Multiple myeloma treatment at relapse after autologous stem cell transplantation: a practical analysis

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Abstract

Over the past decade, significant advances have been made in the field of multiple myeloma. Introduction of the so-called novel agents, proteasome inhibitors (PI) and immunomodulatory drugs (IMiD), and improved supportive care have resulted in significantly better outcome. Standard first line treatment in fit patients include PI and IMiD based induction, high dose melphalan with autologous hematopoietic stem cell transplantation (ASCT) and consolidation/maintenance. However, despite these progresses MM remains incurable for the majority of patients and most patients will relapse. Next generation PI (carfilzomib, ixazomib) and IMiD (pomalidomide) and new therapeutic classes: monoclonal antibody (elotuzumab, daratumumab) and pan-deacetylase inhibitors (panobinostat) have been successfully evaluated in relapse multiple myeloma. Some of these new agents are now approved for multiple myeloma treatment at relapse. However choosing the most appropriate treatment at relapse may be difficult. This review sum up the most important studies and provide evidence to choose the most relevant therapeutic strategy for relapse after ASCT, based on disease, patient and previous treatment related parameters.

Keywords: multiple myeloma, transplant eligible patients, first relapse, autologous stem cell transplantation, new agents, treatment

Clinical situation

The patient is a 60-year-old man with a newly diagnosed multiple myeloma, and no medical history. He is still active, working as a clerk and lives independently with his wife. Baseline assessment shows an IgG lambda multiple myeloma, with a monoclonal IgG protein level of 34 g/L, hemoglobin 10.3 g/dL, calcium 2.4 mmol/L, creatinine 82 μmol/L, albumin 32 g/L and β2-microglobulin 4.2 mg/L (ISS II). The skeletal survey reveals lytic lesions in the skull, the ninth thoracic vertebra and the left humerus, and a bone marrow biopsy shows 45 percent involvement by abnormal plasma cells. There is no t(4;14), nor del17p by FISH. He is treated with induction bortezomib, lenalidomide and dexamethasone (VRD), and serum protein electrophoresis demonstrates a partial response with > 70% decrease in monoclonal IgG protein level (10 g/L). He then receives high dose melphalan (HDM) with autologous hematopoietic stem cell transplantation (ASCT) and support consolidation with 2 additional cycles of VRD. He did not accept to receive any maintenance therapy after ASCT. Response evaluation at 3 months after ASCT (serum electropheresis, immunofixation and bone marrow aspirate) reveal complete remission. However, the patient is concerned about relapse risk and treatment options. He returns to discuss further management.

Challenges in diagnosis of relapse

Multiple myeloma (MM), is the second most common hematologic malignancy[1]. Over the past decade, significant advances have been made in the field of MM. Introduction of the so-called novel agents, proteasome inhibitors (PI) and immunomodulatory drugs (IMiD), and improved supportive care have resulted in significantly better outcome. However, MM remains incurable for the majority of patients. At present, a definition of cure requires a relapse-free interval of at least 10-15 years[2, 3]. After HDM and ASCT, at most 10-15% of patients fall in this category[3]. Therefore, the large majority of MM patients will relapse.

According to the International Myeloma Working Group criteria, progressive disease in MM is defined as an increase of 25% from nadir in the serum (with a minimum value of 0.5 g/dL) or the urine M-component (with a minimum value

of 200 mg/24H), or an increase in the difference between involved and non-involved free-light chain immunoglobulin > 10 mg/dL[4]. In patients who lack measurable paraprotein level, progression is defined by an increase in bone marrow plasma cells ≥ 10%, development of new/increasing size of bone/soft tissue lesion, or unexplained serum calcium > 2.65 mmol/L[4]. Refractory relapse MM is defined as disease progression on therapy or within 60 days of the last treatment in patients who had achieved a minimal response[5], while patients who never achieved a such response and progress while on therapy are defined as "primary refractory"[5]. By definition, a clinical relapse requires direct indicators of increasing disease and end organ dysfunction (CRAB features: symptoms of hypercalcemia, renal insufficiency, anemia and bone disease), in addition to biochemical progression[4].

