Management of relapsed and refractory multiple myeloma patients

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SUMMARY

For the majority of multiple myeloma (MM) patients, their disease will behave as a chronic disorder with episodes of remission followed by disease progression. Whereas the treatment approach in frontline is rather uniform, treatment at relapse has become more heterogeneous, as therapeutic choices at this stage are driven by many factors including disease characteristics and patient status, but also the previous treatment(s), their therapeutic effect and toxicities, and drug availability. With each treatment course patients also tend to become more vulnerable to hematological and non-hematological toxicities. Therefore, particularly at later relapses where there is no standard of care, the benefits and potential risks of therapeutic decisions should be carefully balanced in each individual patient, to minimize excess toxicities. In this review article, an overview is provided of the currently available treatment options for patients with relapsed or refractory MM.

INTRODUCTION

Despite the therapeutic advances made in front-line treatment, multiple myeloma (MM) still remains largely incurable. Around 20-30% of patients will not make it to a next treatment line because of intercurrent diseases or death.[1] For the majority of patients, their myeloma will behave as a chronic disorder with episodes of remission followed by disease progression. Whereas the treatment approach in front-line is rather uniform, treatment at relapse has become more heterogeneous, as therapeutic choices at this stage are driven by many factors including disease characteristics and patient status, but also the previous treatment(s), their therapeutic effect and toxicities, and drug availability. Additionally, one has to keep in mind that at each relapse myeloma will be more difficult to treat due to the emergence of resistant clones.[2] With each treatment course patients also tend to become more vulnerable to hematological and non-hematological toxicities. Therefore, particularly at later relapses where there is no standard-of-care, the benefits and potential risks of therapeutic decisions should be carefully balanced in each individual patient, to minimise excess toxicities. In this paper we discuss some general aspects on the approach to the patient with relapsed MM, followed by a more in depth description of the anti-myeloma drugs and treatment regimens that are currently available, or will become available in the near future.

OPTIMAL TIMING OF TREATMENT INITIATION

According to the International Myeloma Working Group (IMWG) criteria, progressive disease in MM is defined as an increase in the serum M-spike of at least 25% (with a minimum value of 0.5 g/dL), or ≥200 mg in light chain excretion in a 24-hour urine collection. Additional criteria are an increase in the difference of involved and non-involved free-light chains of ≥100 mg/L in patients without a measurable serum or urine M-component. Without clinical signs or symptoms, this is called a biochemical relapse. For patients with non-secretory myeloma, the disease status should be followed by bone marrow aspiration and imaging. A clinical relapse includes biochemical progression associated with end organ damage (CRAB symptoms).[3] For an asymptomatic biochemical relapse, a watch and wait approach is justified with regular follow-up. When a rapid increase in paraprotein

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occurs, anti-myeloma treatment should not be delayed in order to avoid irreversible organ damage or serious disease-related complications. One should also keep in mind that, especially at later relapses, the phenotype of the disease can change with decreased paraprotein secretion despite increased cell growth in the bone marrow or at extramedullary sites.

The diagnostic work-up at relapse should include a careful clinical examination, a full blood count, evaluation of kidney and liver function, and dosage of serum and urine paraprotein. Although not mandatory, a bone marrow aspiration, or bone biopsy is recommended when relapse is suspected but cannot be confirmed by paraprotein measurement, in case of non-secretory myeloma, or unexplained cytopenia.[4] Although FISH for high-risk cytogenetic features should be standard practice at diagnosis, re-assessment at relapse is at the discretion of the treating physician.

THE ROLE OF STEM CELL TRANSPLANTATION AT RELAPSE

Until recently, one of the initial questions to be asked at first relapse was if that particular MM patient was candidate for transplantation, and if not, whether that patient should be retreated with the previous regimen. Historically, a second autologous stem cell transplantation (ASCT) was frequently used as salvage treatment at first relapse in eligible patients. A large survey from the International Center for Blood and Marrow Transplant Research reported that both the progression-free (PFS) and overall survival (OS) were significantly better with a remission duration of at least 3 years after the first ASCT.[5] Nevertheless, the use of highly effective and less toxic combination regimens at relapse make the added value of ASCT less clear, particularly in patients who achieve a deep response with these newer regimens.

The role of allogeneic SCT (allo-SCT) in MM has become even more controversial in the era of many therapeutic alternatives. According to international guidelines, allo-SCT can still be reserved for younger patients with (ultra-)high risk MM with a first chemo-sensitive early relapse and a suitable donor.[6] However, short- and long-term transplant-related complications and the lack of a convincing beneficial effect over less-toxic therapeutic alternatives have made this approach less attractive in relapsed MM. Additionally, historical data repeatedly demonstrated that allo-SCT in the setting of relapsed and refractory MM is doomed to fail.

