Non-Transplant-Eligible Newly Diagnosed Multiple Myeloma

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Multiple myeloma mainly affects the elderly, who are usually not eligible to intensive treatments such as autologous stem cell transplant. The advances in therapeutics have largely benefited elderly patients now renamed “non-transplant-eligible” (NTE) patients. Since the 1960s, and for several decades, chemotherapy was the only treatment for MM. Then, the field was marked by the emergence of targeted therapies in the 2000s, such as immunomodulating agents (thalidomide, lenalidomide, and pomalidomide) and proteasome inhibitors (bortezomib, carfilzomib, and ixazomib), which were the first steps towards an increase in survival. Thereafter, the apparition of monoclonal antibodies (mAbs) was considered a milestone in the treatment of MM for both transplant-eligible and NTE patients. Anti-CD38 mAbs can be safely administered to older patients with an impressive efficacy leading to a never-achieved-before survival rate with the triple association of anti-CD38 mAbs, lenalidomide, and dexamethasone.

multiple myeloma non-transplant-eligible elderly immunotherapy CAR-Ts

1. Introduction

Multiple myeloma (MM) is a plasma cell (PC) malignancy characterized by the proliferation of PCs within the bone marrow, usually in association with the production of a monoclonal immunoglobulin (Ig). MM typically occurs among elderly patients. Indeed, the median age at diagnosis is approximately 70 years old, with nearly one-third of patients above 75 years old. The incidence of MM is increasing as the global population is aging. Therefore, more and more patients are categorized as “older” or “non-transplant-eligible” (NTE) when the treatment decision has to be made. However, most of these patients are non-frail and will likely benefit from most of the drug developments made in younger (transplant-eligible) patients.

The elderly MM population is very heterogeneous, with wide differences in age and physical or biological decline features. Older patients are also potentially at higher risk of treatment-related toxicity. Thus, finding the optimal treatment strategy for these patients has long been a challenge. Fortunately, the last 10 years have been marked by tremendous improvements in MM treatment. The emergence of immunotherapy (IT) has profoundly transformed the armamentarium of MM and particularly benefited the elderly because of the highly acceptable safety profile of immune-based treatments.

Naive anti-CD38 monoclonal antibodies (mAbs), the first immunotherapy to demonstrate clinical activity in MM, are now the backbone of treatment for NTE patients upfront. Furthermore, several new immune-based treatments are

currently being developed and should be used safely in NTE patients. Among these innovative drugs it can find chimeric antigen receptor T cells (CAR-T cells), bispecific antibodies (BsAbs), and antibody drug conjugates (ADC). Overall, IT, and particularly modern IT, is a shift in the treatment paradigm in MM as it provides effective drugs with enhanced activity and an improved expected safety profile.

2. The Beginning: From Alkylating-Based Treatments to Proteasome Inhibitors and IMiDs

The first case of MM was described in 1844, and until the 1960s, the prognosis of patients presenting with MM was abysmal: survival hardly reached a couple of months. In the sixties, alkylating agents were the first treatments to demonstrate anti-tumoral activity in MM, and melphalan thus represented a major breakthrough in the field. At that time, melphalan was the only treatment that could be used, usually given in monotherapy. The efficacy was quite poor, and survival was still very short for MM patients. Corticosteroids were then added to melphalan and rapidly became the gold standard, with a clear improvement in patients' survival. "Melphalan–prednisone" (MP) served as the basis for many treatment associations for several decades as the associated median overall survival (OS) was 3–4 years. Cyclophosphamide (endoxan) was also rapidly made available and appeared to have significant anti-MM activity either as a metronomic treatment taken on a daily basis or on a weekly basis.

The advent of melphalan was followed by the apparition of immunomodulating agents (IMiDs), including thalidomide, in the 2000s. Thalidomide (T) was previously used in the 1950s against nausea and vomiting during pregnancy, but it was also teratogen, and its use was therefore interrupted in most European countries. It was only years after its anti-angiogenic proprieties were discovered, suggesting a potential effect in MM, that the binding to the cereblon protein was described. This results in the degradation of transcriptional factors (IKZF1, IKZF3) important for MM cells' survival. Thalidomide was logically investigated in association with MP with hope for an increased efficacy.