Significant advances have been made in the field of multiple myeloma over the past years and several therapeutic options are available at relapse.

Summary of current practices

Thalidomide (THAL), bortezomib (BTZ) and lenalidomide (LEN) have been extensively studied in relapse or refractory relapse MM[6].

Thalidomide. A systematic review of phase II trials of combination of THAL and dexamethasone (DEX) reported an overall response rate [overall response rate (ORR): complete remission (CR) + partial remission (PR)] of 46% in patients not previously exposed to an IMiD[7]. A phase III prospective study compare THAL + DEX to BTZ + DEX in 131 patients with refractory relapse MM and not previously exposed to an IMiD[8]. Median progression-free survival (PFS) and ORR were similar between the THAL group (respectively, 9.0 months and 55%) and the BTZ group (respectively, 7.2 months and 63%). This study suggest that THAL + DEX have an efficacy comparable to BTZ + DEX in refractory relapse MM patients not previously exposed to IMiDs. However, disappointing results have been reported using THAL at relapse in patients initially treated with IMiDs[9]. Therefore, given that most patients do receive an IMiD as part of first-line treatment, the role of THAL in relapsed MM is very limited. THAL + DEX remains a valid, cost-effective, option in patients not previously exposed to IMiDs.

Bortezomib. A phase II study evaluated retreatment with BTZ, in a cohort of 130 patients responding for at least 6 months to this drug[10]. Such retreatment, without or with DEX, was associated with an ORR of 40%[10]. However, further improvement can be obtained by adding a third drug to BTZ + DEX. This can either be an alkylating agent (cyclophosphamide (Cy)[11, 12], bendamustine[13], melphalan[14]), an anthracycline (pegylated doxorubicin[15]), an IMiD (THAL[16], LEN[17]), or a histone deacetylase inhibitor (panobinostat[18], vorinostat[19]). These combinations lead to higher ORR, from 55% to 87%. Although subcutaneous administration of BTZ significantly decreases the incidence of peripheral neuropathy[20], retreatment with BTZ must be avoided in patients with persistent peripheral neuropathy (Grade ≥2).

Lenalidomide. Two randomized phase 3 trials have evaluated LEN + DEX versus DEX alone in relapsed or refractory relapse MM[21, 22] (**Table 1**). The superiority of the LEN + DEX combination was confirmed at a median follow-up of 48 months in a pooled update of both trials[23]. The median PFS was 11.1 months and the ORR was 60.6% in the LEN + DEX group[23]. Furthermore, there was a significant benefit in overall survival in patients treated with LEN + DEX (median of 38.0 versus 31.6 months, p=0.045), despite the fact that 47.6% of those who were randomized to DEX+ placebo ended up receiving a LEN-based treatment after disease progression or study unblinding[23]. These studies led to approval of the drug, and the combination LEN + DEX is considered a standard for relapsed MM. It has been the backbone for several studies evaluating new agents as part of a three-drug regimen in relapse MM.

Carfilzomib. Stewart et al. reported the results of the randomized phase 3 ASPIRE trial, comparing the combination LEN, DEX and carfilzomib (CFZ) with that of LEN + DEX alone[24]. CFZ is a second-generation epoxyketone proteasome inhibitor, that binds selectively and irreversibly to the constitutive proteasome and immunoproteasome[24]. A series of 792 patients with relapsed MM after a median of two lines of treatment were randomized to receive one of the two combinations. The PFS was significantly improved with CFZ (median, 26.3 months, vs. 17.6 months in the control group; *P*=0.0001). This improved PFS in the CFZ group was observed among patients previously treated with BTZ

