CURRENT DEVELOPMENTS AND PERSPECTIVES IN MULTIPLE MYELOMA

***Michel Delforge,[1] Stefan Knop,[2] Mohamad Mohty[3]**

1. Department of Hematology, University Hospital Leuven, Leuven, Belgium
2. Schwerpunkt Hämatologie / Onkologie, Medizinische Klinik und Poliklinik II der Universität, Würzburg, Germany
3. Hôpital Saint-Antoine, University UPMC, INSERM, Hematology Department, Paris, France
**Correspondence to michel.delforge@uzleuven.be*

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ABSTRACT

In the last decades, advances in the therapeutic management of multiple myeloma (MM) with new drug armamentarium and strategies have significantly improved the outcome and survival of newly diagnosed and relapsed patients. However, the continuing challenges physicians are facing within specific clinical settings and patient subpopulations, whose prognosis with current strategies is extremely poor, call for a paradigm change. New immunomodulators, proteasome inhibitors, histone deacetylase inhibitors, and monoclonal antibodies are being explored to improve first-line outcomes so that a smaller proportion of patients relapse early or fail to respond to induction treatment. Moreover, recent advances and clinical evidence with novel therapies seem to provide patients with relapsed or refractory MM additional survival benefits. Improving clinical outcomes and refining standard of care should help clinicians reduce the burden of multiple and toxic therapy; quality of life (QoL) should be at the core of MM management. Patient selection and stratification needs to be reinforced with the help of comprehensive knowledge on conventional risk factors, and supplemented by molecular pathways in the near future in order to provide tailored options and strategies to patients, including the use of monoclonal antibodies. Numerous drugs are on the horizon and the next few years should witness marked improvements in survival, QoL, and safety of MM management.

Keywords: Multiple myeloma, salvage therapy, targeted therapy, immunomodulators.

INTRODUCTION

Multiple myeloma (MM), also known as Kahler's disease, is an incurable hematological malignancy characterised by the neoplastic proliferation of plasma cells which infiltrate and accumulate in the bone marrow while producing monoclonal immunoglobulins (Igs).[1] The abnormal development of malignant cells in the bone marrow interferes with hematopoiesis and causes considerable bone damage such as osteolytic lesions, osteopaenia, hypercalcaemia, and fractures. In addition to bone pain, the patient can also suffer from anaemia, hypercalcaemia, renal failure, infections, and neurological symptoms.[1]

MM is the second most frequent blood cancer after non-Hodgkin's lymphoma, accounting for 1-2% of all new cancer cases and 10% of hematological malignancies.[2-4] The mean age at diagnosis is 65 years as more than half of newly-diagnosed patients are aged 65 and over, and only a very small proportion of patients are 40 or younger.[5,6] The incidence for MM appears to depend on

ethnicity, with a 2-3-fold higher incidence in Africans and African Americans when compared to Caucasian populations.[7,8] MM accounts for about 2% of all cancer mortality.[9]

The diagnosis is primarily established by the presence of a monoclonal protein in the serum (malignant plasma cells mainly produce IgG, IgA or Ig light chains), the presence of monoclonal light chains (Bence Jones proteinuria) in urine,[10,11] excess clonal bone marrow plasma cells (>10%), and organ impairment.[6,12,13]

The development of novel agents and clinical evidence on combinations have markedly improved the clinical outcomes and overall survival (OS) of MM patients. Over the last decade, median survival has improved from 4-6 years in newly diagnosed young patients,[14-16] while the rates of long-term survival (at 5 and 10 years) in patients aged 50 or younger have increased by 12% and 17%, respectively.[17]

However, the prognosis of MM is still dismal in general and many unmet needs remain unaddressed, as physicians are faced with some challenging clinical settings. This review aims to summarise the current developments and future perspectives of MM management, in which the main objectives are to improve long-term survival with acceptable risk to benefit ratios.

CONTEXT AND CURRENT STANDARDS OF CARE

Management of Newly Diagnosed Multiple Myeloma

The main objective of MM management is to obtain the best possible response, and to maintain it, with acceptable toxicity. Over the last few decades, the OS has been significantly improved by high-dose chemotherapy (HDT) followed by autologous stem-cell transplantation (ASCT), which is the current standard of care (SoC) in medically fit patients aged up to 65-70 years with adequate renal function.[18]

This treatment strategy, when implemented on eligible patients, can yield extended survival and is, therefore, the current SoC for newly diagnosed MM.[19] Indeed, patients achieving a complete response (CR) or a near complete response (nCR) display considerably improved outcomes when compared to those who only achieve a partial response (PR).[20] In a study from the Spanish PETHEMA group,[20] 35% of patients who achieved CR following HDT plus ASCT appeared to benefit from a functional cure. CR in MM was found to be correlated with long-term progression-free survival (PFS) and OS, even in elderly patients.[21] Conversely, Hoering et al.[22] demonstrated that failure to achieve CR and even an early loss of CR is associated with inferior survival, highlighting the importance of achievement of sustained CR.

Overall response rates (ORR) and duration of response were also considerably improved upon the development of novel agents, such as immunomodulatory compounds (thalidomide, lenalidomide) and proteasome inhibitors (bortezomib [BTZ]).[23-29] Combination therapy seems to provide higher ORR and CR than single agent therapy; the most widely used front-line combinations for induction before ASCT are as follows: thalidomide, BTZ, and dexamethasone (VTD); cyclophosphamide, BTZ, and dexamethasone (CyBorD or VCD).[30]

For non-transplant candidates, combination therapies include BTZ, melphalan, and prednisone (VMP) or melphalan, prednisone, and thalidomide (MPT).[31,32] VMP plus thalidomide induction followed by maintenance therapy with BTZ plus thalidomide seems to provide PFS and OS benefits in this patient subpopulation.[33]

Continuous treatment with lenalidomide plus dexamethasone can provide additional survival outcomes in non-transplant candidates. However, longer follow-up is still needed.[34]

The choice of chemotherapy is adapted to the patient's characteristics, patient's choice, and the severity of the disease. Over the course of anti-myeloma therapy, patients should be closely monitored for treatment response, infections, and other treatment-related adverse events, as well as for MM complications.

