RELAPSED/REFRACTORY MULTIPLE MYELOMA: THE CURRENT STATE OF PLAY

***María-Victoria Mateos, Enrique M. Ocio, Verónica González, Julio Dávila**

University Hospital of Salamanca/IBSAL, Salamanca, Spain
**Correspondence to mvmateos@usal.es*

Disclosure: María-Victoria Mateos has received honoraria for lectures and advisory boards from Janssen, Celgene, Novartis, Takeda, Amgen, and BMS. Enrique M. Ocio has received research support from Celgene, Amgen, Pharmamar, Array Pharmaceuticals, and Mundipharma; and honoraria or consultation fees from Bristol-Myers Squibb, Array Pharmaceuticals, Mundipharma, Novartis, Janssen, Celgene, and Amgen. Verónica González and Julio Dávila have declared no conflicts of interest.
Support: The publication of this article was funded by Takeda. The views and opinions expressed are those of the authors and not necessarily of Takeda.
Received: 29.05.15 **Accepted:** 17.07.15
Citation: EMJ Hema. 2015;3[1]:76-85.

ABSTRACT

Multiple myeloma (MM) usually responds to treatment but is incurable. The clinical course is characterised, in most patients, by a series of remissions and relapses. For younger patients, the initial treatment currently usually involves induction with the proteasome inhibitor bortezomib (BOR), alone or in combination, followed by an autologous stem cell transplant (ASCT). Usually only clinical relapses require treatment; the treatment plan should be individualised to take into account factors such as response to previous treatment, duration of the remission, adverse effects experienced, and available treatment options. Evidence suggests that many patients who have responded to BOR will respond to it again. Patients at first relapse should also be considered for a further ASCT or an allotransplant. Clinical studies have led to other drugs being approved for treatment of relapsed MM. These include lenalidomide (an immunomodulatory drug), carfilzomib (another proteasome inhibitor), pomalidomide (an immunomodulatory drug), and most recently panobinostat (a deacetylase inhibitor). The availability of these drugs greatly enhances the therapeutic options available to treat further relapses. Moreover, a bewildering array of other novel agents are at various stages in testing. They include other drugs from the classes already mentioned, as well as monoclonal antibodies, drugs acting on the cell cycle, kinase inhibitors, and signal transduction pathway inhibitors. It seems probable that the introduction of these agents in the coming years will further improve the survival of patients with MM, and may even lead to a cure.

Keywords: Multiple myeloma (MM), relapse, proteasome inhibitor, immunomodulator, monoclonal antibody, deacetylase inhibitor.

INTRODUCTION

Multiple myeloma (MM) is a malignant disease caused by the monoclonal expansion of plasma cells. It affects 6.1 per 100,000 people per year in the USA, where it is the second most common haematological malignancy after non-Hodgkin lymphoma.[1] In the UK, the lifetime risk of developing MM is 1 in 120 for males and 1 in 155 for females.[2] The risk increases sharply in patients >55 years, with the highest rates being in those aged >85 years. There are significant racial differences, with higher rates in black compared with white people. Although MM remains an incurable disease, the survival duration of newly-diagnosed patients has increased markedly in the last decade, mainly due to the efficacy of high-dose melphalan (MLP) followed by autologous stem cell transplantation (ASCT) and novel agents such as thalidomide (THD), bortezomib (BOR), and lenalidomide (LEN). In Europe, either one of the first two agents is usually used as the first-line treatment. In the USA, and increasingly in Europe, LEN is often used as a first-line agent instead of THD. However, all patients eventually relapse and become resistant to these drugs. Almost all patients develop refractory

disease, at which point the median event-free survival time is 5 months, with overall survival (OS) at this stage under a year.[3] This review considers the options available for the treatment of patients with relapsed MM, including those who have become refractory to treatment.

TREATMENT OF RELAPSED AND REFRACTORY MM

Key Clinical Trials

There are a number of drugs and drug combinations approved by both the FDA and the EMA for the treatment of patients with MM who have relapsed or become refractory to treatment. For most, this was based upon the results from Phase III trials,[4-9] although for one drug, carfilzomib (CARF), approval was partly based upon the results of Phase II trials.[10-12] Details of these pivotal trials are summarised in Table 1. Below, we review these and other key clinical trials which currently inform the state-of-the-art treatment of relapsed and refractory MM. The outcome measures for individual studies are the predetermined primary endpoints.

Proteasome Inhibitors

The APEX study compared the use of the intravenous proteasome inhibitor, BOR, with oral dexamethasone (DEX) for the treatment of relapsed MM.[4] The median time-to-progression (TTP) (progression-free survival [PFS] times) were 6.22 versus 3.49 months ($p<0.001$). In a separate trial, BOR alone was compared with the same BOR regimen with the addition of intravenous pegylated liposomal doxorubicin (PLD) for the treatment of relapsed MM.[5] The median PFS durations were 9.3 versus 6.5 months, respectively ($p=0.000004$).