or LEN, and in patients with high-risk cytogenetic (defined by the presence of t(4;14), t(14;16) or deletion 17p). The ORR were 87.1% and 66.7%, in the LEN +DEX + CFZ and the LEN + DEX groups, respectively (P<0.0001). Of note, there were no differences in adverse events of grade 3 or higher, and patients in the CFZ group reported better quality of life. These impressive results led to the approval by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) of CFZ in combination with LEN and DEX in patients with relapsed MM who have received 1 to 3 prior lines of treatment for the FDA or at least one previous line of treatment for the EMA. CFZ promotes a better proteasome inhibition than BTZ[25], is effective in BTZ-refractory patients[24, 26], and is associated with a lower rate of peripheral neuropathy, even when compared to subcutaneous BTZ[26]. Dimopoulos et al. reported recently the results of the randomized phase 3 ENDEAVOR trial comparing the combinations CFZ + DEX and BTZ + DEX in relapse or refractory relapse MM[27]. The median PFS was 18.7 months in the CFZ group versus 9.4 months in the BTZ group (P<0.0001). The ORR were 77% and 63%, in the CFZ and the BTZ groups, respectively (P<0.0001). The number of patients who had grade ≥ 2 peripheral neuropathy, was significantly higher in the BTZ group (32% versus 6% in the CFZ group; P<0.0001). However, we must keep in mind that, while BTZ can be administered subcutaneously, CFZ administration is strictly intravenous and requires 6 infusion visits per 28-day cycle[24]. In addition, proteasome inhibition has the potential of significant cardiac toxicity via the accumulation of intracellular protein aggregate[28]. The ENDEAVOR trial reported a higher incidence of cardiac failure grade ≥ 3 in the CFZ group (4.3% versus 1.7% in the BTZ group)[27]. A pooled analysis of CFZ safety in 526 patients with advanced MM treated as part of clinical trial, reported cardiac failure in 7.2% of patients[26]. Therefore, particular attention must be paid to patients with history of cardiac failure or ongoing cardiac failure.

Ixazomib. Another next generation proteasome inhibitor, Ixazomib (IXA), has been evaluated in combination with LEN and DEX in the randomized phase 3 TOURMALINE-MM1 trial[29]. IXA is a reversible proteasome inhibitor, which has the advantage of being orally administered. A total of 722 patients with refractory relapse MM were randomized to receive LEN, DEX and IXA or LEN and

DEX alone. The PFS was significantly improved with IXA (median, 20.6 months, vs. 14.7 months in the control group; *P* =0.012). The ORR was also improved in the IXA group, being 78% vs. 72% in the control group (p=0.035). No increase in overall toxicity was reported in the IXA group. Although addition of IXA to LEN and DEX resulted in a higher rate of peripheral neuropathy (27% versus 22% in the control group)[29], the incidence of grade 3 events was only 2% compared to 3% in patients who received CFZ[24] and 6% in those treated with subcutaneous BTZ[20]. This study led to the approval by the FDA of IXA in combination with LEN and DEX in relapsed MM patients who had received at least one prior therapy. IXA also received a positive opinion of the Committee for Medicinal Products for Human Use of EMA on September 16, 2016. Of note, IXA is the first in class oral proteasome inhibitor and the LEN + DEX + IXA triplet offers the advantage of being fully orally administered.

Monoclonal antibodies. Several studies evaluated triplet combinations including a monoclonal antibody, elotuzumab (ELO) or daratumumab (DARA). ELO is an immunostimulatory monoclonal antibody targeting signaling lymphocytic activation molecule F7 (SLAMF7), a glycoprotein expressed on myeloma and natural killer cells but not on normal tissues, that enables selective killing of myeloma cell with minimal effect on healthy tissue[30]. The randomized phase 3 ELOQUENT-2 trial evaluated ELO in combination with LEN and DEX, as compared with LEN and DEX alone in 646 patients with refractory relapse MM[31]. The median PFS in the ELO group was 19.4 versus 14.9 months in the control group (*P*<0.001). The ORR was 79% versus 66% in the control group (*P*<0.001). There was no difference in the serious adverse event incidence between the two groups. These findings led to the approval by the FDA and the EMA of ELO in combination with LEN and DEX in patients with relapsed MM who had received ≥ 1 prior lines of treatment (up to 3 for the FDA). ELO has also been evaluated in combination with a PI and steroids. A randomized phase II trial compared the combination of ELO, BTZ and DEX versus BTZ and DEX alone in 152 patients with refractory relapse MM[32]. The median PFS in the ELO group was 9.7 months, versus 6.9 months in the control group (*P*=0.09), with corresponding ORR of 66% versus 63%. This study suggests that the addition of