After ASCT, once an initial response is achieved, consolidation therapy with BTZ or a BTZ-based regimen may be performed in order to consolidate ASCT benefits and result in longer time to progression (TTP) and higher OS (in contrast with maintenance therapy, which is defined by the prolonged administration of low-dose chemotherapy to prevent disease progression).[35,36] Longer progression time and OS have also been

observed with lenalidomide maintenance,[35,37] while short-term consolidation therapy with VTD has been reported to improve PFS after tandem ASCT, but not OS.[25] As of yet, a sequential approach has not been explored (i.e. continuous single agent lenalidomide following single agent BTZ).

Management of Relapsed or Refractory Multiple Myeloma

Nearly all patients with MM will eventually relapse from first-line therapy and experience relapsing or refractory MM (RRMM). Initial or emerging drug resistance is a hallmark of the disease and represents a significant challenge in MM management, as they hinder the efficacy of most agents.

Refractory or end-stage myeloma is associated with a poor prognosis, with an average survival of less than a year, and represents a great challenge to physicians.[38,39] Relapsed MM refers to progressive disease in which at least a PR was previously achieved following first-line treatment or salvage therapy, while refractory MM indicates progressive disease when the patient is either unresponsive initially (primary refractory MM) or following treatment (within the last 60 days).[40]

There is no SoC or optimal choice for RRMM, and therapeutic options must be selected according to initial therapy, TTP, and the patient's condition and quality of life (QoL), while balancing the benefit-to-risk ratio for each case. Retreatment with the initial regimen remains a possibility, as well as switching to other agents. Moreover, a second ASCT as salvage therapy can be an option for patients achieving a good response after their initial ASCT. It should be offered to the patient whenever possible.[41,42] By contrast, a repeat or tandem ASCT, performed within 3-6 months, is a first-line therapeutic option.[41]

Chemotherapy with thalidomide, lenalidomide, or BTZ was demonstrated to be effective in second-line therapy, and prolongs OS in RRMM patients.[18,43,44] Indeed, thalidomide is associated with second-line response rates of 25-35%; these are higher when used in combination with dexamethasone and cyclophosphamide or with conventional chemotherapy, although prolonged exposure to thalidomide is inevitably associated with peripheral neuropathy in the majority of patients.[45-47] One interesting feature of thalidomide is that it does not warrant usual dose adjustments in patients with renal impairment, including patients on dialysis.[48,49]

Lenalidomide, approved in 2006 by the FDA as second-line therapy, yields good ORR (61%) and low toxicity when associated with dexamethasone.[50,51] Celgene has recently submitted an application to the FDA and the EMA for approval of lenalidomide with weekly dexamethasone as therapy for newly diagnosed MM.

Finally, BTZ is a proteasome inhibitor approved as a second-line option since 2008. It is highly effective in RRMM, particularly when combined with other agents.[52-60] Similarly to thalidomide, BTZ does not require dose adjustments in patients with renal impairment.[61,62] Nevertheless, its clinical applicability can be complicated by peripheral neuropathy, although this side-effect can be significantly reduced by subcutaneous administration of bortezomib.

Nonmyeloablative allogeneic stem-cell transplant (allo-SCT) remains debatable in RRMM despite the advantages of the infusion of tumour-free stem cells with a possible graft-versus-lymphoma effect. In a European study on 413 RRMM patients, the OS was 24.7 months for a median PFS of 9.6 months, and a 5-year survival rate of about 30%.[63]

According to the type of transplant, non-relapse mortality varies between 10% and 30%.[38] In relapsed MM, allo-SCT should only be considered for high-risk selected patients with a first treatment-responsive relapse and, at present, it is not recommended outside of clinical trials.[64]

LIMITATIONS OF CURRENT THERAPEUTIC OPTIONS

About 30% of patients will develop renal insufficiency over the course of the disease, and 20% will present renal failure.[65,66] The latter subpopulation is frequently excluded from aggressive strategies and HDT prior to ASCT (as being at higher risk of disease and treatment-related complications), which consequently lowers their prognosis. Novel agents such as BTZ can successfully restore renal function by relieving the MM burden in a proportion of patients, but early detection of renal impairment and prevention are essential to avoid complications.

In addition to being more sensitive to renal impairment, elderly patients over the age of

65 often present concurrent diseases, which exclude them from ASCT eligibility criteria. These patients have a lower physical reserve and are more prone to treatment-related side-effects and toxicities. While standard therapy in this clinical setting used to be melphalan plus prednisone for several decades, the addition of either BTZ[67-69] or thalidomide[30,70] has demonstrated additional benefits in terms of response, PFS, and OS.[71]

Moreover, chemotherapy-related adverse events are challenging and affect health-related QoL; BTZ and thalidomide can induce peripheral neuropathies, while thalidomide and lenalidomide can be involved in the development of deep vein thrombosis and pulmonary embolism.[72] Overall, there still remain patient subpopulations and challenging clinical settings which need to be addressed, and whose prognosis with current strategies is extremely poor. Immunotherapeutic approaches could be one of the emerging and promising frameworks with which to close the gap and provide longer OS and PFS to these patients.

RECENT ADVANCES AND NOVEL THERAPIES

Novel therapies are being explored to improve first-line outcomes so that a smaller proportion of patients relapse or develop refractory disease. They also seem to provide RRMM patients with additional survival benefits (Table 1).