After thalidomide, proteasome inhibitors (PIs), a new class of anti-MM drugs, were successfully introduced to the MM therapeutic landscape. The proteasome plays a major role in protein homeostasis and physiological mechanisms by leading to the degradation of some proteins, including proteins that control apoptosis, cell cycle progression, etc. MM cells have higher levels of proteasome activity; therefore, PIs allow the accumulation of malformed proteins, thus causing cellular apoptosis. Bortezomib (V) was the first-in-class PI to be used in MM. Nevertheless, MP was kept as the backbone for most associations, as in the MPV (melphalan, prednisone, bortezomib) regimen. The phase three VISTA trial [1] studied the association MPV in comparison to MP alone. Bortezomib was administered intravenously. MPV, which led to a median progression-free survival (PFS) of 21 months and a median OS of 56 months.

Second-generation PI carfilzomib (K), with the advantage of less polyneuropathy but increased cardiac risk (cardiac failure, high blood pressure), was also tested for NTE patients [2][3]. This attempt can be considered a failure, as the phase three CLARION trial [4] (KMP vs. VMP) did not demonstrate any superiority in terms of PFS

with the use of carfilzomib versus bortezomib (median PFS 22.3 months for KMP vs. 22.1 months with VMP, p = 0.906). The utilization of carfilzomib is therefore limited in the NTE population.

In the same period, the IFM group (Institut Francophone du Myélome) and others have studied the role of bendamustine [5] (alkylating agent combined to nucleosidic analogue) with dexamethasone (Bd) and in association with bortezomib and dexamethasone (BVd) for elderly patients. These regimens have never been studied head-to-head with the MP-triplet-based combinations, and although they have been part of the armamentarium in guidelines, they have never been in a position to compete with either MPT or MPV.

3. A Major Step Forward: Lenalidomide-Based Regimens

The apparition of the second generation IMiD, lenalidomide (R) (in 2005), represented a major step forward in the treatment of NTE MM. Lenalidomide is usually better tolerated than thalidomide with decreased risk of neuropathy and can therefore be administered in the long run, upon management of diarrhea and neutropenia. Furthermore, its administration being entirely oral was seen as more convenient than the use of bortezomib, for example.

The phase three FIRST study [6] demonstrated the superiority of the association lenalidomide–dexamethasone (Rd) given until progression over the alkylating agent-based association MPT, which was regarded as one of the gold standards at that time. Indeed, median PFS with continuous Rd was 25.5 months and 21.2 months with MPT (p < 0.001). In terms of OS, Rd was also superior, with an improved median OS of 10 months (59.1 months vs. 49.1, p = 0.0023).

Although the Rd regimen showed great efficacy and an acceptable safety signature, the triplet associations were already installed in the therapeutic management of MM. Indeed, triplet associations lead to deeper responses, including for high-risk MM patients, and, consequently, to improved survival. The objective was therefore to find the best partner to Rd. The first attempt run by the Italian group GIMEMA (Gruppo Italiano Malattie EMatologiche dell'Adulto) in 2006 with the association of melphalan, prednisone, and lenalidomide (MPR) [7] was unsuccessful given the safety profile issues, mainly cytopenia, that impaired the development of that regimen.

Thus, an adapted VRd version was introduced called "VRd lite" [8] in order to reduce the toxicity associated with this regimen. VRd lite was given over a 35-day cycle (based on the VMP scheme) with oral lenalidomide 15 mg on days 1–21, bortezomib subcutaneous 1.3 mg/m^2 on days 1, 8, 15, and 22, combined with dexamethasone 20 mg for nine cycles, followed by six cycles of consolidation by VR, similarly to the initial VMP design. Median PFS was 35.1 months (95% CI 30.9; ∞) and median OS was not reached at a median of follow-up of 30 months. There is also a "VRd lite" version given over a 28-day cycle (as per the Rd scheme) with oral lenalidomide 25 mg on days 1–21, bortezomib subcutaneous 1.3 mg/m^2 on days 1, 8, and 15, combined with dexamethasone 20 mg for up to six to twelve cycles followed by Rd maintenance treatment.