ELO to BTZ and DEX may improve PFS, however confirmatory studies are necessary.

The second monoclonal antibody with an advanced clinical development, DARA, targets CD38. A phase 1/2 trial evaluates DARA in combination with LEN and DEX[33]. The first phase was a dose escalation study to identify DARA maximum tolerated dose. The second part was a cohort expansion to evaluate DARA, administered at the maximum tolerated dose (16 mg/kg), in combination with LEN and DEX. In the 32 patients treated in the expansion cohort, the ORR was 81%, including 6 (19%) PR and 9 (28%) very good partial responses, 3 (9%) CR and 8 (25%) stringent CR. These impressive results and the good tolerance of the combination, lead to a prospective randomized phase 3 study POLLUX, evaluating the addition of DARA to the combination of LEN and DEX versus LEN and DEX alone[34]. 569 patients with refractory relapse MM were included. With a median follow-up of 13.5 months, the median PFS was not yet reached in the DARA group, versus 18.4 months in the control group (P<0.001). A significantly higher ORR was observed in the DARA group than in the control group (93% versus 76%, P<0.001), as was a higher rate of CR or better (43% versus 19%, P<0.001). Furthermore, in the DARA group, 22% of patients had results below the threshold for minimal residual disease as compared with 5% of those in the control group (P<0.001). No increase in overall toxicity was reported in the DARA group beside infusion reactions related to DARA. Infusion reactions were reported in 48% of patients receiving DARA and were mostly grade 1/2 with only 5% experiencing grade 3.

DARA efficacy has also been evaluated in combination with BTZ and DEX in the prospective randomized phase 3 study CASTOR[35]. A total of 498 patients with refractory relapse MM were randomized to receive DARA, BTZ and DEX or BTZ and DEX alone. With a median follow-up of 7.4 months, the median PFS was not yet reached in the DARA group, versus 7.2 months in the control group (P<0.001). The ORR was also improved in the DARA group, being 79% versus 66% in the control group (P<0.001), similarly the rate of CR or better was significantly improved in the DARA group compared to the control group (19% versus 9%; P=0.001) No increase in overall toxicity was reported in the DARA group. Although in the DARA group, 45% of patients presented DARA infusion-

related reaction, with a majority of grade 1/2 reaction and 9% of grade 3 reaction.

Currently, DARA monotherapy is approved by the FDA in refractory relapse MM patients who have received at least 3 prior lines of therapy, including a proteasome inhibitor and an IMiD agent, or who are double refractory to a proteasome inhibitor and an IMiD agent, based on the phase 2 MMY2002 and the phase 1/2 GEN501 monotherapy studies[36, 37]. DARA monotherapy is also approved by the EMA in refractory relapse MM patients whose prior therapy, included a proteasome inhibitor and an IMiD agent and who have demonstrated desease progression on the last treatment.

