CURRENT DEVELOPMENTS AND PERSPECTIVES IN MULTIPLE MYELOMA

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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.\textsuperscript{7,8} MM accounts for about 2\% of all cancer mortality.\textsuperscript{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,\textsuperscript{10,11} excess clonal bone marrow plasma cells (>10%), and organ impairment.\textsuperscript{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\textsuperscript{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.\textsuperscript{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.\textsuperscript{18}

This treatment strategy, when implemented on eligible patients, can yield extended survival and is, therefore, the current SoC for newly diagnosed MM.\textsuperscript{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).\textsuperscript{20} In a study from the Spanish PETHEMA group,\textsuperscript{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.\textsuperscript{21} Conversely, Hoering et al.\textsuperscript{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]).\textsuperscript{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).\textsuperscript{30}

For non-transplant candidates, combination therapies include BTZ, melphalan, and prednisone (VMP) or melphalan, prednisone, and thalidomide (MPT).\textsuperscript{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.\textsuperscript{33}

Continuous treatment with lenalidomide plus dexamethasone can provide additional survival outcomes in non-transplant candidates. However, longer follow-up is still needed.\textsuperscript{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).\textsuperscript{35,36} Longer progression time and OS have also been
observed with lenalidomide maintenance, while short-term consolidation therapy with VTD has been reported to improve PFS after tandem ASCT, but not OS. 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. 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).

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. By contrast, a repeat or tandem ASCT, performed within 3-6 months, is a first-line therapeutic option.

Chemotherapy with thalidomide, lenalidomide, or BTZ was demonstrated to be effective in second-line therapy, and prolongs OS in RRMM patients. 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. One interesting feature of thalidomide is that it does not warrant usual dose adjustments in patients with renal impairment, including patients on dialysis.

Lenalidomide, approved in 2006 by the FDA as second-line therapy, yields good ORR (61%) and low toxicity when associated with dexamethasone. 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. Similarly to thalidomide, BTZ does not require dose adjustments in patients with renal impairment. 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%.

According to the type of transplant, non-relapse mortality varies between 10% and 30%. 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.

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. 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 or thalidomide has demonstrated additional benefits in terms of response, PFS, and OS.

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. 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. When associated with low doses of dexamethasone, the response rates increase and range from 47-63%. 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). An extension study is currently ongoing to evaluate the pomalidomide monotherapy in subjects who discontinued treatment with high-dose dexamethasone due to disease progression.

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. 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.

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. 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) and evaluates carfilzomib plus lenalidomide and dexamethasone versus lenalidomide plus dexamethasone. Another ongoing Phase III study, the FOCUS study, 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 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 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. A Phase I/II study is currently ongoing in highly refractory MM patients, including those presenting with carfilzomib resistance, in combination with dexamethasone. Another Phase I/II study is evaluating marizomib in combination with pomalidomide and dexamethasone in RRMM, including patients who are resistant to carfilzomib.

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

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

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<tr>
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<th>Study Type/Name</th>
<th>Clinical setting</th>
<th>Treatment arms</th>
<th>Main findings</th>
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<tr>
<td>Proteasome inhibitors</td>
<td>Ixazomib (MLN9708-MLN 2238)</td>
<td>Phase I/II87</td>
<td>First-line therapy of newly diagnosed MM</td>
<td>IXA + LEN + DEX</td>
<td>• 95% of responses (21% stringent CRs, 5% CRs, 11% nCRs, 38% very good PRs, and 20% PRs)</td>
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<td>NCT01383928</td>
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<td>• Median duration of response of 14 months</td>
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<td>Oprozomib (ONX0912)</td>
<td>Phase Ib/II88</td>
<td>RRMM</td>
<td>OPZ + DEX</td>
<td>• Ongoing</td>
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<td>Histone deacetylase inhibitors</td>
<td>Panobinostat</td>
<td>Phase III - PANORAMA-191,92</td>
<td>RRMM</td>
<td>PAN or placebo + BTZ + DEX</td>
<td>• PAN significantly extended PFS</td>
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<td>• Full results are still being evaluated</td>
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<td>Phase II -PANORAMA-291</td>
<td>Relapsed and BTZ-refractory MM</td>
<td>PAN + BTZ + DEX</td>
<td>• Ongoing</td>
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<td>Vorinostat (MK-0683)</td>
<td>Phase I/II93,94</td>
<td>RRMM</td>
<td>VOR + BTZ + DOX + DEX</td>
<td>• Interim analysis: the ORR was of 65%, for a clinical benefit rate of 89%</td>
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<td>Rocilinostat (ACY-1215)</td>
<td>Phase Ib95</td>
<td>RRMM</td>
<td>ROC + LEN + DEX</td>
<td>• 100% of responses, 69% achieved a PR or better (6% CR, 19% very good PRs, 44% PRs)</td>
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<td>Monoclonal antibodies</td>
<td>Elotuzumab</td>
<td>Phase III - ELOQUENT-197</td>
<td>Newly diagnosed, previously untreated MM</td>
<td>ELO + LEN + DEX</td>
<td>• Ongoing</td>
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<td>Phase III - ELOQUENT-298</td>
<td>RRMM</td>
<td>ELO + LEN + DEX</td>
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<td>Daratumumab</td>
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<td>DAR</td>
<td>• Ongoing</td>
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<td>Phase I/II100</td>
<td>RRMM</td>
<td>DAR + LEN + DEX</td>
<td>• Ongoing</td>
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<td>NCT01615029</td>
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<td>Phase III101</td>
<td>RRMM</td>
<td>DAR + BTZ + DEX vs. BTZ + DEX alone</td>
<td>• Ongoing</td>
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<td>SAR650984</td>
<td>Phase I102</td>
<td>CD38+ hematological malignancies</td>
<td>Dose-escalation study</td>
<td>• SAR650984 shown encouraging single-agent activity in pts with heavily pretreated RRMM</td>
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Preliminary reported adverse events include fatigue, nausea, vomiting, dizziness, weight loss, and shortness of breath, but so far no peripheral neuropathy, anaemia or thrombocytopenia were observed.94

Ixazomib

Ixazomib (MLN9708) is the first oral proteasome inhibitor95 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 thrombocytopenia, neutropenia, 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,101,111 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.\textsuperscript{13}

**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.\textsuperscript{14}\textsuperscript{4} 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.\textsuperscript{15}\textsuperscript{5}

**Other Emerging Therapies**

Other emerging agents for the treatment of MM include filanesib (ARRY-520),\textsuperscript{16} a kinesin spindle protein inhibitor, and the Akt inhibitor afuresertib (PKB115125).\textsuperscript{117} Bendamustine, an older alkylating agent also continues to be investigated in MM.\textsuperscript{118,119}

**REFERENCES**


**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.


57. Orloński 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
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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).


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).