CARF is a second-generation proteasome inhibitor. It was approved by the FDA, but not the EMA, on the basis of results from three Phase II trials for its use as a single agent in patients with relapsed MM.[10-12] These trials had very different designs and study populations. Overall response rates (ORRs) to intravenous CARF of 17.1%, 59.3%-64.2%, and 23.7% were obtained in patients previously exposed to BOR,[11] patients naïve to BOR,[12] and in a mixed group of patients, some of whom had been exposed to BOR,[10] respectively. All three studies concluded that the results demonstrated that CARF was potentially effective for treating relapsed MM. FOCUS was a Phase III trial that compared CARF single agent with low-dose corticosteroids and optional cyclophosphamide (CYC) in patients with relapsed MM. The primary endpoint was OS; this was not reached, although there were significant differences in some secondary endpoints.[13] Subsequently, a Phase III trial (ASPIRE) compared the use of intravenous CARF combined with LEN and DEX with a control group of patients treated with LEN and DEX alone.[14] The median PFS times were 26.3 versus 17.6 months, respectively. Recently, the pre-planned interim analysis of a Phase III trial (ENDEAVOR) that compared intravenous CARF combined with DEX and BOR combined with DEX for relapsed MM showed that PFS was significantly better with the former (18.7 versus 9.4 months). The dose of CARF used in the ENDEAVOR trial[15] (56 mg/m^2) was significantly higher than that used in most previous studies, including ASPIRE (27 mg/m^2). These findings suggested that CARF may be the best in its class for the treatment of relapsed MM.

Numerous new third-generation proteasome inhibitors are currently being investigated for MM. They differ both in terms of the catalytic subunits of the targeted proteasome and in the reversibility of the inhibition. It is hoped that they will have similar or superior efficacy rates to BOR, be better tolerated, and be able to overcome BOR resistance. A Phase III trial of ixazomib (IXZ), which is given orally weekly, has recently been completed. It compared IXZ with placebo, in combination with LEN and DEX. Press releases suggest that patients treated with the active drug had longer PFS times compared with those treated with placebo. Oprozomib, a structural analogue of CARF, is also given orally.[16] Both oprozomib and marizomib, which is given intravenously, appear to confer promising outcomes in early clinical studies.

Immunomodulatory Drugs

Two very similar studies, one from North America and the other from a consortium encompassing Europe, Israel, and Australia compared the combination of oral LEN, an immunomodulatory drug, and DEX with placebo and DEX for the treatment of relapsed MM.[6,7] The median PFS times in the two studies were 11.1 versus 4.7 months ($p<0.001$) and 11.3 versus 4.7 months ($p<0.001$), respectively. The median TTP was not significantly related to the previous exposure to THD in either study of patients receiving LEN. LEN combined with DEX (40 mg weekly) is the

control arm in a number of ongoing Phase III trials investigating the efficacy of novel agents. Depending on the results of these, three-drug combinations may become increasingly utilised.

Table 1: Key clinical studies leading to FDA and EMA approval.

Drug	Study	Patient group	Treatment	Comparator	Principle outcome measure	Other outcome measures (selected)	Adverse events (selected)
BOR	Multicentre, randomised, OL, Phase III[4]	N=669; 1-3 previous treatments	BOR 1.3 mg/m^2 on d. 1, 4, 8, & 11 for 8 3-wk. cycles, then on d. 1, 8, 15, & 22 for 3 5-wk. cycles	DEX 40 mg on d. 1 through 4, 9 through 12, & 17 through 20 for 4 5-wk. cycles, then on d. 1 through 4 for 5 4-wk. cycles	Median time to DP: 6.22 vs. 3.49 mth. (HR for the BOR group, 0.55; p<0.001)	RR: 38% vs. 18% (p<0.001) 1-year SR: 80% vs. 66% (p=0.003) Median DR: 8 vs. 5.6 mth.	Grade 3 or 4 adverse events: 75% vs. 60%
BOR-PLD	Multicentre, randomised, OL, Phase III[5]	N=646; >1 previous treatment	BOR 1.3 mg/m^2 on d. 1, 4, 8, & 11 of an every 21-d. cycle, + PLD 30 mg/m^2 on d. 4	BOR 1.3 mg/m^2 on d. 1, 4, 8, & 11 of an every 21-d. cycle	Median time to DP: 9.3 vs. 6.5 mth. (HR for the PLD-BOR group 1.82)		Grade 3 or 4 adverse reactions: 80% vs. 64%
LEN	Multicentre, randomised, DB, OL, PC, Phase III[7]	N=293; >1 previous treatment and measurable disease not resistant to DEX	LEN 25 mg on d. 1 to 21 of a 28-d. cycle + 40 mg DEX on d. 1 to 4, 9 to 12, & 17 to 20 for the first 4 cycles. Then DEX 40 mg only on d. 1 to 4	Placebo 25 mg on d. 1 to 21 of a 28-day cycle + DEX on d. 1 to 4, 9 to 12 & 17 to 20 for the first 4 cycles. Then DEX 40 mg only on d. 1 to 4	Median time to DP: 11.1 vs. 4.7 mth. (HR for the LEN group 0.35)	RR: 44% vs. 41% (n.s.) 15 mth. SR: 76% vs. 65% (p=0.03) Median DR: 10.2 vs. 7 mth. (p=0.0008)	Grade 3 or 4 adverse reactions: 85% vs. 73%
LEN	As above[6]	As above, except N=351	As above	As above	Median time to DP: 11.1 vs. 4.7 mth. (HR for the LEN group 2.85)	RR: 61% vs. 20% (p<0.001) Median SR: 29.6 vs. 20.2 mth. (p<0.001) OS sig. improved in the LEN group in those on prior THD (p=0.03)	The primary toxic effects of LEN were haematologic, and were manageable
CARF	Multicentre, SA, OL, Phase II[10]	N=266; >2 previous treatments	CARF 20 mg/m^2 x 2 weekly for 3 of 4 weeks in cycle 1, then 27 mg/m^2 for <12 cycles		RR: 24%	RR: 60% vs. 24% (p<0.001) Median time to DP for those on prior THD: 8.4 vs. 4.6 mth. (p<0.001)	Adverse events were 'manageable'