Pan-deacetylase inhibitors. Pan-deacetylase inhibitors, which are epigenetic modulators, have emerged as a novel class of anti-myeloma drug. A randomized phase-3 trial, PANORAMA-1, evaluated panobinostat (PAN), a pan-deacetylase inhibitor, in combination with BTZ and DEX, versus placebo, BTZ and DEX, in relapsed or refractory relapse MM[18]. Patients were in an early relapse setting (1 to 3 previous lines of treatment). The median PFS was significantly higher in the PAN group: 11.99 versus 8.08 months in the control group (P<0.0001). The ORR was not significantly different between the PAN, 60.7% and the control group, 54.6% (P=0.09). PAN, in combination with BTZ and DEX, is approved by the FDA and the EMA for patients having received ≥ 2 lines of treatment, including BTZ and an IMiD. However, in the PANORAMA-1 trial, the association PAN + BTZ + DEX was associated with an increased incidence of grade 3 thrombocytopenia, diarrhea, asthenia and peripheral neuropathy. Therefore, while use of SC instead of IV BTZ may improve the safety profile, this combination must be handled cautiously.

Another histone deacetylase inhibitor, vorinostat (VOR), has been evaluated in early relapse MM[19]. The phase-3 VANTAGE-088 trial randomized patients to VOR + BTZ or BTZ alone[19]. The median PFS was significantly higher in the VOR group, 7.63 versus 6.83 months in the control group (P=0.01). However, with a difference of less than a month, the clinical relevance of this combination is small and limited[19].

Pomalidomide. Pomalidomide (POM), a third generation IMiD, have been evaluated in a randomized phase 3 study in patients with relapsed or refractory

relapse MM, previous BTZ and LEN failure and adequate prior alkylating therapy[38]. Patients were randomized to receive either POM and low-dose DEX or high-dose DEX alone. In those heavily pretreated patients (median of 5 previous lines of treatment), the median PFS was significantly higher in the POM group: 4.0 versus 1.9 months in the control group. An phase 3b study, confirms a median PFS of 4.6 months on a similar population of 682 patients[39]. These results were the basis for POM approval by the FDA and the EMA (in combination with low-dose DEX in Europe) for patients who had received ≥ 2 previous lines of treatment, including LEN and DEX, and progressive under previous therapy. POM was also evaluated in combination with BTZ + DEX and CFZ + DEX as part of a phase 1/2 clinical trial in refractory relapse MM, paving the way for the use of a triplet regimen including POM at first relapse.

Cyclophosphamide. Cyclophosphamide is an alkylating agents used orally or intravenously and usually well tolerated in MM. Several triplet regimens including Cy in combination with THAL, LEN or BTZ in refractory relapse MM have been reported. Kyriakou et al. reported an ORR of 79% and a 2-years PFS of 34% using the combination of Cy, THAL and DEX in a phase I/II study[40]. Two phases I/II study evaluate the combination of Cy, LEN and either DEX[41] or prednisone[42] in refractory relapse MM with an ORR of 81% and 94% respectively. 2-years PFS was 56% with the combination of Cy + LEN + DEX, and median PFS was 16.4 months using the combination of Cy + LEN + prednisone. Kropff et al. performed a phase II study evaluating the combination of Cy, BTZ and DEX for refractory relapse MM[12]. This combination was associated with an ORR of 22% and a median PFS of 12 months. Similarly, the combination of Cy, BTZ and prednisone have been evaluated in a phase I/II study with an ORR of 89% at the highest dose level and a 1-year PFS of 83%[11]. Overall, triplet regimens combining IMiD or BTZ with steroids and Cy appear to be an effective strategy, particularly cost-effective compared to the new agents based triplet regimens.

Second ASCT. The role of second HDM-ASCT in relapsed MM has also been investigated. A randomized phase 3 study, included patients with first progressive or relapsed disease at least 18 months after a previous ASCT[43]. All eligible patients received BTZ, doxorubicin and DEX induction therapy, and

peripheral blood stem cell mobilization and harvesting. Patients with adequate stem-cell harvest were randomized to HDM 200 mg/m^2 plus salvage ASCT or oral Cy. The median PFS was significantly longer in the ASCT group (19 compared to 11 months in the Cy group; p<0.0001)[43]. Furthermore, a recently published update, confirm that ASCT improve PFS and show an advantage in OS in the ASCT group: median OS was significantly higher in the ASCT group, 67 months, versus 35 months in the Cy group (*P*=0.0169)[44]. However, the results of this study must be interpreted with caution. Oral Cy is not a standard treatment for first relapse after HDM-ASCT, in contrast to the highly effective combination therapies including PI and IMiD. Therefore, a decision to proceed to a second HDM-ASCT must be carefully weighed against a combination of new agents. A second HDM-ASCT should probably be considered only in fit, transplant-eligible patients, with a long PFS after the first HDM-ASCT (≥18 months)[45].