With the introduction of several new drugs and drug-combinations for relapsed MM, and prolonged rather than short-term treatment in first-line, the issue of retreatment *vs.* therapeutic switch has also become less important. Nevertheless, retreatment can be considered in case the response duration with a particular regimen was longer than the average time reported in clinical trials and no serious toxicity issues occurred.

OPTIMISING DRUG-BASED TREATMENT AT RELAPSE

IMMUNOMODULATORY DRUGS (IMiDS)

In 1999 the activity of single-agent thalidomide was reported in refractory MM.[7] However, prolonged use of thalidomide is associated with an increased risk for severe side effects, particularly irreversible peripheral neuropathy.[8] The therapeutic efficacy of thalidomide in MM stimulated the search for more potent and less toxic thalidomide analogues. In 2007 lenalidomide was approved in relapsed MM based on two multicentre, randomised trials (MM-009, MM-010) comparing the combination of lenalidomide 25 mg/day for 21 days/month plus high-dose dexamethasone (Len/Dex) with dexamethasone (Dex) alone. Compared with Dex, Len/Dex significantly improved the response rates and prolonged the time to progression, and OS. With standard doses of Len/Dex, a partial response or better could be obtained in around 60% of patients having previously received one to three treatment lines, with a median time to progression of around one year.[9,10] In contrast to thalidomide, long-term exposure to lenalidomide is usually well tolerated with mild myelosuppression, asthenia, muscle cramps, skin eruptions or chronic diarrhoea as the most commonly reported adverse events.[11] Over the following years, dexamethasone doses were reduced to once weekly administration (further referred to as Rd regimen) with similar efficacy but significantly less toxicity. Building further on the success of Rd as treatment for relapsed MM, several large phase III studies evaluated the addition a third drug to the Rd-backbone. These included the second-generation proteasome inhibitors carfilzomib (KRd)[12], ixazomib (IRd)[13], and the monoclonal antibodies daratumumab (DRd)[14] or elotuzomab (ERd).[15] These four studies have been conducted in comparable patient groups (after 1 to 3 previous lines of treatment) and had similar endpoints. All four studies have proven a significant prolongation of the PFS and a significant increase in the response rates in favour of the lenalidomide-based triplet with KRd also showing an OS benefit. Based on the current data, it is beyond doubt that DRd is associated with the longest PFS, mirroring a higher rate of complete responses (CRs) with some patients even reaching minimal residual disease (MRD) negativity. However, a priority listing on depth of response and response duration only would narrow the clinical decision making. Other factors like patient age, patient preference and cytogenetic risk profile can also influence the physician's choice. The Belgian registration and reimbursement of KRd, IRd, DRd and ERd from first relapse and beyond is a rather