Table 1 continued.

Drug	Study	Patient group	Treatment	Comparator	Principle outcome measure	Other outcome measures (selected)	Adverse events (selected)
CARF	Multicentre, SA, OL, Phase II[12]	N=129; 1-3 previous treatments; naïve to BOR	Cohort 1: CARF 20 mg/m^2 for all treatment cycles	Cohort 2: CARF 20 mg/m^2 for cycle 1 and then 27 mg/m^2	RR cohort 1 vs. cohort 2: 42% vs. 52% (lower bound of the 95% CI was not exceeded)		
CARF	Multicentre, SA, OL, Phase II[11]	N=35; 1-3 previous treatments; BOR non-naïve	CARF 20 mg/m^2 in a twice-weekly, consecutive-day dosing schedule for 12 monthly cycles		Response rate: 17%	Median DR: 7.8 mth. Median OS: 15.6 mth.	
CARF	Multicentre, OL, randomised, Phase III[14]	N=792; 1-3 previous treatments	CARF – d. 1, 2, 8, 9, 15, & 16 (starting dose, 20 mg/m^2 d. 1 & 2 of cycle 1; target dose, 27 mg/m^2 thereafter) during cycles 1 through 12 and on d. 1, 2, 15, & 16 during cycles 13 through 18.+ LEN & DEX as for comparator	LEN 25 mg on d. 1 through 21. DEX 40 mg on d. 1, 8, 15, & 22	Median PFST: 26.3 vs. 17.6 mth. (HR for progression or death 0.69)	RR: 87% vs. 67% 24 mth. SR: 73% vs. 65%	Grade 3 or higher adverse events: 84% vs. 81%
POM	Multicentre, OL, randomised Phase III[8]	N=455 Relapsed on at least 2 consecutive cycles of BOR and/or LEN	28 d. cycles of POM 4 mg/day on d. 1–21, orally + DEX 40 mg/d. on d. 1, 8, 15, & 22 until progression or toxicity	28 d. cycles of POM 4 mg/d. on d. 1–21, orally + DEX 40 mg/d. on d. 1-4, 9-12, and 17-20	Median PFST: 4.0 vs. 1.9 mth. (HR 0.48)		
PAN	Multicentre, randomised, PC, Phase III study[9]	N=768; 1-3 previous treatments	21 d. cycles of PAN 20 mg on d. 1, 3, 5, 8, 10, 12, orally) + BOR 1.3 mg/m^2 on d. 1, 4, 8, 11 + DEX 20 mg on d. 1, 2, 4, 5, 8, 9, 11, 12	As before, but substitute PAN for placebo	Median PFST: 12.0 vs. 8.1 mth. (HR 0.63)	RR: 61% vs. 55% (p=0·09) CRR or NCRR: 13.4 vs. 10.9 mth. (p=0·00006) Median DR: 13.4 vs. 10.9 mth.	Serious adverse events: 60% vs. 40%

BOR: bortezomib; PLD: pegylated liposomal doxorubicin; LEN: lenalidomide: CARF: carfilzomib; POM: pomalidomide; PAN: panobinostat, DEX: dexamethasone; THD: thalidomide; PC: placebo-controlled; OL: open label; DB: double blind, SA: single agent; HR: hazard ratio; RR: response rate; CRR: complete response rate; NCRR: near-complete response rate; SR: survival rate; OS: overall survival; DR: duration of response; DP: disease progression; PFST: progression-free survival time; d: day(s); wk: week(s); mth: month(s); CI: confidence interval; n.s.: not significant; vs: versus.

Pomalidomide (POM) is a second-generation immunomodulatory drug. Early clinical trials have demonstrated that it has limited efficacy for the treatment of relapsed MM patients when used as a single agent, but showed possible synergistic effects when combined with DEX. The NIMBUS trial compared oral POM combined with low-dose DEX with high-dose DEX in patients with relapsed and refractory MM that have exhausted treatment with BOR and LEN.[8] The median PFS time was significantly better in the former group than in the latter (4.0 versus 1.9 months). The findings from STRATUS,[17] a larger Phase IIIb study of POM and low-dose DEX, were comparable. Current clinical trials are investigating POM and low-dose DEX combined with other agents, such as CYC, BOR, and PLD.[18,19]