Immunomodulators

Pomalidomide

Pomalidomide is a structural analogue of thalidomide and lenalidomide that was approved by the FDA in 2013 for patients who underwent at least two prior lines of treatment, with disease progression occurring in the first 60 days of the last therapy course. Monotherapy with pomalidomide has demonstrated efficacy in RRMM by overcoming drug resistance encountered with lenalidomide and BTZ.[73-77] When associated with low doses of dexamethasone, the response rates increase and range from 47-63%.[75,78,79]

These results were confirmed by the recent results of a Phase III trial with patients treated with pomalidomide plus low-dose dexamethasone (versus high-dose dexamethasone). The OR was of 32% (versus 11%), with 1% of CR (versus 0%), 6% of very good PR (versus 1%), and 25% of PR (versus 10%), for a median duration of response of 7.5 months (versus 5.1 months).[80] An extension study is currently ongoing to evaluate the pomalidomide monotherapy in subjects who discontinued treatment with high-dose dexamethasone due to disease progression.[81]

This novel immunomodulator has a different and improved safety profile when compared to thalidomide. Indeed, pomalidomide-related peripheral neuropathies are rare, but the most common adverse event is myelosuppression.[44] Pomalidomide can be combined with several other agents including proteasome inhibitors. As an example, updated Phase II results for the combination of pomalidomide plus carfilzomib and dexamethasone were recently presented. In heavily pre-treated patients with RRMM the OR was 70%, with 27% very good PRs, for a median PFS of 9.6 months.[82]

Proteasome Inhibitors

Carfilzomib

Carfilzomib (PR-171) is a novel proteasome inhibitor approved by the FDA in 2012 for patients who have undergone at least two prior lines of treatment with disease progression occurring in the first 60 days of the last therapy course. This approval was a consequence of the very promising results of a Phase II clinical trial.[83] Indeed, carfilzomib has been shown to provide clinically meaningful responses, even in heavily pre-treated and BTZ-refractory patients with RRMM: the ORR was 23.7% with a median OS of 15.6 months for a median duration of response of 7.8 months.

A Phase III clinical trial is currently ongoing (namely the ASPIRE trial)[84] and evaluates carfilzomib plus lenalidomide and dexamethasone versus lenalidomide plus dexamethasone. Another ongoing Phase III study, the FOCUS study,[85] is aimed at comparing carfilzomib with the best supportive care in MM patients who no longer respond to treatment. Enrolment is complete and early results for both studies are expected later in 2014.

Two other clinical trials of carfilzomib are currently recruiting participants: the ENDEAVOR Phase III study[86] will evaluate carfilzomib plus dexamethasone against BTZ plus dexamethasone in patients with MM whose disease has relapsed after at least one, but not more than three prior therapeutic regimens; the CLARION study[87] aims to compare carfilzomib plus melphalan

and prednisone versus BTZ plus melphalan and prednisone in first-line therapy.

Marizomib

In February 2014, the FDA granted the Orphan Drug designation to marizomib (NPI-0052) for the treatment of MM following the early results of four Phase I/II studies.[88-91] A Phase I/II study is currently ongoing in highly refractory MM patients, including those presenting with carfilzomib resistance, in combination with dexamethasone.[92] Another Phase I/II study is evaluating marizomib in combination with pomalidomide and dexamethasone in RRMM, including patients who are resistant to carfilzomib.[80,91,93]

Table 1: Recent findings and future perspectives in MM research.

Class	Compound	Study Type/Name	Clinical setting	Treatment arms	Main findings
Immuno-modulators	**Pomalidomide**	Phase II[71] NCT01464034	Heavily pre-treated pts with RRMM	POM + CFZ + DEX	• OR: 70%, with 27% very good PRs, 36% of PRs • Median PFS: 9.6 months
		Phase III - MM-003; NIMBUS[69] NCT01311687	RRMM	POM + low-dose DEX vs. high-dose DEX alone	• OR: 32% (vs. 11%), with 1% of CRs (vs. 0%), 6% of very good PRs (vs. 1%), and 25% of PRs (vs. 10%) • Median duration of response: 7.5 months (vs. 5.1)
		Phase III (NIMBUS extension study)[70] NCT01324947	Pts who discontinued high-dose DEX (disease progression)	POM monotherapy	• Ongoing
Proteasome inhibitors	**Carfilzomib (PR-171)**	Phase II - PX-171-003-A[172] NCT00511238	Heavily pre-treated and BTZ-refractory pts with RRMM	CFZ monotherapy	• ORR: 23.7% • Median OS: 15.6 months • Median duration of response: 7.8 months
		Phase III - ASPIRE[73] NCT01080391	RRMM	CFZ + LEN + DEX vs. LEN + DEX	• Ongoing
		Phase III - FOCUS[74] NCT01302392	MM pts who no longer respond to treatment	CFZ vs. BSC	• Ongoing
		Phase III – ENDEAVOR[75] NCT01568866	Pts relapsing after 1-3 therapeutic regimens	CFZ + DEX vs. BTZ + DEX	• Ongoing
		CLARION[76] NCT01818752	Newly diagnosed MM	CFZ + MEL + P vs. BTZ + MEL + P	• Ongoing
	Marizomib (NPI-0052)	Phase I/II[81] NCT00461045			• Ongoing
		Phase I/II[82] NCT02103335	Highly refractory MM pts, including CFZ resistance	MAR + POM + DEX	• Ongoing

Table 1 continued.

