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Multiple myeloma - Section 3

New approaches to myeloma treatment in 2017

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Take-home messages

- Better tools for diagnosis and monitoring treatment efficacy are being implemented.
- Early treatment and the use of more efficient drugs upfront prolong survival.
- The treatment goal is to find the best possible balance between efficacy, toxicity and cost, particularly at the time of relapse.

Introduction

The treatment goal for multiple myeloma should be to find a balance between efficacy, toxicity and cost, with the ultimate aim of achieving a cure for the disease. The outcome for multiple myeloma (MM) patients has significantly improved in the last 15 years, mainly due to the use of proteasome inhibitors (bortezomib, carfilzomib, ixazomib) and immunomodulatory agents (thalidomide, lenalidomide, pomalidomide), and more recently, monoclonal antibodies (daratumumab, elotuzumab) and other novel drugs with a singular mechanism of action. Moreover, the introduction of new criteria for early diagnosis of symptomatic MM and the possibility of early intervention are opening new therapeutic avenues. The new response criteria, particularly the concept of minimal residual disease, should contribute to individualized treatment based on highly sensitive methods for monitoring treatment efficacy.

Smouldering and early myeloma

The Spanish group has shown that early intervention in smouldering multiple myeloma (SMM) is associated with a highly significant prolongation of time to progression (TTP) (hazard ratio, HR: 0.24) and overall survival (OS) (HR: 0.43).[1] These results, along with the availability of more sensitive diagnostic tools, have prompted a revision of the criteria for diagnosing early myeloma requiring immediate treatment: patients without CRAB symptoms, but with >1 focal lesions detected by MRI or 60% plasma cells (PCs) in bone marrow (BM) or a free light chain (FLC) ratio >100.[2]

Treatment of newly diagnosed transplant candidate patients

Currently, treatment of young patients usually includes 3-6 cycles of induction therapy, intensification with autologous stem cell transplantation (SCT) and the possibility of consolidation and maintenance therapy.
Using induction with bortezomib (Bz)-based triplet combinations, either with alkylators or immunomodulatory drugs (IMiDs), >90% of patients respond including 20-30% complete responses (CR), and around 10% minimal residual disease (MRD) negative cases.[3,4] Preliminary data with new proteasome inhibitors (PI) such as carfilzomib (K) and ixazomib (Ixz) in combination with len-dex (Rd) (lenalidomide [R] with low-dose dexamethasone [d]) also shows a high level of activity. The former is probably the more potent triplet in terms of depth of response, while the latter is very attractive due to its oral formulation. The efficacy of these induction triplets will probably be enhanced by the addition of CD38 monoclonal antibodies (MoAb); accordingly, we foresee the combination of a MoAb plus a triplet based on a PI-IMiD-Dex as the future standard for induction. Intensification with autologous stem cell transplantation (ASCT) is still the standard of care, since it enhances the response rates obtained with these new induction regimens.[5,6] Four randomized trials comparing early and

late ASCT have demonstrated the benefit in progression-free survival (PFS) of early ASCT, although not yet in OS. Two European trials have shown that tandem ASCT is superior to single ASCT, although this was not reproduced in the US STaMINA trial. The role of consolidation therapy is also controversial, while maintenance treatment with lenalidomide (until progression or at least for 1-2 years) is associated with a marked prolongation of PFS (median prolongation of 18 months), and an estimated 2.5-year increase in median OS, according to a meta-analysis.[7] Many aspects of maintenance treatment remain to be clarified, such as the optimal duration, the long term toxicity, the benefits for specific cohorts, and the effects of adding corticosteroids, oral PI (ixazomib) and MoAb. Allogeneic transplant should not be recommended for newly diagnosed patients outside clinical trials.[8] The high efficacy of these treatment strategies has revealed the need for more sensitive techniques (MRD) to evaluate the depth of response both outside the bone marrow (BM) (e.g., using imaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography) and inside the BM (e.g., using immunophenotyping by multiparametric flow cytometry, and molecular analysis by next-generation sequencing). Accordingly, new, revised response criteria have recently been implemented and should also help to avoid over- and under-treatment, and may become a surrogate biomarker for OS and an operational cure.[9]