Allogeneic transplantation. The feasibility of allogeneic hematopoietic stem cell transplantation (allo-HCT) with a reduced intensity conditioning regimen (RIC) in relapsed MM has been demonstrated in several studies[46-48]. However, RIC allo-HCT is still associated with high non-relapse mortality, around 20–25% at 1 year, and a high relapse incidence, leading to a 2 year PFS of 26–38%[46-48]. Therefore, allo-HCT should not be performed routinely outside clinical trials; it may be an option in very few selected patients, particularly those with high-risk disease[45].

General management approaches

The immediate aim of treatment at relapse is disease control to treat/prevent CRAB symptoms, relieve the patient's symptoms and avoid end organ damage. The impact of the depth of the response on survival is still controversial in the relapse setting[6]. However, growing amount of data suggest a relationship between the two parameters, demonstrating that a better quality of response may be associated with an improved outcome, even beyond first line treatment[6, 49-51]. Therefore, patients with good performance status at relapse should receive therapy designed to achieve the deepest possible response in order to improve survival[6].

At relapse, treatment choice must be individualized in order to identify the treatment with the best efficacy versus toxicity balance for each patient. Overall, disease-related, patient-related, and previous treatment-related parameters must be taken into account for the treatment selection in MM at relapse.

Disease-related parameters. The clinical course of MM is very different from one patient to another. In patients with symptomatic relapse with CRAB features, threatening or not, treatment is mandatory and cannot be delayed. In contrast, in patients with asymptomatic relapse, the decision to treat depends on the paraprotein kinetic increase. Those with a doubling of the M-component within 2 months should be treated[5]. For the remainder, a careful watch and wait policy every 1-3 months is recommended[5].

In addition, the therapeutic strategy will be different in patients with a standard-risk from that for high-risk MM. The latter must receive immediate combination therapy at relapse. Based on the International Myeloma Working Group (IMWG) recommendations for treatment of high-risk MM, BTZ and CFZ treatment improve CR, PFS and OS in t(4;14) and del(17p) whereas LEN may be associated with improved PFS in (4;14) and del(17p) and POM show promising results in del(17p)[52]. Therefore, we suggest to use a treatment combining a PI and an IMiD in high-risk cytogenetic. Monoclonal antibodies may be used in those patients, however data are required to know they overcome the bad prognosis of high-risk cytogenetic. For patients with threatening CRAB features/aggressive relapse, attention must be paid to the kinetic of response expected, in order to favor treatment with a quick expected response. Response to new generation PI, CFZ and IXA, in combination with LEN + DEX, is quite quick with a median time to first response of one month[24, 27]. For monoclonal antibody, kinetic of response to DARA monotherapy is similar to that of PI, about a month[36, 37], while response to ELO, in combination with LEN + DEX, is rather slow, with a median time to first response of 50 days[53]. Median time to first response using pan-deacetylase inhibitors in combination with BTZ +/- DEX is also longer compare to PI, ranging from 36 days using VOR[19] to 1.5 months with PAN[18, 54]. Finally response to POM + DEX is also rather slow with a median time to first response of 1.9 months.[55] Whenever possible, these patients should be included in a clinical trial evaluating novel agents. High-risk MM are patients

with extramedullary disease or plasma cell leukemia, adverse cytogenetics (del17p or t(4;14)), a high-risk gene expression profile, or an International Staging System (ISS) 3 (low albumin and high β2-microglobulon level) and high lactate dehydrogenase[56-58].