Class	Compound	Study Type/Name	Clinical setting	Treatment arms	Main findings
Proteasome inhibitors	**Ixazomib (MLN9708-MLN 2238)**	Phase I/II[87] NCT01383928	First-line therapy of newly diagnosed MM	IXA + LEN + DEX	• 95% of responses (21% stringent CRs, 5% CRs, 11% nCRs, 38% very good PRs, and 20% PRs) • Median duration of response of 14 months
	Oprozomib (ONX0912)	Phase Ib/II[88] NCT01832727	RRMM	OPZ + DEX	• Ongoing
Histone deacetylase inhibitors	**Panobinostat**	Phase III - PANORAMA-1[91,92] NCT01023308	RRMM	PAN or placebo + BTZ + DEX	• PAN significantly extended PFS • Full results are still being evaluated
	Panobinostat	Phase II -PANORAMA-2[91] NCT01083602	Relapsed and BTZ-refractory MM	PAN + BTZ + DEX	• Ongoing
	Vorinostat (MK-0683	Phase I/II[93,94] NCT01394354	RRMM	VOR + BTZ + DOX + DEX	• Interim analysis: the ORR was of 65%, for a clinical benefit rate of 89%
	Rocilinostat (ACY-1215)	Phase Ib[95] NCT01583283	RRMM	ROC + LEN + DEX	• 100% of responses, 69% achieved a PR or better (6% CR, 19% very good PRs, 44% PRs)
Monoclonal antibodies	**Elotuzumab**	Phase III - ELOQUENT-1[97] NCT01335399	Newly diagnosed, previously untreated MM	ELO + LEN + DEX	• Ongoing
		Phase III - ELOQUENT-2[98] NCT01239797	RRMM	ELO + LEN + DEX	• Ongoing
	Daratumumab	Phase I/II[99] NCT00574288	RRMM	DAR	• Ongoing
		Phase I/II[100] NCT01615029	RRMM	DAR + LEN + DEX	• Ongoing
		Phase III[101]	RRMM	DAR + BTZ + DEX vs. BTZ + DEX alone	• Ongoing
	SAR650984	Phase I[102] NCT01084252	CD38+ hematological malignancies	Dose-escalation study	• SAR650984 shown encouraging single-agent activity in pts with heavily pretreated RRMM

BSC: best supportive care; BTZ: bortezomib; CFZ: carfilzomib; CR: complete response; DAR: daratumumab; DEX: dexamethasone; DOX: doxorubicin; ELO: elotuzumab; IND: indatuximab; IXA: ixazomib; LEN: lenalidomide; MAR: marizomib; MEL: melphalan; MM: multiple myeloma; nCR: near complete response; OPZ: oprozomib; OR: overall response; ORR: overall response rate; P: prednisone; PAN: panobinostat; PFS: progression-free survival; POM: pomalidomide; PR: partial response; pts: patients; ROC: rocilinostat; RRMM: relapsed or refractory multiple myeloma; VOR: vorinostat.

Preliminary reported adverse events include fatigue, nausea, vomiting, dizziness, weight loss, and shortness of breath, but so far no peripheral neuropathy, anaemia or thrombocytopaenia were observed.[94]

Ixazomib

Ixazomib (MLN9708) is the first oral proteasome inhibitor[95] and has demonstrated a more favourable pharmacokinetic and pharmacodynamic profile when compared with BTZ in pre-clinical studies.[96] In a Phase I/II study of ixazomib in combination with lenalidomide and dexamethasone for first-line therapy of newly diagnosed MM,[97] 95% of the 56 patients achieved a response (21% of stringent CR, 5% of CR, 11% of nCR, 38% of very good PRs, and 20% of PRs) for a median duration of response of 14 months. These results are very encouraging, as observed in similar studies for carfilzomib plus lenalidomide and dexamethasone.

Oprozomib

Oprozomib (ONX0912) is a newly formulated proteasome inhibitor which is an analogue to carfilzomib.[98] It is presently being developed as an oral therapy in a Phase Ib/II study.[99] The optimal administration (2/7 versus 5/14 days) still needs to be determined as the maximum tolerated dose. Gastrointestinal toxicities seem to be the most challenging adverse effects.

Histone Deacetylase Inhibitors

New histone deacetylase inhibitors are under evaluation in MM. Phase I results have shown a very favourable safety profile but their efficacy as single agents is moderate. Phase II clinical trials have established promising results as combination therapies with BTZ and dexamethasone.[100]

Panobinostat

Recent results from a Phase III clinical trial (PANORAMA-1)[101] investigating panobinostat in combination with BTZ and dexamethasone showed that this new combination significantly extended PFS in RRMM when compared with BTZ plus dexamethasone alone. While these results represent a high therapeutic potential, full results from this study are still being evaluated. Additionally, a Phase II study (PANORAMA-2) is currently ongoing to assess the efficacy of panobinostat in patients with relapsed and BTZ-refractory MM.[102] In June 2014, Novartis submitted an application to the FDA for the approval of panobinostat, and the drug was granted priority review.[103]

Vorinostat

Whilst the results of the combination of vorinostat plus BTZ were rather disappointing with a PFS benefit of only 1 month,[104] preliminary results of a Phase I/II study on vorinostat associated with BTZ, doxorubicin, and dexamethasone were recently presented at the 2013 American Society for Hematology (ASH) meeting. A response was observed in 65% of patients. 22% of patients experienced severe adverse events; the most common reported Grade 3/4 adverse events were thrombocytopaenia, neutropaenia, and anaemia.[104,105]

Rocilinostat

This novel agent was assessed in a Phase Ib study in combination with lenalidomide and dexamethasone for RRMM. Early results were reported at the 2013 ASH meeting:[106] 100% of patients experienced a response, with 69% achieving a PR or better (6% CR, 19% very good PRs, 44% PRs). Overall, rocilinostat was well tolerated.

Monoclonal Antibodies (mAbs)

Elotuzumab

mAb therapy in MM is a very promising perspective. Elotuzumab as a single agent shows limited efficacy, but good results were achieved in combination with lenalidomide and low-dose dexamethasone.[107] Two Phase III clinical trials (ELOQUENT-1108 and ELOQUENT-2109) are currently ongoing or recruiting participants to evaluate elotuzumab plus lenalidomide and dexamethasone for newly-diagnosed MM or RRMM, respectively.