Deacetylase Inhibitors

Deacetylase inhibitors are not effective treatments for MM when given as single agents, but act synergistically with other agents, including proteasome inhibitors. Panobinostat (PAN) is an oral pan-deacetylase inhibitor. When combined with BOR and DEX (PANORAMA-1 trial), the median PFS time was significantly better than that in controls who were given placebo and combined BOR and DEX (11.99 versus 8.08 months).[9] In contrast, a Phase III trial of vorinostat and BOR recently reported no improvement in OS.[20]

Combinations of PAN and second-generation proteasome inhibitors and immunomodulatory drugs are also being evaluated. A Phase I/II study of PAN and DEX with CARF found an ORR of 82%,[21] and a Phase I study is exploring PAN and DEX with IXZ.[22] Rocilinostat is a deacetylase inhibitor with a narrower spectrum of activity than most other agents. It is hoped this may be associated with fewer adverse effects (AEs), whilst maintaining efficacy.[23]

Monoclonal Antibodies

There is a bewildering array of monoclonal antibodies (mAbs) currently being tested for the treatment of MM patients. They are specifically directed against antigens present in the surface of tumour cells. Thereafter, they have a number of different mechanisms of action which include direct cytotoxicity by inducing apoptosis, direct cytotoxicity as a consequence of conjugation to radioisotopes or toxins, and enhancing the immune response through antigen-dependent cellular cytotoxicity or via inducing complement-dependent cytotoxicity. Other novel mechanisms include targeting and sequestering of interleukins and targeting B-cell activating factor, which promotes the survival of malignant B cells. mAbs are being investigated both as single agent treatments and in combination with other drugs.

The most thoroughly investigated mAb for MM to date is elotuzumab (Elo). Its results are particularly encouraging when used with LEN and DEX; an ORR of 82% was found in a Phase I study.[24] When combined with BOR in another Phase I study, an ORR of 48% was obtained.[25] The ELOQUENT2 trial was a Phase III trial which compared LEN and DEX with and without Elo.[26] The rates of PFS at 1 and 2 years were 68% versus 57% and 41% versus 27%, respectively, and the median PFS times were 19.4 versus 14.9 months, respectively ($p<0001$).

Daratumumab (DARA) is a mAb directed against CD38. It appears to have at least three separate mechanisms of action. In a Phase II study of DARA as a single agent, an ORR of 29.2% was obtained.[27] It has been designated by the FDA as a breakthrough therapy that is considered to have the potential to address an important area of unmet clinical need.[27] Phase III trials are evaluating it in combination with LEN and DEX (MMY3003-POLLUX) and in combination with BOR and DEX (MMY3004-CASTOR).

Treatment of First and Second Relapses

When a patient with MM relapses, it is important to first determine if this is a biochemical or a clinical relapse. CRAB symptoms (elevated calcium, renal failure, anaemia, and bone lesions) should be assessed.[28] Purely biochemical relapses generally do not require treatment, but the patient should be monitored closely for evidence of clinical relapse. Exceptions to this rule include patients with particularly aggressive disease at diagnosis, and those with a rapid increase in paraprotein concentration.

The principle factors to consider when determining the appropriate treatment option for the first relapse in patients with MM are as follows: the treatment regimen already used, the adequacy and duration of the response obtained, any AEs that occurred and that may be ongoing, the nature of the relapse, and the available treatment options. Most patients with MM who are considered to be suitable transplant candidates will have received an ASCT during their initial treatment.