Ixazomib, a new oral PI, was also added to the bitherapy "Rd" in phase three of the TOURMALINE-MM2 trial [9] (Rd vs. IRd). Ixazomib was given at 4 mg on days 1, 8, and 15 plus Rd at the classical dosage from cycle one to

eighteen, then the ixazomib dose was reduced to 3 mg and R to 10 mg until progression or toxicity. Median PFS was 35.3 months with IRd vs. 21.8 months with Rd, and for the high-risk group 23.8 vs. 18 months, respectively. There was no difference between the two groups regarding toxicity; AEs were mostly grade 1 or 2. This entirely oral association can be appealing for NTE patients as it has a limited impact on quality of life with no or few hospitalizations.

4. The Rise of Anti-CD38 Monoclonal Antibodies

Immunotherapy is surely one of the most impressive and successful drug developments in the history of MM, first with the discovery of anti-CD38 mAbs after long years of failing attempts to develop a monoclonal antibody for therapeutic use in MM. Abs were developed in the late 1970s after George Kohler and Cesar Milstein invented the hybridoma technology, allowing for the creation of immortal cells producing different antibodies. Thanks to their work, a great range of mAbs were generated. The first mAb to be approved for therapeutic use was the anti-CD20 rituximab in 1997 for the treatment of lymphomas. Logically, rituximab was also investigated, although unsuccessfully, in MM. Many attempts were made to find the right mAb that could allow MM to benefit from the progress of IT, but the search for the optimal target was indeed a long journey.

The first mAb to find its way into MM treatment was the anti-signaling lymphocytic activation molecule 7 (SLAMF7) [10], renamed CS1, elotuzumab. SLAMF7 can be found on different cells whose PCs are natural killer (NK) cells, which are very important for the mechanism of action of elotuzumab. The dual effect of elotuzumab is principally due to the antibody-dependent cellular cytotoxicity (ADCC) on tumor cells, while in parallel activating NK cells that also express CS1 on their cell surface. Lenalidomide was found to exhibit a synergistic activity with elotuzumab, which led to the first approval of a mAb in MM with the association elotuzumab, lenalidomide, and dexamethasone in 2015 for patients with relapse or refractory MM (RRMM), followed by a second approval with the third-generation IMID pomalidomide.

CD38, first described in 1980, is a glycoprotein that serves as a receptor and an adhesion molecule and also has enzymatic functions. CD38 has a major role for survival of PCs. Daratumumab is the first fully humanized mAb targeting CD38, and it was first approved for RRMM combined with either bortezomib or lenalidomide or in monotherapy. Daratumumab adds an anti-enzymatic activity to the classical mAb mechanisms of action, ADCC, CDC (complement-dependent cytotoxicity), ADPC (antibody-dependent cellular phagocytosis), and apoptosis.

After the promising results of studies for RRMM, daratumumab-based trials were specifically designed for NTE NDMM patients. The phase three ALCYONE trial [11] studied the association dara-MPV vs. MPV; median PFS was higher for patients in the daratumumab group (36.4 vs. 19.3 months, $p < 0.0001$) in the primary analysis (median follow-up of 16.5 months).

5. Quadruplet-Based Regimens, Utopia, or Future for Non-Frail NTE NDMM?

With the success of daratumumab came the emergence of novel anti-CD38 mAbs. Isatuximab is the second anti-CD38 chimeric mAb for therapeutic use that has been developed. The mechanism of action of isatuximab is slightly different from daratumumab, although experts in the field consider that the two drugs show quite similar clinical activity. It was then tested upfront specifically for NTE patients in the phase three IMROZ study [12] (NCT03319667) Isatuximab-VRd vs. VRd (primary end point median PFS), and in the IFM 2020-05 BENEFIT trial (NCT04751877, Isatuximab-VRd vs. Isatuximab-Rd, (65–79-year-old NDMM NTE patients)), primary end point 10^{-5} MRD negative rate at 18 months, surrogate to sustained MRD (12 and 18 months). The results of the two studies are awaited but read out is expected in 2023. Daratumumab is also being evaluated as part of a quadruplet regimen, as in the phase three CEPHEUS trial [13], among other studies, dara-VRd vs. VRd (NCT03652064).