***Patient-related parameters*.** Patients' age and performance status must be considered before choosing the best treatment. However, in the setting of the first relapse after ASCT, most patients are usually in good general condition, and frailty is not an issue. More important in these patients, is the evaluation of renal function and pre-existing toxicities. Renal insufficiency at relapse may be caused by either disease progression or associated predisposition conditions. All PIs (BTZ[59], CFZ[26] and IXA[60]) can be used without dose adjustment in patients with impaired renal function. Among IMiDs, while LEN requires dose adjustments, both THAL[61] and POM[62] do not. The histone deacetylase inhibitors PAN and VOR can be used at their standard doses and may be associated with a renoprotective effect[63, 64]. Regarding monoclonal antibodies, ELO can be safely used with no dose adjustment, including in patients with end-stage renal disease[65]. We expected that DARA tolerance will be similar, DARA renal safety has been shown only in patients with moderate renal impairment [34-36]. For alkylating agents, cyclophosphamide does not require dose adjustment, but melphalan does[66]. While ASCT is feasible in MM with renal insufficiency, usually when using a reduced dose of melphalan (140 mg/m^2)[67], data evaluating second ASCT at relapse in patients with renal insufficiency are scarce. Given the increased risk of transplant-related mortality for patient with renal insufficiency compared to those without[67], the decision to proceed to a second ASCT in these patients at relapse must be carefully weighted. Combination therapy is feasible in patients with renal insufficiency, provided any dose adjustments are respected. The International Myeloma Working Group has recently published recommendations for the management and dose adjustment of MM related renal impairment[66].

Previous treatment-related parameters. The patients' tolerability of a previous treatment, in particular pre-existing toxicity, must be carefully checked. In patients with grade ≥ 2 peripheral neuropathy, BTZ should be avoided and replaced by a second generation PI. Retreatment with IMiDs in patients with a

severe history of thromboembolic events must be very cautious and associated with full anticoagulation therapy [68, 69]. In patients who experienced severe myelosuppression during the first line, use of most myelosuppressing agents, such as alkylating drugs, must be avoided. For combination therapy design, lack of overlapping toxicities, such as peripheral neuropathy and myelosuppression, must be favored.

The depth of response and remission duration after the first line of treatment must be evaluated. Patients who relapse within 12 months after ASCT have a poor outcome[70], and should receive combination therapy (triple combination whenever available) including novel agents, if possible within a clinical trial. In contrast, in patients with a longer duration of response, re-treatment with prior therapies is feasible. However, in the setting of the first relapse after ASCT, re-treatment should be done as part of combination therapy, in order to improve the quality of the response. A second ASCT could be considered in patients with a PFS ≥ 18 months[45].

Finally, treatment approval by the FDA or EMA must also be taken into consideration. In this regard, combinations therapy based on the pan-deacetylase inhibitor PAN or POM are only approved for patients having received ≥ 2 lines of treatment and therefore are not the first option for treatment at first relapse after ASCT.

The patient treated in our case vignette ultimately presented a clinical relapse 2 years latter, with a high disease burden. He immediately received a second line treatment combining re-treatment with LEN in association with a second generation PI, CFZ and DEX, followed by a second ASCT. The patient finally achieved a second complete remission.

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Authorship

FM, JLH and MM designed the manuscript, analyzed the literature, and wrote the manuscript

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Figure legend.

Figure 1. Principal regimen available for treatment of first relapse after autologous stem cell transplantation (ASCT) and relevant factors for treatment selection. allo-SCT is for allogeneic stem cell transplantation.