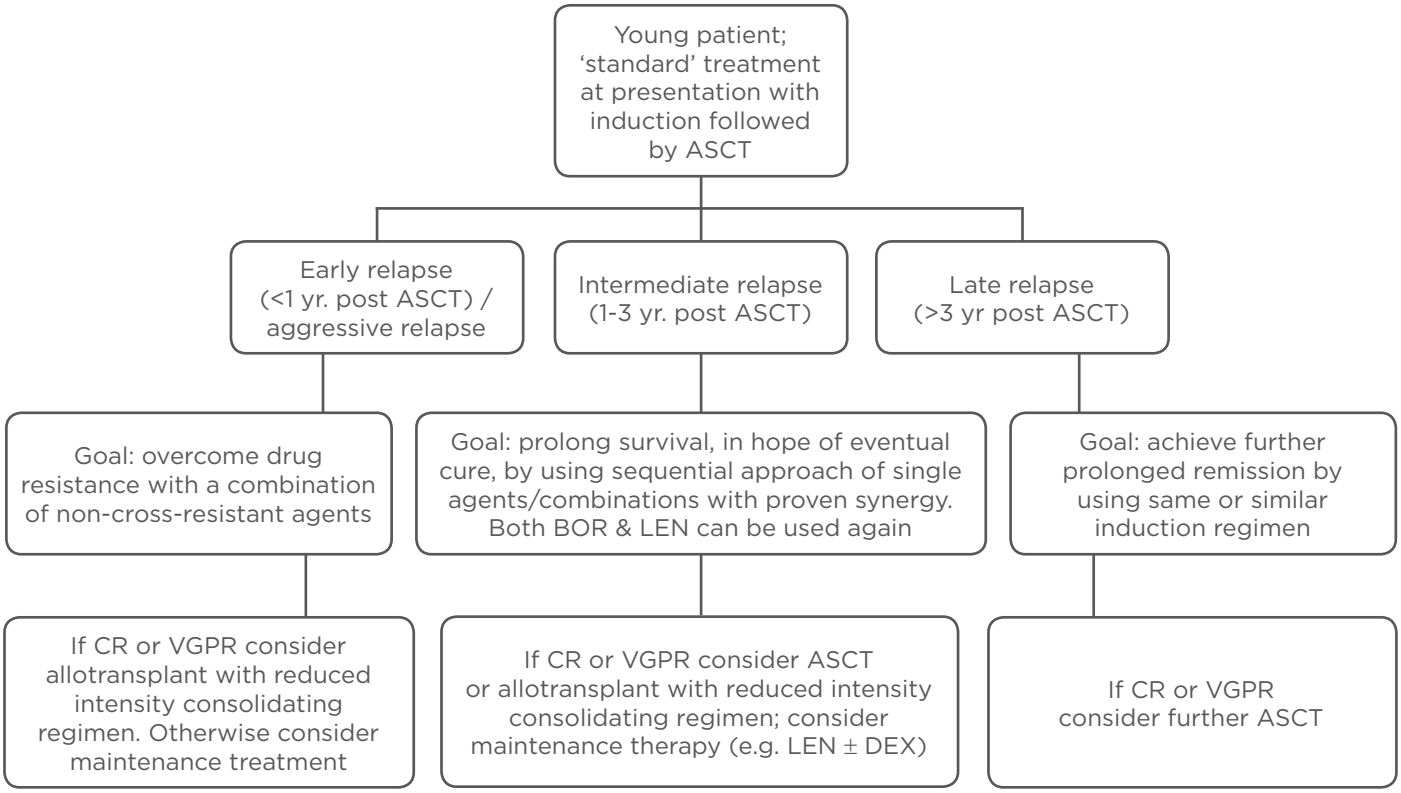

Figure 1: Treatment algorithm for first relapse in multiple myeloma.
ASCT: autologous stem cell transplant; BOR: bortezomib; CR: complete response; LEN: lenalidomide; VGPR: very good partial response; DEX: dexamethasone; yr: year(s).

There has been much debate as to whether, with the availability of modern drug treatments, it is necessary to include ASCT at first presentation of MM; the alternative is that it might only be used after the first relapse. A recently reported Phase III open-label, randomised study compared high-dose MLP + ASCT with MLP-prednisone-LEN (MPR), and also compared LEN maintenance therapy with no maintenance therapy in patients with newly diagnosed MM. Both PFS and OS durations were significantly longer with high-dose MLP + ASCT than with MPR. The median PFS was significantly longer with LEN maintenance than with no maintenance, but 3-year OS times were not significantly prolonged.[29]

Patients treated recently are likely to have received BOR and possibly also LEN and/or MLP. Those treated some time ago may have received THD or agents such as vincristine or doxorubicin (DOXO). It is important to consider the initial regimen in detail, the response to the various agents in it, and AEs. The nature of the response to initial treatment helps to determine the time to disease progression; this is likely to be short in those who showed only a minimal response to initial treatment, intermediate in those who achieved a complete response (no detectable monoclonal protein and <5% of plasma cells in the bone marrow), and longest in those who achieved an immunophenotypic complete response, in which multiparameter flow cytometry fails to detect any myeloma cells.[30-32] However, patients with a rapid and major response but with high-risk genetics can have a rapid and aggressive relapse. An aggressive relapse favours the use of multidrug combinations.

The patient's bone marrow reserve should be considered, as should issues related to previous AEs, such as peripheral neuropathy and deep venous thrombosis (DVT). Other patient factors which may be relevant include comorbidities such as diabetes mellitus and cardiac disease, physical fitness, quality of life (QoL), renal function, and social support. In a young patient (defined as <60 years) who has an early relapse (<1 year post ASCT), the goal should be to overcome drug resistance using a combination of non-cross-resistant agents (Figure 1).[33] Until recently, this situation pertained to around 5-10% of young patients with MM. There are a number of options available, including the following: the VDL-

PACE regimen (BOR with DEX, THD, and a 4-day continuous infusion of cisplatin, DOXO, CYC, and etoposide); the VRD regimen (BOR, LEN, and DEX); the VRD regimen with the addition of CYC; and the RAD regimen (LEN, adriamycin, and DEX).[34-36] In those patients with a complete or very good partial response, this treatment may be followed by an allotransplant by a reduced-intensity consolidating regimen, or else with a maintenance regimen.[37]

In a young patient with a late relapse (>3 years post ASCT), re-induction with the same initial regimen or a novel combination regimen followed by a further ASCT is appropriate (Figure 1).[33] At least until recently, approximately 10% of young patients with MM fell into this category. With the recent early use of new drug treatments, including in combination and of ASCT, the current median first remission time, of around 5 years, is significantly longer than it was just a few years ago. Consequently, more patients are likely to be candidates for a second ASCT.