Physicians are investigating quadruplets for this subset of patient with the objective of achieving deeper responses and longer remissions, and maybe allowing some patient to be treated with only one line of treatment throughout their disease course. The concept of giving four drugs to older patients was only permitted due to the noticeably good safety profile of immune-based treatments. However, compliance to treatment remains a key issue, along with the continuous administration of these drugs. It is expected that some patients might not be fit for such regimens, particularly the frail and intermediate frail NDMM NTE patients. Tailoring treatments to each patient is still a major challenge with the elderly.

6. Modern Immunotherapies: Suitable for NTE Patients?

Progress in the field of molecular biology and immunology has allowed us to imagine structural modification and change in specificity of T cells without being limited by the major complex of histocompatibility recognition. CARs are genetically engineered receptors expressed by T cells (or any cells), thus conferring them specific properties, e.g., anti-tumor activity. CAR-Ts were first developed in the early 1990s by Zelig Esshar in Israel but were not clinically active. The first clinical application was made possible in the early 2010s following the work of Carl June in the United States. In 2012, a seven-year-old patient suffering from acute lymphoid leukemia successfully received the first anti-CD19 CAR-T cell [14].

In MM, most CAR-Ts are second-generation, i.e., with a co-stimulation molecule (4-1bb or CD28). Two CAR-Ts are advanced in their development, idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel), both targeting B cell maturation antigen (BCMA) expressed by MM cells. BCMA has a role in PC and MM cells' proliferation and survival. CAR-T cells are now reserved for highly advanced MM, but they should soon benefit patients in early lines of therapy. Ide-cel was evaluated in the phase two KarMMA study [15].

CAR-T cells are usually well tolerated or at least their toxicity is now considered predictable and manageable. Indeed, the main risk with the use of CAR-T cells is the CRS. The neurological toxicity associated with CAR-T cells, either CRS/ICANS (usually an early event), or later parkinsonian-like syndrome, is quite rare in the context of anti-BCMA CAR-T cells used in MM but has to be closely monitored. However, long-term complications, such as cytopenia, hypogammaglobinemia, and infections, can also be observed and should be acknowledged during a patient's follow-up. Given this relatively low toxicity, it is considered possible to administer CAR-T cells to the

elderly without a specific limit of age, although this requires careful patient selection, and data focusing on NTE patients are sparse. This is why studies specifically designed for patients who will not have an ASCT are planned, such as CARTITUDE-5 (VRd followed by cilta-cel versus VRd followed by Rd, NCT04923893).

Currently, these novel immune-based treatments are not being used in daily practice for NDMM and especially transplant ineligible NDMM patients. However, unlike ASCT, theoretically they seem suitable for the latter as their safety profile seems manageable for most patients. Careful screening of patients will be required to better determine who can receive this type of treatment without experiencing severe treatment-related toxicities. However, progress is being made in AE management as different strategies are being evaluated, such as the early use of tocilizumab or novel CAR designs. Interestingly, these treatments may also allow us to observe an immunological effect that will probably contribute to achieving MRD negativity and sustained responses, consequently allowing for prolonged survival.

7. Conclusions

The treatment options for NTE patients have greatly evolved over the past 30 years. Overall, it moved from melphalan-based induction regimens to bortezomib and lenalidomide-based associations and now to anti-CD38 based treatments. For a long time, specific drug developments were missing for elderly patients, but technological improvements in drugs have made them more suitable for these patients, which has led to great successes. In parallel, the growing interest in NTE patients has helped to better understand their specificities and to adapt the objectives of the treatment strategy. Still, some questions are left unanswered, such as the duration of the treatment, which is still a debate among MM physicians. Continuous treatment is currently the standard of care, but the new approved treatments allow deep remissions (with high rates of MRD negativity) similar to those achieved for younger patients, which usually translate into prolonged survival and could therefore question the possibility of developing fixed-duration schemes. Armed immunotherapies, such as CAR-Ts and BsAbs, are making a sensational entrance into MM treatment options and seem fitting for NTE patients.

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