Daratumumab

Daratumumab, a very promising anti-CD38 antibody, was granted 'breakthrough therapy designation' from the US FDA for the treatment of patients with MM who have received at least three prior lines of therapy. Daratumumab is currently being evaluated in two Phase I/II studies on RRMM,[110,111] either as a single-agent or in combination with lenalidomide and dexamethasone. Additionally, a Phase III study on daratumumab in combination with BTZ and dexamethasone versus BTZ and dexamethasone alone in RRMM was recently announced.[112] Daratumumab's sponsor has

also announced a high-priority Phase III registration trial of lenalidomide plus dexamethasone versus lenalidomide plus dexamethasone and daratumumab in RRMM.[113]

Other mAbs

Other mAbs such as SAR650984 and indatuximab have displayed impressive single-agent activity in MM and are currently being evaluated in several phases of the disease. SAR650984 was recently evaluated in a Phase I/II study and demonstrated encouraging single-agent activity in heavily pre-treated RRMM patients.[114] Indatuximab is part of a novel approach, an antibody-drug conjugate, where it is combined to the cytotoxic agent DM4. Early results are very encouraging.[115]

Other Emerging Therapies

Other emerging agents for the treatment of MM include filanesib (ARRY-520),[116] a kinesin spindle protein inhibitor, and the Akt inhibitor afuresertib (PKB115125).[117] Bendamustine, an older alkylating agent also continues to be investigated in MM.[118,119]

CONCLUSIONS

Advances in the therapeutic management of MM with new strategies and a developed armamentarium have significantly improved outcomes and extended survival in RRMM patients. However, the continuing challenges within specific clinical settings and patient subpopulations, whose prognosis with current strategies is extremely poor, call for a paradigm change.

The development of new combination strategies and novel therapies is crucial to improve the clinical outcome and to overcome resistance in MM. This should help clinicians to reduce the burden of multiple and toxic therapies, as QoL should be at the core of MM management. Patient selection and stratification need to be reinforced with the help of comprehensive knowledge on molecular pathways, in order to provide tailored options in therapeutic strategies. Numerous drugs are on the horizon and the next few years should witness marked improvements in terms of OS, PFS, QoL, and safety. As of yet, predictive biomarkers as guidance for treatment are largely lacking, making the approach to patients still an empirical one.

REFERENCES

1. Raab MS et al. Multiple myeloma. Lancet. 2009;374(9686):324-39.
2. Phekoo KJ et al. A population study to define the incidence and survival of multiple myeloma in a National Health Service Region in UK. Br J Haematol. 2004;127(3):299-304.
3. Smith A et al. Incidence of haematological malignancy by sub-type: a report from the Haematological Malignancy Research Network. Br J Cancer. 2011;105(11):1684-92.
4. Sant M et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood. 2010;116(19):3724-34.
5. Blade J, Kyle RA. Multiple myeloma in young patients: clinical presentation and treatment approach. Leuk Lymphoma. 1998;30(5-6):493-501.
6. Kyle RA et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clinic Proc. 2003;78(1):21-33.
7. Shirley MH et al. Incidence of haematological malignancies by ethnic group in England, 2001-7. Br J Haematol. 2013;163(4):465-77.
8. Waxman AJ et al. Racial disparities in incidence and outcome in multiple myeloma: a population-based study. Blood. 2010;116(25):5501-6.
9. American Cancer Society. Cancer facts & figures 2013. Atlanta, Ga: American Cancer Society; 2013.
10. Végh Z et al. Monoclonal free light chains in urine and their significance in clinical diagnostics: are they really tumor markers? J Clin Lab Anal. 1990;4(6): 443-8.
11. Rajkumar SV, Kyle RA. Multiple myeloma: diagnosis and treatment. Mayo Clin Proc. 2005;80(10):1371-82.
12. Smith A et al. Guidelines on the diagnosis and management of multiple myeloma 2005. Br J Haematol. 2006;132(4):410-51.
13. International Myeloma Working G. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol. 2003;121(5):749-57.
14. Kumar SK et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood. 2008;111(5):2516-20.
15. Kumar SK et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leuk. 2014;28(5):1122-8.
16. Turesson I et al. Patterns of improved survival in patients with multiple myeloma in the twenty-first century: a population-based study. J Clin Oncol. 2010;28(5): 830-4.
17. Brenner H et al. Recent major improvement in long-term survival of younger patients with multiple myeloma. Blood. 2008;111(5):2521-6.
18. Attal M et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. N Engl J Med. 1996;335(2):91-7.
19. Roussel M et al. Firstline treatment and maintenance in newly diagnosed multiple myeloma patients. Recent Results Cancer Res. 2011;183:189-206.
20. Martinez-Lopez J et al. Long-term prognostic significance of response in multiple myeloma after stem cell transplantation. Blood. 2011;118(3): 529-34.
21. Gay F et al. Complete response correlates with long-term progression-free and overall survival in elderly myeloma treated with novel agents: analysis of 1175 patients. Blood. 2011;117(11):3025-31.

22. Hoering A et al. Complete remission in multiple myeloma examined as time-dependent variable in terms of both onset and duration in total therapy protocols. Blood. 2009;114(7):1299-305.

23. Harousseau JL et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. J Clin Oncol. 2010;28(30):4621-9.

24. Lokhorst HM et al. A randomized phase 3 study on the effect of thalidomide combined with adriamycin, dexamethasone, and high-dose melphalan, followed by thalidomide maintenance in patients with multiple myeloma. Blood. 2010;115(6):1113-20.

25. Cavo M et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. Lancet. 2010;376(9758):2075-85.

26. Rajkumar SV et al. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol. 2006;24(3):431-6.

27. Lokhorst HM et al. Thalidomide in induction treatment increases the very good partial response rate before and after high-dose therapy in previously untreated multiple myeloma. Haematologica. 2008;93(1):124-7.

