It provides irreversible proteasome inhibition that leads to a more sustained response than seen with the reversible proteasome inhibitor, BTZ. Single-agent activity was observed in phase I testing.[8]

In a multicenter phase II trial, carfilzomib was administered at a dose of 20 mg/m^2 IV on a QDx2 consecutive day schedule for 3 weeks every 4 weeks in cycle one then at 27 mg/m^2 for up to 12 cycles in 257 patients with MM who had relapsed from at least two prior therapies and who were refractory to BTZ and exposed to IMiDs.[14] Clinical benefit response was 34%. PR was seen in 24% of patients with median duration of remission of 8.3 months and median overall survival of 15 months. Time to response was rapid, frequently occurring in the first cycle. Carfilzomib was generally well tolerated.[14,15] The most common reported adverse events were non-hematological and included fatigue and nausea. Worsening of hematologic parameters were largely grades 1 and 2. Grade 1 and 2 peripheral neuropathy

was already present at baseline in 78% of patients despite which exacerbation of peripheral neuropathy was rare and did not lead to dose reductions or discontinuation of the study.

In 110 BTZ-naive but relapsed patients, overall response rate was 54%.[16] Carfilzomib is now being studied in combination with lenalidomide and dexamethasone in newly diagnosed patients[17] and in a phase III trial in early relapse (unpublished data).

In newly diagnosed patients, this regimen can allow escalation of carfilzomib to 36 mg/m^2 dosing and produces a 100% response rate and 75% complete remission after eight cycles.

Histone Deacetylase Inhibitors

Histone acetylation modulates gene expression, cellular differentiation, and survival, and is regulated by the opposing activities of histone acetyltransferases and histone deacetylases (HDACs). Thus, HDAC inhibition could function as a master switch that could simultaneously affect multiple pathways critical for MM cells. Two HDACs have advanced to phase III testing. The first of these is vorinostat. As a single agent, vorinostat has limited activity[18] but seems to improve outcomes in BTZ refractory patients given the combination of BTZ and vorinostat.[19] A phase III clinical trial in 637 patients was then conducted comparing this combination to BTZ alone. Response rates were higher with the combination compared to BTZ alone (56 versus 41%), but duration of response was only minimally improved by a few weeks and overall survival was identical.[20] Furthermore, this came at the cost of increased toxicity with fatigue and gastrointestinal side effects being prominent. The second HDAC in phase III testing is panobinostat.[21] Again there are suggestions that panobinostat may have ability to overcome BTZ resistance[22] despite limited single-agent activity and a phase III trial is underway.[23] The bottom line is that the jury is still out on this class of agents.

Monoclonal Antibodies

A monoclonal antibody in myeloma would be of high value and many are being studied.[24] Potential surface antigen targets on MM cells include CD38, FCRH5, CS-1, CD40, CD56, CD138, and CD74. Preclinical studies have validated either humanized or murine Abs conjugated with toxin against these antigens. Their clinical effectiveness to date has however been limited. Anti-CSl (elotuzumab)[24] is perhaps most interesting to date although the antibody showed no response or only stable disease as a single agent. A surprising but encouraging result has been seen however when this antibody is combined with lenalidomide and dexametahsone with an 82% overall response rate in 73 patients in a phase II testing.[25] This antibody is now in phase III testing in combination with lenalidomdie and dexamethasone both in newly diagnosed and relapsed patients.

Targeted Therapies

To date targeted therapy approaches have been disappointing. Small molecules and antibodies targeting FGFR3 are being explored in phase II testing.[26] Other kinase targets have not, to date, proven to be of high value. Some promise in targeting AKT/PKB[27] or CDK5[28] has been observed and clinical trials are underway examining these two kinase targets.

Summary

A number of novel proteasome inhibitors are being studied in clinical trials. Carflllzomib is particularly active with favorable toxicity profile and is in advanced clinical testing. Pomalidomide will also likely join the therapeutic arsenal as an IMiD which can overcome

relapsed refractory disease. Beyond that numerous agents with novel targets including panobinostat, elotuzumab as well as AKT and CDK5 inhibitors have shown early clinical promise thus it seems likely that new agents will soon be available for patients.