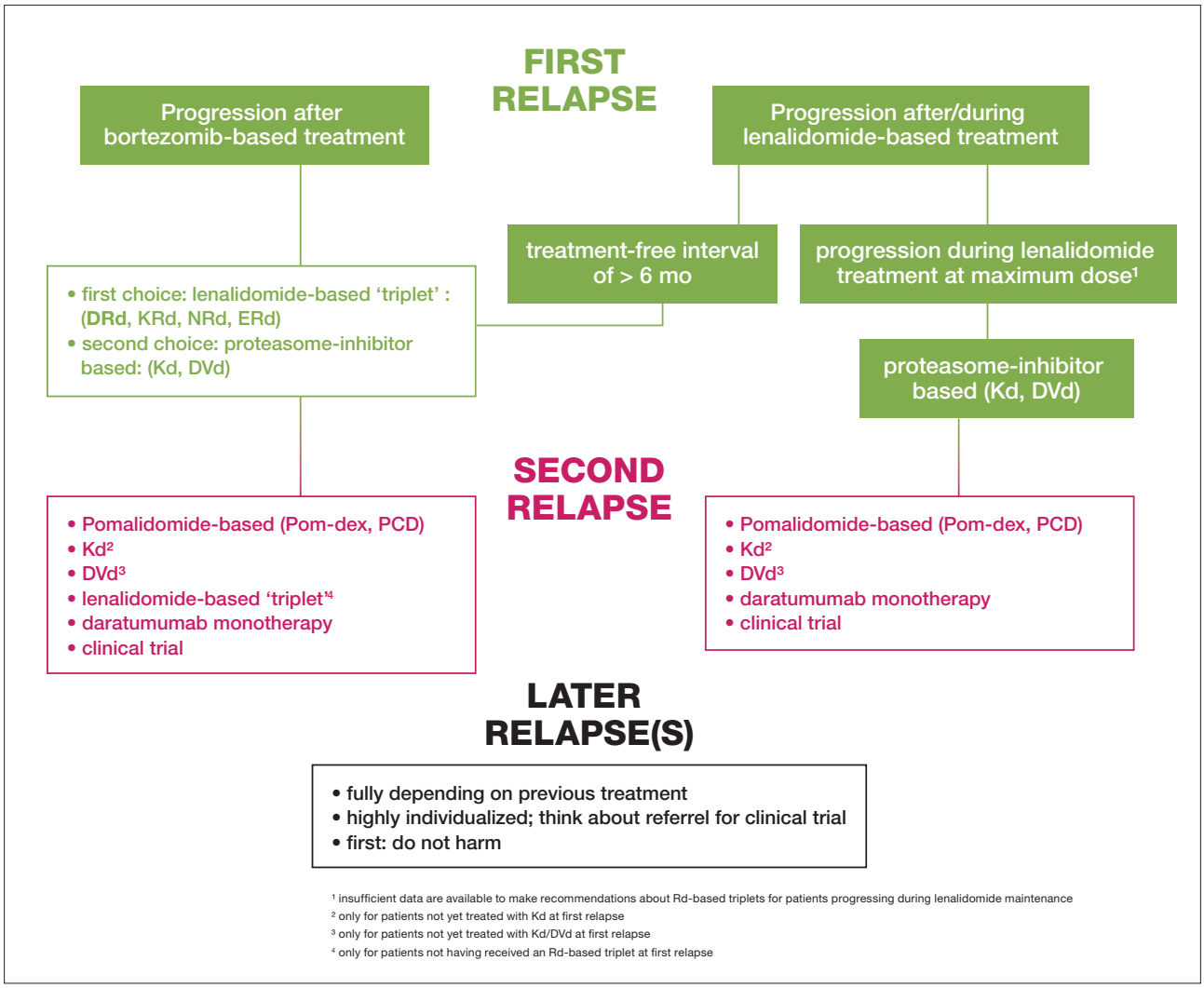

FIGURE 1. Practical algorithm for the management of patients with relapsed multiple myeloma.
List of abbreviations: DRd: daratumumab, lenalidomide, dexamethasone; DVd: daratumumab, bortezomib, dexamethasone; ERd: elotuzumab, lenalidomide, dexamethasone; Kd: carfilzomib, dexamethasone; KRd: carfilzomib, lenalidomide, dexamethasone; NRd: ixazomib, lenalidomide, dexamethasone; Pom-dex: pomalidomide, dexamethasone; PCD: pomalidomide, cyclophosphamide, dexamethasone

unique situation, creating extensive opportunities for myeloma patients and their treating physicians. However, since the overall myeloma treatment landscape is evolving rapidly, more complexity is generated in the therapeutic decision making at relapse. Changes in the frontline setting will inevitably have an impact on the treatment at relapse. For instance, long-term or continuous Rd at diagnosis will influence the therapeutic efficacy of Rd-based 'triplets' at relapse. Likewise, the potential impact of upfront daratumumab use in regimens like D-VMP on the later use of DRd is currently unclear.[16] Finally, in a few years from now it is expected that some of the Rd based triplets like ERd, IRd and DRd will also be registered for newly diagnosed, non-transplant eligible patients which will in turn impact the treatment choice at relapse.

The third IMiD is pomalidomide and, as for thalidomide and lenalidomide, this agent has synergistic activity with dexamethasone. Pomalidomide 4 mg/day 21 days/month with weekly dexamethasone (Pom/dex) is registered for MM patients who have failed treatment with a proteasome inhibitor and IMiD.[17] In this heavily pre-treated patient group, clinically meaningful responses can still be obtained with Pom/dex, although responses can further be enhanced by addition of a third drug like cyclophosphamide, bortezomib or even clarithromycin. Combinations of pomalidomide with monoclonal antibodies like elotuzumab, daratumumab or isatuximab have been explored in phase III studies, but their eventual impact on the treatment paradigm at later relapse is to be awaited. The side effect profile of pomalidomide is comparable with lenalidomide although its myelosuppressive

effect is more pronounced, particularly during the first treatment cycles. According to international guidelines, all patients receiving IMiD-based combinations should receive thromboprophylaxis for the whole duration of their treatment.[11]

PROTEASOME INHIBITORS (PIs)

In 2005, the Phase III APEX trial resulted in the approval of bortezomib for MM patients relapsing after first-line treatment.[18] As for lenalidomide, bortezomib is administered together with dexamethasone (Vd regimen). Over the years, bortezomib has gradually moved from salvage treatment for relapsed/refractory patients, to earlier relapses, and has become a standard first-line treatment regimen in both transplant candidates (VTD, VCD) and in elderly myeloma patients (VMP). The upfront use of bortezomib, the introduction of more potent second-generation PI's and the success of the Rd based triplets all have resulted in a decreased use of bortezomib in patients with relapsed/refractory MM (RRMM). However, we might be witnessing a bortezomib revival, with the recent registration and reimbursement of the DVd regimen where daratumumab is added to Vd.[19] Finally, the combination of bortezomib with the histone deacetylase inhibitor panobinostat is also registered and reimbursed.[20] However, this combination is hardly used because of its side effect profile and, more importantly, the availability of more potent therapeutic alternatives.