28. Rajkumar SV et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol. 2010;11(1):29-37.

29. Fayers PM et al. Thalidomide for previously untreated elderly patients with multiple myeloma: meta-analysis of 1685 individual patient data from 6 randomized clinical trials. Blood. 2011;118(5):1239-47.

30. Facon T et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. Lancet. 2007;370(9594):1209-18.

31. Lonial S et al. Treatment options for relapsed and refractory multiple myeloma. Clin Cancer Res. 2011;17(6):1264-77.

32. Castelli R et al. Current and emerging treatment options for patients with relapsed myeloma. Clin Med Insights Oncol. 2013;7:209-19.

33. Palumbo A et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: updated follow-up and improved survival. J Clin Oncol. 2014;32(7):634-40.

34. Palumbo A et al. Second primary malignancies with lenalidomide therapy for newly diagnosed myeloma: a meta-analysis of individual patient data. Lancet Oncol. 2014;15(3):333-42.

35. McCarthy PL et al. Phase III intergroup study of lenalidomide versus placebo maintenance therapy following single autologous hematopoietic stem cell transplantation (AHSCT) for multiple myeloma: CALGB 100104 [abstract 37]. Blood (ASH Annual Meeting Abstracts). 2010;116(21):37.

36. Sonneveld P et al. HOVON-65/GMMG-HD4 randomized phase III trial comparing bortezomib, doxorubicin, dexamethasone (PAD) vs VAD followed by high-dose melphalan (HDM) and maintenance with bortezomib or thalidomide in patients with newly diagnosed multiple myeloma (MM). Blood. 2010;116:40.

37. Attal M et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012;366(19):1782-91.

38. Kyle RA, Rajkumar SV. Multiple myeloma. N Engl J Med. 2004;351(18):1860-73.

39. Kumar SK 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(1):149-57.

40. Anderson KC et al. Clinically relevant end points and new drug approvals for myeloma. Leukemia. 2008;22(2):231-9.

41. Morris C et al. Benefit and timing of second transplantations in multiple myeloma: clinical findings and methodological limitations in a European Group for Blood and Marrow Transplantation registry study. J Clin Oncol. 2004;22(9):1674-81.

42. Ludwig H et al. European perspective on multiple myeloma treatment strategies: update following recent congresses. Oncologist. 2012;17(5):592-606.

43. Moehler T, Goldschmidt H. Therapy of relapsed and refractory multiple myeloma. Recent Results Cancer Res. 2011;183:239-71.

44. Castelli R et al. Immunomodulatory drugs in multiple myeloma: from molecular mechanisms of action to clinical practice. Immunopharmacol Immunotoxicol. 2012;34(5):740-53.

45. Dimopoulos MA et al. Pulsed cyclophosphamide, thalidomide and dexamethasone: an oral regimen for previously treated patients with multiple myeloma. Hematol J. 2004;5(2):112-7.

46. Garcia-Sanz R et al. The oral combination of thalidomide, cyclophosphamide and dexamethasone (ThaCyDex) is effective in relapsed/refractory multiple myeloma. Leukemia. 2004;18(4):856-63.

47. Kropff M et al. Thalidomide versus dexamethasone for the treatment of relapsed and/or refractory multiple myeloma: results from OPTIMUM, a randomized trial. Haematologica. 2012;97(5):784-91.

48. Eriksson T et al. Pharmacokinetics of thalidomide in patients with impaired renal function and while on and off dialysis. J Pharm Pharmacol. 2003;55(12):1701-6.

49. Arai A et al. [Analysis of plasma concentration of thalidomide in Japanese patients of multiple myeloma with renal dysfunction]. Rinsho Ketsueki. 2009;50(4):295-9.

50. Dimopoulos M et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med. 2007;357(21):2123-32.

51. Weber DM et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. New Engl J Med. 2007;357(21):2133-42.

52. Richardson PG et al. Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the APEX trial. Blood. 2007;110(10):3557-60.

53. Jagannath S et al. Bortezomib appears to overcome the poor prognosis conferred by chromosome 13 deletion in phase 2 and 3 trials. Leukemia. 2007;21(1):151-7.

54. Neben K et al. Administration of bortezomib before and after autologous stem cell transplantation improves outcome in multiple myeloma patients with deletion 17p. Blood. 2012;119(4):940-8.

55. Jagannath S et al. Updated survival analyses after prolonged follow-up of the phase 2, multicenter CREST study of bortezomib in relapsed or refractory multiple myeloma. Br J Haematol. 2008;143(4):537-40.

56. Berenson JR et al. Phase I/II trial assessing bortezomib and melphalan combination therapy for the treatment of patients with relapsed or refractory multiple myeloma. J Clin Oncol. 2006;24(6):937-44.

57. Orlowski RZ et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. J

Clin Oncol. 2007;25(25):3892-901.

58. Kropff M et al. Bortezomib in combination with intermediate-dose dexamethasone and continuous low-dose oral cyclophosphamide for relapsed multiple myeloma. Br J Haematol. 2007;138(3):330-7.

59. Palumbo A et al. Bortezomib, doxorubicin and dexamethasone in advanced multiple myeloma. Ann Oncol. 2008;19(6):1160-5.

60. Popat R et al. Bortezomib, low-dose intravenous melphalan, and dexamethasone for patients with relapsed multiple myeloma. Br J Haematol. 2009;144(6):887-94.

61. Haynes R et al. Myeloma kidney: improving clinical outcomes? Advances in chronic kidney disease. 2012;19(5):342-51.

62. Dimopoulos MA et al. The role of novel agents on the reversibility of renal impairment in newly diagnosed symptomatic patients with multiple myeloma. Leukemia. 2013;27(2):423-9.

63. Auner HW et al. Reduced intensity-conditioned allogeneic stem cell transplantation for multiple myeloma relapsing or progressing after autologous transplantation: a study by the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant. 2013;48(11):1395-1400.