Recently, the role of re-ASCT at the time of first relapse was investigated in a Phase III study of patients with MM who had suffered a relapse ≥18 months after their first ASCT.[38] Patients received BOR, DOXO, and DEX induction therapy and were then randomised to high-dose MLP 200 mg/m^2 + salvage ASCT or oral CYC (400 mg/m^2 per week for 12 weeks). The median TTP was significantly longer in those who received a further ASCT compared with those who did not (19 versus 11 months). Although the results support the wider use of re-ASCT in selected patients, it should be noted that 41% of potentially eligible patients were not randomised because of a failure to collect the necessary stem cells to allow ASCT, as a consequence of comorbidities, or because consent was withdrawn.

For the remaining ≈80% of young patients who relapse 1-3 years after initial treatment, the aim should be to prolong survival, hopefully until a curative treatment is available.[33] Until recently, this would probably have been achieved by the use of novel agents not used during the initial treatment. However, Phase II studies have demonstrated that retreatment with BOR,[39] and also with LEN,[40] is often successful with acceptable toxicity. Consequently, treatment of the first relapse can reasonably involve a further course of either of these agents for the majority of patients (Figure 1).

A further consideration is whether to treat for a fixed number of cycles, or with continued therapy until disease progression. The former is favoured in patients with indolent disease, and in those in whom further therapeutic possibilities exist. The latter is favoured following aggressive relapses and if treatment options are exhausted.[37] LEN with DEX is therefore a good choice; this two-drug combination remains a standard treatment for relapses. However, combinations of three drugs are being increasingly advocated, informed by trials such as ASPIRE14 and ELOQUENT2.[41] This trend may be changed to a two-drug combination such as CARF + DEX, according to the results of the ENDEAVOR trial.[15] However, in taking this decision, prior therapies and their efficacies must be considered.

In patients who have exhausted BOR and, more especially, LEN, the combination of POM + low-dose DEX would be a good choice, possibly optimised by the addition of a third agent (CYC or BOR) depending on the results of ongoing clinical trials. Relapsed elderly patients, who are not considered suitable for ASCT, should be assessed clinically as to whether they are suitable for active treatment. If so, the approach should be similar to that described for younger patients, but often using smaller drug doses. Both BOR and LEN have been shown to be effective in the elderly, as have the combinations of agents investigated in the ASPIRE, ENDEAVOR, and ELOQUENT studies. For others, treatment with oral CYC and prednisone should be offered.

Subsequent Relapses

In patients with MM who have further relapses, the recent availability of second and third-generation proteasome inhibitors, as well as immunomodulatory drugs and the deacetylase inhibitor PAN, adds significantly to the therapeutic possibilities. Once again, the possibility of using drugs to which the patient has responded to previously should be considered. When deciding whether to use single agents or combinations of drugs, the evidence for true synergy, rather than a purely additive effect, should be considered. Trial evidence suggests synergy between immunomodulatory drugs and DEX and between proteasome inhibitors and deacetylase inhibitors.

Future Possibilities

Despite the marked improvement in the survival of patients with MM over recent years, the condition

remains incurable; relapse is all but inevitable, even in those with the most favourable prognostic indicators. The relapsing nature of MM means that existing licenced treatment options will eventually become exhausted. There is therefore an on-going unmet clinical need for new treatments to be developed and made available. Currently, a plethora of potential novel treatments are emerging for relapsed disease, some still in the early stages of development, and others that may soon be approved. The following is a brief summary of some of the more promising agents in development, emphasising the breadth of different drug classes under investigation. More comprehensive reviews can be found elsewhere.[42]

Not all agents under investigation are new. For example, bendamustine (BDM) is an alkylating drug that has been investigated in MM patients over many years; it is now undergoing clinical trials in relapsed patients.[43] Furthermore, MLP-flufenamide is a dipeptide prodrug of MLP which appears to have greater potency than the parent drug.[44] However, a number of novel drugs have shown early promise, including filanesib,[45] which arrests cells in mitosis, tanespimycin, an Hsp90 inhibitor, combined with proteasome inhibitors,[46] and drugs that block signalling pathways, such as perifosine (an AKT inhibitor), and everolimus and temsirolimus (which target the mammalian target of rapamycin pathway).[47] Less promising have been studies of tyrosine and serine kinase inhibitors, and attempts to synchronise tumour cells with seliciclib, rendering them more susceptible to BOR.

CONCLUSIONS AND TREATMENT STRATEGIES

The treatment of patients with MM has moved from the era of chemotherapy to that of targeted drug therapy. This has been accompanied by improved survival outcomes. However, MM remains an incurable disease and the drugs used to manage it, although often less toxic than past chemotherapeutic regimens, still often cause significant morbidity as a consequence of AEs, including bone marrow suppression, DVT, and peripheral neuropathy, amongst others. As new treatments are developed to address the clear clinical need for these patients, a focus on safety and tolerability should be emphasised, as well as efficacy. It is crucial that attempts to prolong the patient's life do not ignore the importance of their QoL. The principal role of the treating clinician is to choose management strategies that maximise the therapeutic potential of the new agents available, whilst minimising the negative impacts on the patient and their family. This may mean taking different approaches in patients with similar disease profiles.