As with the IMiDs, the success of bortezomib has stimulated the development of second-generation PI's. Carfilzomib is an irreversible epoxyketone with fewer off-target activities whereas ixazomib is a boronic acid derivative. As discussed previously the addition of carfilzomib to Rd (KRd) significantly prolongs the PFS and OS compared to Rd. A direct head-to-head comparative study between Vd and carfilzomib plus dexamethasone (Kd), revealed a significant superiority of Kd over Vd in terms of response rates, PFS and OS.[21] Importantly, particular attention is needed when using carfilzomib in patients with cardiovascular comorbidities, since hypertension is frequent and cardiac failure can occur, albeit in less than 5% of patients.[21] Ixazomib (a third PI) on the other hand can be associated with diarrhoea and peripheral neuropathy although the latter is less frequent and less serious than what is seen with bortezomib.[13] Of note, ixazomib plus dexamethasone is not registered for use without the addition of lenalidomide.

OTHER THERAPEUTIC OPTIONS

At later relapse, daratumumab monotherapy can induce responses in around one third of patients.[22] Other immunotherapeutic approaches in clinical development include conjugated anti-CD38 antibodies, bispecific antibodies (BiTe) and CAR-T cells directed against BCMA.[23] In addition, the bcl-2 antagonist venetoclax might become the first targeted treatment for patients carrying the t(11;14) in their plasma cells and selinexor, an XPO-1 antagonist has been explored in patients who are refractory to all other registered treatment options.[24,25] Finally, conventional chemotherapy such as bendamustine, or combination regimens such as DCEP or DT-PACE can be used in relapsed and refractory myeloma, but these treatments will not result in durable responses, unless they are used as bridging treatment.[26,27]

CONCLUSION

Major progress has been achieved in the management of RRMM. In addition to the introduction of new agents, it has become clear that as with frontline treatment, more benefit is generated from combined rather than sequential use. One should also keep in mind that myeloma treatment has become very expensive for our society. Therefore, joint efforts between the medical community, pharmaceutical industry and government are required to further optimize the treatment of patients and to improve their therapeutic benefit.

REFERENCES

1. Raab MS, et al. Br J Haematol. 2016;175:66-76.
2. Morgan GJ, et al. Nat Rev Cancer. 2012;12:335-348.
3. Durie BG, et al. Leukemia. 2006;20:1467-1473.
4. Ludwig H, et al. Leukemia. 2014;28:981-992.
5. Michaelis LC, et al. Biol Blood Marrow Transplant. 2013;19:750-6.
6. Lokhorst H, et al. J Clin Oncol 2010;28:4521-30.
7. Singhal S, et al. N Engl J Med. 1999;341:1565-71.
8. Delforge M, et al. Lancet Oncol. 2010;11(11):1086-1095.
9. Dimopoulos M, et al. N Engl J Med. 2007;357(21): 2123-2132.
10. Weber DM, et al. N Engl J Med. 2007; 357(21):2133-2142.
11. Delforge M, et al. Blood. 2017;129:2359-2367.
12. Stewart AK, et al. N Engl J Med. 2015;372:142-152.
13. Moreau P, et al. N Engl J Med. 2016;374: 1621-1634.
14. Dimopoulos M, et al. N Engl J Med. 2007;357:2123-2132.
15. Lonial S, et al. N Engl J Med. 2015;373:621-631.
16. Mateos MV, et al. N Engl J Med. 2018;378:518-552.
17. San Miguel J, et al. Lancet Oncol. 2013;14: 1055-1066.
18. Richardson PG, et al. N Engl J Med. 2005; 352:2487-2498.
19. Palumbo A, et al. N Engl J Med. 2016;375(8):754-766.
20. San Miguel JF, et al. Lancet Oncol 2014;15:1195-206.
21. Dimopoulos MA, et al. Lancet Oncol. 2016;17(1):27-38.
22. Usmani SZ, et al. Blood. 2016;128:37-44.
23. Mikkilineni L, et al. Blood. 2017 Sep 19. pii: blood-2017-06-793869.
24. Moreau P, et al. Blood. 2017 Aug 28. pii: blood-2017-06-788323.
25. Turner JG, et al. Oncotarget. 2016;7(48):78896-78909.
26. Park S, et al. Ann Hematol. 2014;93(1):99-105
27. Gerrie AS, et al. Br J Haematol. 2013;161(6):802-10.