64. Lonial S. Relapsed multiple myeloma. Hematology Am Soc Hematol Educ Program. 2010;2010(1):303-9.

65. Goldschmidt H et al. Multiple myeloma and renal failure. Nephrol Dial Transplant. 2000;15(3):301-4.

66. Dimopoulos MA et al. Pathogenesis and treatment of renal failure in multiple myeloma. Leukemia. 2008;22(8):1485-93.

67. San Miguel JF et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008;359(9):906-17.

68. Mateos MV et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. J Clin Oncol. 2010;28(13):2259-66.

69. Curran MP, McKeage K. Bortezomib: a review of its use in patients with multiple myeloma. Drugs. 2009;69(7):859-88.

70. Hulin C et al. Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. J Clin Oncol. 2009;27(22):3664-70.

71. Durie BG. Treatment of myeloma--are we making progress? N Engl J Med. 2008;359(9):964-6.

72. Abraham J. Advances in multiple myeloma treatment: lenalidomide and bortezomib. Commun Oncol. 2009;6(2):53-7.

73. Streetly MJ et al. Alternate day pomalidomide retains anti-myeloma effect with reduced adverse events and evidence of in vivo immunomodulation. Br J Haematol. 2008;141(1):41-51.

74. Schey S, Ramasamy K. Pomalidomide therapy for myeloma. Expert Opin Investig Drugs. 2011;20(5):691-700.

75. Lacy MQ 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(11):2970-5.

76. Richardson PG et al. Phase 1 study of pomalidomide MTD, safety, and efficacy in patients with refractory multiple myeloma who have received lenalidomide and bortezomib. Blood. 2013;121(11):1961-7.

77. Forsberg PA, Mark TM. Pomalidomide in the treatment of relapsed multiple myeloma. Future Oncol. 2013;9(7):939-48.

78. Lacy MQ et al. Pomalidomide (CC4047) plus low dose dexamethasone (Pom/dex) is active and well tolerated in lenalidomide refractory multiple myeloma (MM). Leukemia. 2010;24(11):1934-9.

79. Lacy MQ et al. Pomalidomide (CC4047) plus low-dose dexamethasone as therapy for relapsed multiple myeloma. J Clin Oncol. 2009;27(30):5008-14.

80. San Miguel J et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013;14(11):1055-66.

81. Study to evaluate the safety and efficacy of pomalidomide monotherapy in subjects with refractory or relapsed refractory multiple myeloma, NCT01324947. http://clinicaltrials.gov/show/NCT01324947 Accessed: 19th May, 2014.

82. Shah JJ et al. Phase I/II dose expansion of a multi-center trial of carfilzomib and pomalidomide with dexamethasone (Car-Pom-d) in patients with relapsed/refractory multiple myeloma. ASH 2013 Annual Meeting, Abstract 690.

83. Siegel DS et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. Blood. 2012;120(14):2817-25.

84. Phase 3 study comparing carfilzomib, lenalidomide, and dexamethasone (CRd) vs lenalidomide and dexamethasone (Rd) in subjects with relapsed multiple myeloma, NCT01080391. http://clinicaltrials.gov/show/NCT01080391. Accessed: 1st May, 2014.

85. A study of carfilzomib vs best supportive care in subjects with relapsed and refractory multiple myeloma (FOCUS), NCT01302392. http://clinicaltrials.gov/show/NCT01302392. Accessed: 1st May, 2014.

86. Phase 3 study with carfilzomib and dexamethasone versus velcade and dexamethasone for relapsed multiple myeloma patients (ENDEAVOR), NCT01568866. http://clinicaltrials.gov/show/NCT01568866. Accessed: 1st May, 2014.

87. Phase 3 study of carfilzomib, melphalan, prednisone vs bortezomib, melphalan, prednisone in newly diagnosed multiple myeloma (CLARION), NCT01818752. http://clinicaltrials.gov/show/NCT01818752. Accessed: 1st May, 2014.

88. Richardson P et al. Phase 1 clinical trial of NPI-0052, a novel proteasome inhibitor in patients with multiple myeloma. Blood (ASH Annual Meeting Abstracts). 2008;112(11):Abstract 2770.

89. Richardson PG et al. Phase 1 clinical evaluation of twice-weekly Marizomib (NPI-0052), a novel proteasome inhibitor, in patients with relapsed/refractory multiple myeloma (MM). Blood. 2011;118(2):140-1.

90. Chauhan D et al. A novel proteasome inhibitor NPI-0052 as an anticancer therapy. Br J Cancer. 2006;95(8):961-5.

91. Triphase receives FDA orphan drug designation for marizomib in multiple myeloma. Triphase. http://triphaseco.com/wp-content/uploads/2014/02/20140226_Triphase_orphan_drug_news-release_final.pdf. Accessed: 1st May, 2014.

92. Phase 1/2 clinical trial of NPI-0052 in patients with relapsed or relapsed/refractory multiple myeloma, NCT00461045. http://clinicaltrials.gov/ct2/show/NCT00461045. Accessed: 19th May, 2014.

93. Combination study of pomalidomide, marizomib, and dexamethasone in relapsed or refractory multiple myeloma, NCT02103335. http://clinicaltrials.gov/show/NCT02103335. Accessed: 1st May, 2014.

94. Marizomib may be an effective treatment for relapsed and/or refractory myeloma patients. Myeloma UK. http://www.myeloma.org.uk/news/marizomib-may-be-an-effective-treatment-for-relapsed-andor-refractory-myeloma-patients/. Accessed: 1st May, 2014.

95. Lee EC 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(23):7313-23.

96. Chauhan D et al. In vitro and in vivo selective antitumor activity of a novel orally bioavailable proteasome inhibitor

MLN9708 against multiple myeloma cells. Clin Cancer Res. 2011;17(16):5311-21.