There is no widely accepted standard treatment pathway for patients with MM. The development of an internationally accepted, evidence-based treatment pathway for patients with MM would not only be welcomed by patients and clinicians alike, but would go some way to highlight the treatment gaps that patients with MM face. In those patients who can tolerate ASCT, initial treatment with an induction regimen with the first-generation proteasome inhibitor, BOR (alone or in combination with, for example, an immunomodulatory drug) followed by an ASCT is probably the most common current approach.

When the first relapse occurs, the most suitable response requires a detailed consideration of a range of factors described above. Usually, only symptomatic relapses are treated. In those patients who respond optimally to the initial treatment, re-induction with the same or modified regimen as used before, followed by a further ASCT, is an appropriate strategy. On the other hand, if the initial response was poor and short-lived, and/or if the relapse is aggressive, overcoming resistance using combinations of three or more drugs, including a proteasome inhibitor and an immunomodulatory drug, is appropriate. Making the choice between available proteasome inhibitors and immunomodulatory drugs should take into account what was used initially and the consequent AEs. For example, for patients previously exposed to BOR, either using the second-generation proteasome inhibitor CARF or the immunomodulatory drug LEN would be a good choice. In a patient treated with THD who had developed peripheral neuropathy, LEN or even POM would be suitable. In responders, a subsequent ASCT or allotransplant with a reduced-intensity conditioning regimen may be considered.

The approach during subsequent relapses is similar. Fortunately, the availability of third-generation proteasome inhibitors, immunomodulatory drugs, and PAN greatly increases the options available. The role of older drugs, such as MLP and BDM, should not be forgotten, and novel agents should be considered as they become available. The most promising of these include the deacetylase

inhibitors, the mAbs Elo and DARA, and signal transduction pathway inhibitors.

To conclude, it seems probable that for the treatment of MM the next decade will prove even more exciting than the last. Treatments that are becoming available offer the prospect of radically changing the survival curve for MM. While this curve may not plateau in the near future, the rate of relapse will become very low. The aims of researchers within this field are to bring to the bedside a range of safe drugs with low toxicity profiles and proven efficacy, which are capable of establishing a prolonged period of remission and even a cure for a subset of patients with MM.

Acknowledgements

Thanks are given to Dr Colin Ferrie and Dr Natalie Morris of Oxford Science Editing Ltd. for assistance with the preparation of the text of this manuscript.

REFERENCES

1. National Cancer Institute. SEER Stat Fact Sheets: Myeloma. 2015. Available at: http://seer.cancer.gov/statfacts/html/mulmy.html. Last accessed: 28 May 2015.

2. Cancer Research UK. Myeloma incidence statistics. 2014. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/incidence#heading-One. Last accessed: 28 May 2015.

3. Kumar SK et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood. 2008;111(5):2516-20.

4. Richardson PG et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med. 2005;352(24):2487-98.

5. 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.

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

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

8. San Miguel JF 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.

9. San Miguel JF et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol. 2014;15(11):1195-206.

10. 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.

11. Vij R et al. An open-label, single-arm, phase 2 study of single-agent carfilzomib in patients with relapsed and/or refractory multiple myeloma who have been previously treated with bortezomib. Br J Haematol. 2012;158(6):739-48.

12. Vij R et al. An open-label, single-arm, phase 2 (PX-171-004) study of single-agent carfilzomib in bortezomib-naive patients with relapsed and/or refractory multiple myeloma. Blood. 2012;119(24):5661-70.

13. Ludwig H et al. LBA28 Carfilzomib (K) vs low-dose corticosteroids and optional cyclophosphamide (CY) in patients (PTS) with relapsed and refractory multiple myeloma (RRMM): results from a phase 3 study (FOCUS). Ann Onc. 2014;25(suppl_4);doi:10.1093/annonc/mdu438.29. [Epub ahead of print].

14. Stewart AK et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med. 2015;372(2):142-52.

15. Dimopoulos MA et al. Carfilzomib and dexamethasone (Kd) vs bortezomib and dexamethasone (Vd) in patients (pts) with relapsed multiple myeloma (RMM): Results from the phase III study ENDEAVOR. Abstract 8509. ASCO Annual Meeting, 29 May – 2 June 2015.

16. Allegra A et al. New orally active proteasome inhibitors in multiple myeloma. Leuk Res. 2014;38(1):1-9.

17. Dimopoulos MA et al. The STRATUS trial (MM-010): A single-arm phase 3b study of pomalidomide plus low-dose dexamethasone (POM + LoDEX) in refractory or relapsed and refractory multiple myeloma. Abstract TPS8625. ASCO Annual Meeting, 29 May – 2 June 2015.

18. Larocca A et al. Pomalidomide, cyclophosphamide, and prednisone for relapsed/refractory multiple myeloma: a multicenter phase 1/2 open-label study. Blood. 2013;122(16):2799-806.

19. Hilger JD et al. A phase I/II study (NCT01541332) of pomalidomide (POM), dexamethasone (DEX), and pegylated liposomal doxorubicin (PLD) for patients with relapsed/refractory (R/R) multiple myeloma (MM). Abstract 8598. ASCO Annual Meeting, 31 May – 4 June 2013.

20. 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.