Treatment of newly diagnosed elderly and non-transplant candidate patients

Six randomized trials have compared thalidomide (T) + melphalan and prednisone (MP) (MPT) with MP alone, showing a median of 6-month prolongation of PFS and OS and it was approved as a standard of care.[10] Administering Rd until progression has become a new standard for elderly MM patients, based on its superiority over MPT in terms of PFS (26.0 *vs.* 21.9 months) and OS (59 *vs.* 49 months).[11] Btz in combination with MP (BzMP) for 9 cycles was associated with a longer TTP (24.0 *vs.* 16.6 months) and one-year prolongation of OS (56 *vs.* 43 months) compared with MP, and has been approved as another standard of care.[12] The Spanish group has combined BzMP (9 cycles) followed by Rd (9 cycles) obtaining a PFS of approximately 3-years. Carfilzomib in combination with MP has shown similar efficacy to BzMP in terms of PFS (22.3 *vs.* 22.1 months) and OS (although the latter data are not yet mature). Investigations of carfilzomib and ixazomib in combination with Rd are yielding encouraging results, particularly for the former combination.

Options for treatment at relapse

Figure 1 summarizes therapeutic options at relapse. The second-generation proteasome inhibitor, carfilzomib in combination with low-dose dexamethasone (Kd) has twice the PFS as bortezomib-dex (btz-dex) (HR: 0.53) and the triplet carfilzomib+len-dex (KRd) is also significantly superior to Rd in terms of PFS (HR: 0.69) and OS (HR: 0.79).[13] Carfilzomib is associated with a very low incidence of peripheral neuropathy but higher cardiovascular toxicity. The oral protease inhibitor, ixazomib has a very good safety profile and, in combination with Rd (IRd), also yielded a longer PFS than Rd (HR: 0.74) but with no significant difference in OS.[14] Pomalidomide, a third-generation IMiD, in combination with low-dose dexamethasone has been approved for treatment of double-refractory patients,[15] and the efficacy can be increased by adding cyclophosphamide or bortezomib.

The use of MoAbs represents a major step forward in MM treatment. Elotuzumab (anti-SLAMF7) has no activity as a single agent but in combination with Rd is significantly superior to Rd alone in terms of PFS (HR: 0.73) and OS (HR: 0.72).[16] The results are even more promising with anti-CD38 (daratumumab, isatuximab, MOR202), since they already demonstrate activity in monotherapy, with an approximately 30% response rate in double-refractory patients. Impressive results have been reported for daratumumab in combination with Rd, with 43% complete response (CR) (including 10% MRD-cases at 10^{-6}) in relapsing patients and a 63% reduction in risk of progression or death compared with Rd (HR: 0.36).[17] Similarly, Daratumumab in combination with btz-dex is also highly superior to btz-dex alone (CR: 20 *vs.* 9%; HR: 0.39 for PFS).[18]

Other immunotherapeutic strategies are being investigated. Anti-BCMA conjugated with monomethyl auristatin-F has produced a clinical benefit in 25% of patients. CD19-CART and BCMA-CART have been tested, and the second one has shown 4 out of 12 partial responses (PRs) in highly refractory patients. The anti-PD-1 drug, pembrolizumab, in combination with lenalidomide or pomalidomide plus dexamethasone gave 36-55% responses in double-refractory patients.

Panobinostat (a hystone deacetylase inhibitor [HDAC]) has been approved for the use in combination with btz-dex for patients who have received at least two lines including btz and len.[19] More selective HDAC inhibitors (HDAC6, acetylon) with improved tolerability are under investigation. Filanesib (a kinesin spindle protein inhibitor) plus dexamethasone has shown ≥22% PR in double-refractory patients. Selinexor (exportin-1 inhibitor) plus dex yielded 20% overall response

rate (ORR) in pentarefractory patients and is synergistic with proteasome inhibitors. The BCL-2 inhibitor venetoclax has shown an ORR of 21%, with 12 of 14 responding patients harbouring t(11;14), and it is also being investigated in combination with Btz-dex.

Future perspectives

Myeloma should no longer be considered as a single entity. This, in conjunction with new monitoring tools, will contribute to treatment individualization. The combination of a MoAb plus a triplet based on PI-IMiD-Dex may become the future upfront standard. Immunotherapy will play an important role in achieving our ultimate goal of curing MM.