References

1. Stewart AK, Richardson PG, San-Miguel JF. How I treat multiple myeloma in younger patients. Blood. 2009; 114:5436–5443. [PubMed: 19861683]
2. Kumar SK, Lee JH, Lahuerta JJ, Morgan G, Richardson PG, Crowley J, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. Leukemia. 2012; 26:149–157. [PubMed: 21799510]
3. Streetly MJ, Gyertson K, Daniel Y, Zeldis JB, Kazmi M, Schey SA. Alternate day pomalidomide retains anti-myeloma effect with reduced adverse events and evidence of *in vivo* immuno-modulation. Br J Haematol. 2008; 141:41–51. [PubMed: 18324965]
4. Lacy MQ, Hayman SR, Gertz MA, Dispenzieri A, Buadi F, Kumar S, et al. Pomalidomide (CC4047) plus low-dose dexamethasone as therapy for relapsed multiple myeloma. J Clin Oncol. 2009; 27:5008–5014. [PubMed: 19720894]
5. Lacy MQ, Hayman SR, Gertz MA, Short KD, Dispenzieri A, Kumar S, et al. Pomalidomide (CC4047) plus low dose dexamethasone (Pom/dex) is active and well tolerated in lenalidomide refractory multiple myeloma (MM). Leukemia. 2010; 24:1934–1939. [PubMed: 20827286]
6. Lacy MQ, Allred JB, Gertz MA, Hayman SR, Short KD, Buadi F, et al. Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: comparison of 2 dosing strategies in dual-refractory disease. Blood. 2011; 118:2970–2975. [PubMed: 21690557]
7. Piva R, Ruggeri B, Williams M, Costa G, Tamagno I, Ferrero D, et al. CEP-18770: a novel, orally active proteasome inhibitor with a tumor-selective pharmacologic profile competitive with bortezomib. Blood. 2008; 111:2765–2775. [PubMed: 18057228]
8. O'Connor OA, Stewart AK, Vallone M, Molineaux CJ, Kunkel LA, Gerecitano JF, et al. A phase 1 dose escalation study of the safety and pharmacokinetics of the novel proteasome inhibitor carfllzomib (PR-171) in patients with hematologic malignancies. Clin Cancer Res. 2009; 15:7085–7091. [PubMed: 19903785]
9. Richardson P, Hofmeister CC, Zimmerman TM, Chanan-Khan AA, Spear MA, Palladino MA, et al. Phase 1 clinical trial of NPI-0052, a novel proteasome inhibitor in patients with multiple myeloma. ASH Annual Meeting Abstracts. 2008; 112:2770.
10. Chauhan D, Hideshima T, Anderson KC. A novel proteasome inhibitor NPI-0052 as an anticancer therapy. Br J Cancer. 2006; 95:961–965. [PubMed: 17047643]
11. Richardson PG, Spencer A, Cannell P, Harrison SJ, Catley L, Underhill C, et al. Phase 1 clinical evaluation of twice-weekly Marizomib (NPI-0052), a novel proteasome inhibitor, in patients with relapsed/refractory multiple myeloma (MM). ASH Annual Meeting Abstracts. 2011; 118:302.
12. Lee EC, Fitzgerald M, Bannerman B, Donelan J, Bano K, Terkelsen J, et al. Antitumor activity of the investigational proteasome inhibitor MLN9708 in mouse models of B-cell and plasma cell malignancies. Clin Cancer Res. 2011; 17:7313–7323. [PubMed: 21903769]
13. Khan ML, Stewart AK. Carfllzomib: a novel second-generation proteasome inhibitor. Future Oncol. 2011; 7:607–612. [PubMed: 21568676]
14. Wang L, Siegel DS, Jakubowiak AJ, Wong AF, Dixon S, Rebau TE, et al. The speed of response to single-agent carfllzomib in patients with relapsed and/or refractory multiple myeloma: an exploratory analysis of results from 2 multicenter phase 2 clinical trials. ASH Annual Meeting Abstracts. 2011; 118:3969.
15. Singhal S, Siegel DS, Martin T, Vij R, Wang L, Jakubowiak AJ, et al. Integrated safety from phase 2 studies of mono-therapy carfllzomib in patients with relapsed and refractory multiple myeloma (MM): an updated analysis. ASH Annual Meeting Abstracts. 2011; 118:1876.
16. Vij R, Kaufman JL, Jakubowiak AJ, Wang M, Jagannath S, Kukreti V, et al. Final results from the bortezomib-naive group of PX-171-004, a phase 2 study of single-agent carfllzomib in patients with relapsed and/or refractory MM. ASH Annual Meeting Abstracts. 2011; 118:813.