21. Berdeja JG et al. A phase I/II study of the combination of panobinostat (PAN) and carfilzomib (CFZ) in patients (pts) with relapsed or relapsed/refractory multiple myeloma (MM). Abstract 8513. ASCO Annual Meeting, 29 May – 2 June 2015.

22. Case Comprehensive Cancer Center. MLN9708 (ixazomib) in combination with panobinostat and dexamethasone in multiple myeloma. 2015. NCT02057640. https://clinicaltrials.gov/ct2/show/NCT02057640.

23. Laubach JP et al. Current strategies for treatment of relapsed/refractory multiple myeloma. Expert Rev Hematol. 2014;7(1):97-111.

24. 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.

25. Jakubowiak AJ et al. Phase I trial of anti-CS1 monoclonal antibody elotuzumab in combination with bortezomib in the treatment of relapsed/refractory multiple myeloma. J Clin Oncol. 2012;30(16): 1960-5.

26. Lonial S et al. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. N Engl J Med. 2015:doi:10.1056/NEJMoa1505654.

27. Lonial S et al. Phase II study of daratumumab (DARA) monotherapy in patients with ≥ 3 lines of prior therapy or double refractory multiple myeloma (MM): 54767414MMY2002 (Sirius). Abstract LBA8512. ASCO Annual Meeting, 29 May – 2 June 2015.

28. Vincent Rajkumar S. Multiple myeloma: 2014 Update on diagnosis, risk-stratification, and management. Am J Hematol. 2014;89(10):999-1009.

29. Palumbo A et al. Autologous transplantation and maintenance therapy in multiple myeloma. N Engl J Med. 2014;371(10):895-905.

30. Niesvizky R et al. The relationship between quality of response and clinical benefit for patients treated on the bortezomib arm of the international, randomized, phase 3 APEX trial in relapsed multiple myeloma. Br J Haematol. 2008;143(1):46-53.

31. Harousseau JL et al. Better quality of response to lenalidomide plus dexamethasone is associated with improved clinical outcomes in patients with relapsed or refractory multiple myeloma. Haematologica. 2010;95(10):1738-44.

32. Dimopoulos MA et al. Optimizing the use of lenalidomide in relapsed or refractory multiple myeloma: consensus statement. Leukemia. 2011;25(5):749-60.

33. San Miguel JF. Relapse/Refractory myeloma patient: potential treatment guidelines. J Clin Oncol. 2009;27(34):5676-7.

34. Knop S et al. Lenalidomide, adriamycin, and dexamethasone (RAD) in patients with relapsed and refractory multiple myeloma: a report from the German Myeloma Study Group DSMM (Deutsche Studiengruppe Multiples Myelom). Blood. 2009;113(18):4137-43.

35. Kapoor P et al. Bortezomib combination therapy in multiple myeloma. Semin Hematol. 2012;49(3):228-42.

36. Dicato M et al. Management of multiple myeloma with bortezomib: experts review the data and debate the issues. Oncology. 2006;70(6):474-82.

37. Bladé J et al. How I treat relapsed myeloma. Blood. 2015;125(10):1532-40.

38. Cook G et al. High-dose chemotherapy plus autologous stem-cell transplantation as consolidation therapy in patients with relapsed multiple myeloma after previous autologous stem-cell transplantation (NCRI Myeloma X Relapse [Intensive trial]): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15(8):874-85.

39. Petrucci MT et al. A prospective, international phase 2 study of bortezomib retreatment in patients with relapsed multiple myeloma. Br J Haematol. 2013;160(5):649-59.

40. Madan S et al. Efficacy of retreatment with immunomodulatory drugs (IMiDs) in patients receiving IMiDs for initial therapy of newly diagnosed multiple myeloma. Blood. 2011;118(7):1763-5.

41. Romano A et al. Salvage therapy of multiple myeloma: the new generation drugs. Biomed Res Int. 2014;2014:456037.

42. Ocio EM et al. New drugs and novel mechanisms of action in multiple myeloma in 2013: a report from the International Myeloma Working Group (IMWG). Leukemia. 2014;28(3):525-42.

43. Pönisch W et al. Combined bendamustine, prednisolone and thalidomide for refractory or relapsed multiple myeloma after autologous stem-cell transplantation or conventional chemotherapy: results of a Phase I clinical trial. Br J Haematol. 2008;143(2):191-200.

44. Chauhan D et al. In vitro and in vivo antitumor activity of a novel alkylating agent, melphalan-flufenamide, against multiple myeloma cells. Clin Cancer Res. 2013;19(11):3019-31.

45. Shah JJ et al. The Novel KSP Inhibitor ARRY-520 Is Active Both with and without Low-Dose Dexamethasone in Patients with Multiple Myeloma Refractory to Bortezomib and Lenalidomide: Results From a Phase 2 Study. Abstract 449. ASH Annual Meeting, 8-11 December 2012.

46. Richardson PG et al. Perifosine plus bortezomib and dexamethasone in patients with relapsed/refractory multiple myeloma previously treated with bortezomib: results of a multicenter phase I/II trial. J Clin Oncol. 2011;29(32):4243-9.

47. Gentile M et al. Perspectives in the treatment of multiple myeloma. Expert Opin Biol Ther. 2013;13 Suppl 1:S1-S22.