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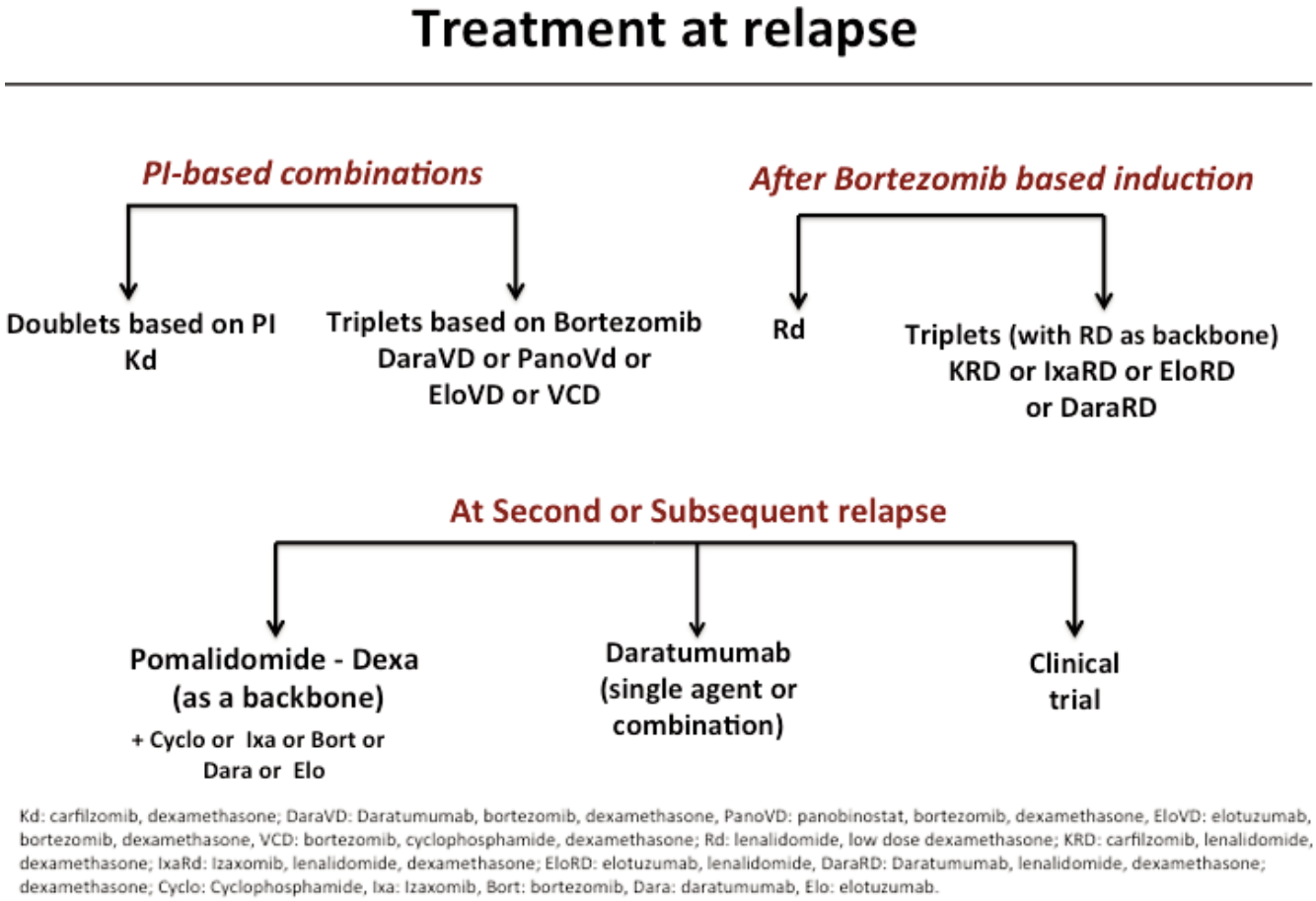

Figure 1. Proposal of therapeutic options at relapse in MM in 2017. The figure summarizes potential therapies for the treatment of relapse patients depending on the sensitivity or refractoriness status to the prior lines of treatment.

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