17. Jakubowiak AJ, Dytfeld D, Jagannath S, Vesole DH, Anderson TB, Nordgren BK, et al. Final results of a frontline phase 1/2 study of carfllzomib, lenalidomide, and low-dose dexamethasone (CRd) in multiple myeloma (MM). ASH Annual Meeting Abstracts. 2011; 118:631.

18. Richardson PG, Mitsiades CS, Colson K, Reilly E, McBride L, Chiao J, et al. Final results of a phase I trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) in patients with advanced multiple myeloma. ASH Annual Meeting Abstracts. 2007; 110:1179.

19. Weber D, Badros AZ, Jagannath S, Siegel D, Richon V, Rizvi S, et al. Vorinostat plus bortezomib for the treatment of relapsed/refractory multiple myeloma: early clinical experience. ASH Annual Meeting Abstracts. 2008; 112:871.

20. Dimopoulos MA, Jagannath S, Yoon S-S, Siegel DS, Lonial S, Hajek R, et al. Vantage 088: vorinostat in combination with bortezomib in patients with relapsed/refractory multiple myeloma: results of a global, randomized phase 3 trial. ASH Annual Meeting Abstracts. 2011; 118:811.

21. Siegel D, Sezer O, San MJF, Mateos MV, Prosser I, Cavo M, et al. A phase IB, multicenter, open-label, dose-escalation study of oral Panobinostat (LBH589) and I.V. bortezomib in patients with relapsed multiple myeloma. ASH Annual Meeting Abstracts. 2008; 112:2781.

22. Richardson PG, Alsina M, Weber DM, Coutre SE, Lonial S, Gasparetto C, et al. Phase II study of the pan-deacetylase inhibitor panobinostat in combination with bortezomib and dexamethasone in relapsed and bortezomib-refractory multiple myeloma (PANORAMA 2). ASH Annual Meeting Abstracts. 2011; 118:814.

23. San-Miguel JF, de Moraes Hungria VT, Yoon S-S, Wiktor-Jedrzejczak W, Elghandour A, Siritanaratkul N, et al. Update on a phase III study of panobinostat with bortezomib and dexamethasone in patients with relapsed multiple myeloma: PANORAMA 1. ASH Annual Meeting Abstracts. 2011; 118:3976.

24. Anderson KC. The 39th David A. Karnofsky Lecture: bench-to-bedside translation of targeted therapies in multiple myeloma. J Clin Oncol. 2012; 30(4):445–452. [PubMed: 22215754]

25. Lonial S, Jakubowiak AJ, Jagannath S, Raab MS, Facon T, Vij R, et al. A phase 2 study of elotuzumab in combination with lenalidomide and low-dose dexamethasone in patients with relapsed/refractory multiple myeloma. ASH Annual Meeting Abstracts. 2011; 118:303.

26. Trudel S, Li ZH, Wei E, Wiesmann M, Chang H, Chen C, et al. CHIR-258, a novel, multitargeted tyrosine kinase inhibitor for the potential treatment of t(4;14) multiple myeloma. Blood. 2005; 105:2941–2948. [PubMed: 15598814]

27. Spencer A, Yoon S-S, Harrison SJ, Morris S, Smith D, Freedman SJ, et al. Novel AKT inhibitor GSK2110183 shows favorable safety, pharmacokinetics, and clinical activity in multiple myeloma. Preliminary results from a phase I first-time-in-human study. ASH Annual Meeting Abstracts. 2011; 118:1856.

28. Tiedemann RE, Zhu YX, Schmidt J, Yin HW, Shi C-X, Que Q, et al. Kinome-wide RNAi studies in human multiple myeloma identify vulnerable kinase targets, including a lymphoid restricted kinase, GRK6. Blood. 2010; l15:1594–1604. [PubMed: 19996089]