Table 1. Overview of recent studies investigating newer agent combinations in relapsed multiple myeloma

Study	Phase	N	Regimen	Prior lines	ORR %	≥CR %	PFS m	OS m	Median FU m
Dimopoulos et al. 2007[21]	III	176	Rd	≥1	60.2	15.9	11.3	NT	16.4
MM-010		175	D		24.0	3.4	4.7	20.6	
Weber et al. 2007[22]	III	177	Rd	≥1	61.0	14.1	11.1	29.6	17.6
MM-009		176	D		19.9	0.6	4.7	20.2	
Stewart et al. 2015	III	396	CFZ-Rd	2 (1-3)	87.1	31.8	26.3	NR	32.3
ASPIRE[24]		396	Rd		66.7	9.3	17.6	NR	31.5
Dimopoulos et al. 2016	III	464	CFZ-d	2 (1-2)	77	13	18.7	NR	12.5
ENDEAVOR[27]		465	BTZ-d		63	6	9.4	NR	11.9
Moreau et al. 2016	III	360	IXA-Rd	1 (1-3)	78.3	12	20.6	NR	23.3
TOURMALINE-MM1[29]		362	Rd		71.5	7	14.7	NR	22.9
Lonial et al. 2015	III	321	ELO-Rd	2 (1-4)	79	4	19.4	NR	24.5
ELOQUENT-2[31]		325	Rd		66	7	14.9	NR	
Jakubowiak et al. 2016[32]	II	77	ELO-BTZ-d	1 (1-3)	66	4	9.7	NR	15.9
		75	BTZ-d	1 (1-3)	63	3	6.9	NR	11.7
Dimopoulos et al. 2016	III	286	DARA-Rd	1 (1-11)	93	43	NR	NR	13.5
POLLUX[34]		283	Rd	1 (1-8)	76	19	18.4	NR	
Palumbo et al. 2016	III	251	DARA-BTZ-d	2 (1- ≥4)	83	19	NR	NR	7.4
CASTOR[35]		247	BTZ-d	2 (1- ≥4)	63	9	7.2	NR	
San-Miguel et al. 2014	III	387	PAN-Vd	1 (1-3)	60.7	11	11.99	33.6	6.5

Treatment MM relapse after ASCT

PANORAMA-1[18]		381	Vd		54.6	6	8.08	30.4	5.6
Dimopoulos et al. 2013	III	317	VOR-Vd	2 (1-3)	56	8	7.63	NR	14.2
VANTAGE-088[19]		320	Vd		41	5	6.83	28	
San Miguel et al. 2013	III	302	POM-d	5 (2-14)	31	1	4	11.9	10
MM-003[38]		153	D	5 (2-17)	10	0	1.9	7.8	
Cook et al. 2014	III	89	HDM-ASCT	1	83	39	19	67	50
NCRI Myeloma X Relapse[43, 44]		85	Cy		75	22	11	52	54

Abbreviations: ORR, overall response rate; CR, complete remission; PFS, progression free survival; m, month; OS, overall survival; FU, follow-up; Rd, lenalidomide-dexamethasone; D, high dose dexamethasone, CFZ, carfilzomib; IXA, ixazomib; ELO, elotuzumab; DARA, daratumumab; PAN, panobinostat; Vd, bortezomib-dexamethasone; VOR, vorinostat; POM, pomalidomide.

ASCT (melphalan 200) based frontline treatment

First relapse

Consider:

- Disease related parameters
  - Symptomatic
  - High-risk disease
- Patient related parameters
  - Age, performance status
  - Renal insufficiency
- Previous treatment related parameters
  - Neuropathy
  - Thromboembolic events
  - Remission duration

Bortezomib + dexamethasone in combination with:

- **Cyclophosphamide**
- **Pegylated doxorubicin**
- **Thalidomide or lenalidomide**
- **Panobinostat**
- **Daratumumab**

Lenalidomide + dexamethasone in combination with:

- **Cyclophosphamide**
- **Carfilzomib**
- **Ixazomib**
- **Elotuzumab**
- **Daratumumab**

others

- **carfilzomib + dexamethasone**
- **pomalidomide + dexamethasone**
- **second ASCT, allo-SCT**

Highlights

- No standard of care for multiple myeloma relapse after autologous transplantation
- Combination regimen including one or two novels agents are generally preferred
- Treatment is individualized based on toxicity, patient and disease characteristics