97. Richardson PG et al. Twice-weekly oral MLN9708 (Ixazomib Citrate), an investigational proteasome inhibitor, in combination with lenalidomide (Len) and dexamethasone (Dex) in patients (Pts) with newly diagnosed multiple myeloma (MM): final phase 1 results and phase 2 data. ASH Annual Meeting. 2013;Abstract 535 (oral presentation).

98. Chauhan D et al. A novel orally active proteasome inhibitor ONX 0912 triggers in vitro and in vivo cytotoxicity in multiple myeloma. Blood. 2010;116(23):4906-15.

99. Phase 1b/2, multicenter, open-label study of oprozomib and dexamethasone in patients with relapsed and/or refractory multiple myeloma, NCT01832727. http://clinicaltrials.gov/ct2/show/NCT01832727. Accessed: 19th May, 2014.

100. Richardson PG et al. Preclinical data and early clinical experience supporting the use of histone deacetylase inhibitors in multiple myeloma. Leuk Res. 2013;37(7):829-37.

101. San-Miguel JF et al. Update on a phase III study of panobinostat with bortezomib and dexamethasone in patients with relapsed multiple myeloma: PANORAMA 1. J Clin Oncol. 2013;31(29):3696-703.

102. Efficacy of panobinostat in patients with relapsed and bortezomib-refractory multiple myeloma (MACS1271), NCT01083602. http://clinicaltrials.gov/ct2/show/NCT01083602. Accessed: 1st May, 2014.

103. Novartis submits panobinostat for FDA approval as new treatment for multiple myeloma, gains priority review. The Myeloma Beacon. http://www.myelomabeacon.com/news/2014/06/02/panobinostat-fda-approval-priority-review/. Accessed: 19th June, 2014.

104. Dimopoulos M et al. Vorinostat or placebo in combination with bortezomib in patients with multiple myeloma (VANTAGE 088): a multicentre, randomised, double-blind study. Lancet Oncol. 2013;14(11):1129-40.

105. Kleber M et al. Vorinostat (V) in combination with bortezomib (B), doxorubicin (D) and dexamethasone (D) (VBDD) in patients with refractory or relapsed multiple myeloma: an interim phase I/II analysis. ASH Annual Meeting. 2013;Abstract 3202 (poster presentation).

106. Yee A et al. ACY-1215, a selective histone deacetylase 6 inhibitor, in combination with lenalidomide and dexamethasone, is well tolerated without dose limiting toxicity in patients with multiple myeloma at doses demonstrating biologic activity: interim results of a phase 1b trial. ASH Annual Meeting. 2013; Abstract 3190 (poster presentation).

107. Lonial S et al. Elotuzumab in combination with lenalidomide and low-dose dexamethasone in relapsed or refractory multiple myeloma. J Clin Oncol. 2012;30(16):1953-9.

108. Phase III study of lenalidomide and dexamethasone with or without elotuzumab to treat newly diagnosed, previously untreated multiple myeloma (ELOQUENT - 1), NCT01335399. http://www.clinicaltrials.gov/ct2/show/NCT01335399. Accessed: 1st May, 2014.

109. Phase III study of lenalidomide and dexamethasone with or without elotuzumab to treat relapsed or refractory multiple myeloma (ELOQUENT - 2), NCT01239797. http://clinicaltrials.gov/show/NCT01239797. Accessed: 1st May, 2014.

110. Daratumumab (HuMax®-CD38) safety study in multiple myeloma, NCT00574288. http://clinicaltrials.gov/ct2/show/NCT00574288. Accessed: 19th May, 2014.

111. Daratumumab in combination with lenalidomide and dexamethasone in relapsed and relapsed-refractory multiple myeloma, NCT01615029. http://clinicaltrials.gov/ct2/show/NCT01615029. Accessed: 19th May, 2014.

112. Genmab announces new phase III study of daratumumab in multiple myeloma & improves 2014 financial guidance. Genmab, Copenhagen, Denmark. http://ir.genmab.com/releasedetail.cfm?ReleaseID=844643. Accessed: 19th May, 2014.

113. Genmab announces phase III study of daratumumab in relapsed or refractory multiple myeloma. Genmab, Copenhagen, Denmark. http://ir.genmab.com/releasedetail.cfm?ReleaseID=830280. Accessed: 4th June, 2014.

114. Martin TG et al. SAR650984, a CD38 monoclonal antibody in patients with selected CD38+ hematological malignancies—data from a dose-escalation phase I study. Blood. 2013;122(21):284.

115. Kelly KR et al. Indatuximab Ravtansine (BT062) in combination with lenalidomide and low-dose dexamethasone in patients with relapsed and/or refractory multiple myeloma: clinical activity in Len/Dex-refractory patients. ASH Annual Meeting. 2013;Abstract 758 (oral presentation).

116. Lonial S et al. Prolonged survival and improved response rates with ARRY-520 in relapsed/refractory multiple myeloma patients with low α-1 acid glycoprotein levels: results from a phase 2 study. ASH Annual Meeting. 2013;Abstract 285 (oral presentation).

117. Peter M Voorhees et al. Novel AKT inhibitor afuresertib in combination with bortezomib and dexamethasone demonstrates favorable safety profile and significant clinical activity in patients with relapsed/refractory multiple myeloma. ASH Annual Meeting. 2013;Abstract 283 (oral presentation).

118. Lentzsch S et al. Combination of bendamustine, lenalidomide, and dexamethasone (BLD) in patients with relapsed or refractory multiple myeloma is feasible and highly effective: results of phase 1/2 open-label, dose escalation study. Blood. 2012;119(20):4608-13.

119. Pönisch W et al. Lenalidomide, bendamustine and prednisolone exhibits a favourable safety and efficacy profile in relapsed or refractory multiple myeloma: final results of a phase 1 clinical trial OSHO - #077. Br J Haematol. 2013;162(2):202-9.