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Roadmap to cure multiple myeloma

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ABSTRACT

Despite significant advances in the treatment of multiple myeloma which had led to unprecedented rates of response and survival, patients still relapse, and cure remains elusive. We propose in this review a roadmap to achieve the dream of cure for multiple myeloma based on five complementary strategies. First, to increase knowledge about disease pathogenesis with a focus on the biology of circulating tumor cells, responsible for dissemination and extramedullary disease, and minimal residual disease clones who represent the reservoir of clonal evolution and disease recurrence. Second, to consider undetectable measurable residual disease (MRD), defined by high-sensitive techniques, as the new endpoint of therapy. Third, to treat disease causation instead of symptomatology through early detection and intervention. Thereby, by treating high-risk smoldering myeloma patients early, we may not only contribute to delay disease progression into active disease but also to increase the cure rates. Fourth, to use the most active scheme in standard-risk patients if the cure is in the horizon. Fifth, to investigate experimental therapies in newly diagnosed patients with high-risk MM, implementing early rescue intervention strategies with the goal of eradicating all tumor clones, and achieving minimal residual disease negativity.

Introduction

Despite significant advances in the treatment of patients with multiple myeloma (MM), which led to unprecedented response rates and prolonged survival, most patients eventually relapse and cannot be cured. We propose in this review a roadmap to achieve the dream of cure for MM based on five complementary strategies. First, to gain better understanding of myelomagenesis and the biology of aggressive clones. Second, to consider undetectable measurable residual disease (MRD), defined by high-sensitive techniques, as the new endpoint of therapy. Third, to treat disease causation instead of symptomatology through early detection and intervention. Fourth, to use the most active scheme in standard-risk patients. Fifth, to investigate experimental therapies in newly diagnosed patients with high-risk MM.

Deep characterization of aggressive tumor clones

It is well established that all MM patients are preceded by a monoclonal gammopathy of undetermined significance (MGUS), and that only a small fraction of MGUS (1% per year) evolve into active MM [1,2]. What determines if a pre-malignant cell will remain dormant for greater than 30 years or transform, remains unknown. It could be expected that stepwise-acquisition of genetic alterations drives disease evolution, but even adverse abnormalities such as del(17p13) and t(4;14) are detectable in small percentages of cases with MGUS [3,4]. Therefore, additional factors must contribute onto malignant transformation.

To understand the pathogenesis of MM it is important to consider clonal evolution during disease progression, but also the interaction between the tumor and other microenvironment cells [5], and the effect of treatment preasure [6]. Genetic characterization of myeloma cells has shown that virtually all patients are cytogenetically abnormal, and presence of specific alterations has a major impact on disease outcome [7]. Moreover, the advent of high-throughput sequencing is uncovering the enormous complexity of MM cells. Overall, translocations involving the immunoglobulin heavy chain locus and copy number alterations leading to aneuploidy, are genetic hallmarks in most patients. On top of this, treatment exposure also plays a significant role in the genomic landscape at relapse. Thus, treatment with high-dose melphalan in the context of ASCT or with platinum-based agents has been shown to be

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responsible for a considerable proportion of new mutations on the MM propagating cell at relapse. Moreover, it has been shown that MM seeding is promoted by an evolutionary process in which distinct clones harboring distinct drivers are selected and expanded at varying anatomic sites contributing to spacial clonal heterogeneity and this systemic seeding of MM can occur in a very short time window after chemotherapy exposure [6]. Regarding the microenvironment, it plays a relevant role in bone destruction, tumor cell growth, survival, egress and drug resistance [8,9]. Importantly, recent work by de Jong et al. [10]., using single-cell transcriptomic analysis, has identify the presence of myeloma-specific inflammatory mesenchymal stromal cells (iMSC), which spatially colocalize with the tumor and immune cells in the bone marrow and were not present in non-cancer patient samples. These iMSCs transcribe myeloma cell survival factors and inflammatory genes implicated in immune cell recruitment and immune modulation. Importantly, MM-associated inflammatory changes in the bone marrow microenvironment along with iMSCs, persisted after induction treatment even in patients achieving MRD negativity, predicting a role for mesenchymal stromal cells in disease persistence.

In addition, and to gain further insights into MM pathogenesis, our group has decided to concentrate research efforts towards two cell types that could be the Achilles' heel of MM: circulating tumor cells (CTCs) and the MRD clone (Fig. 1).

CTCs are responsible for dissemination and extramedullary disease. Using high sensitive methods, CTCs can be detected in half of MGUS and virtually all MM patients, with significantly higher numbers found in active myeloma as compared to MGUS and smoldering MM (SMM) [11–14]. Moreover, the number of CTCs has an impact in the risk of transformation of MGUS and smoldering into active MM, and it is also associated with significantly poorer outcomes in patients with active disease [15]. To better understand the biological signature of CTCs, we have compared their transcriptional signature to that of patient-matched bone marrow (BM) tumor cells; both displayed overlapping gene expression profiles with only 50 genes significantly deregulated in CTCs, many of them involved in regulatory networks related to cellular trafficking [12]. Our current model for MM dissemination suggests that the presence of fully occupied and hypoxic BM niches together with a pro-inflammatory microenvironment, would force cancer cells to stop proliferating, recirculate in peripheral blood and seek other BM niches to continue growing.

Regarding the MRD clone, it represents a reservoir of clonal evolution and disease recurrence. We have performed a transcriptomic comparison between paired samples of diagnostic versus resistant/residual cells following six cycles of bortezomib, lenalidomide and dexamethasone. A total of 40 cases were included in the study, 28 corresponding to standard risk patients while the remaining 12 had high risk cytogenetics. We found that MRD cells displayed a total of 762 genes significantly deregulated as compared with the paired diagnostic cells. Interestingly, there were 9-fold higher deregulated genes in MRD cells of standard risk patients compared to high-risk patients. Accordingly, our hypothesis is that in standard risk there is greater clonal selection or transcriptomic adaptation in order to resist treatment, while in high risk patients, the corresponding adverse cytogenetic abnormality is the driver that will predispose cells to resist treatment [16].

All this information reinforces the concept that *MM should no longer be considered as a single entity, but several disease subtypes embedded in the term MM. This concept together with the unprecedented discovery of new drugs with novel mechanisms of action should contribute to individualized treatment with the aim of increasing the cure rate.*

High-sensitive undetectable MRD as the new treatment endpoint

Depth of response is the key element to evaluate treatment efficacy and predict survival (Fig. 2). Eradicating all tumor cells is necessary to cure most malignancies and this requires achieving and maintaining the deepest response possible. Unfortunately, the definition of complete response (CR) in MM is suboptimal because it relies on low sensitive techniques such as immunofixation and conventional morphology that is not able to distinguish residual tumor cells from the polyclonal plasma cells. Therefore, more sensitive techniques should be used to define the deepest response possible.

Flow cytometry immunophenotyping enables the distinction between tumor and normal plasma cells through the identification of aberrant phenotypes. Using next generation flow (NGF) cytometry, this can be performed with a sensitivity of $2x10^{-6}$ (detection of two tumor cells within one million normal cells) in almost 90% of MM patients. Sequencing immunoglobulin gene rearrangements enables the identification of clonotypic B and plasma cells. Whereas ASO-PCR has been used

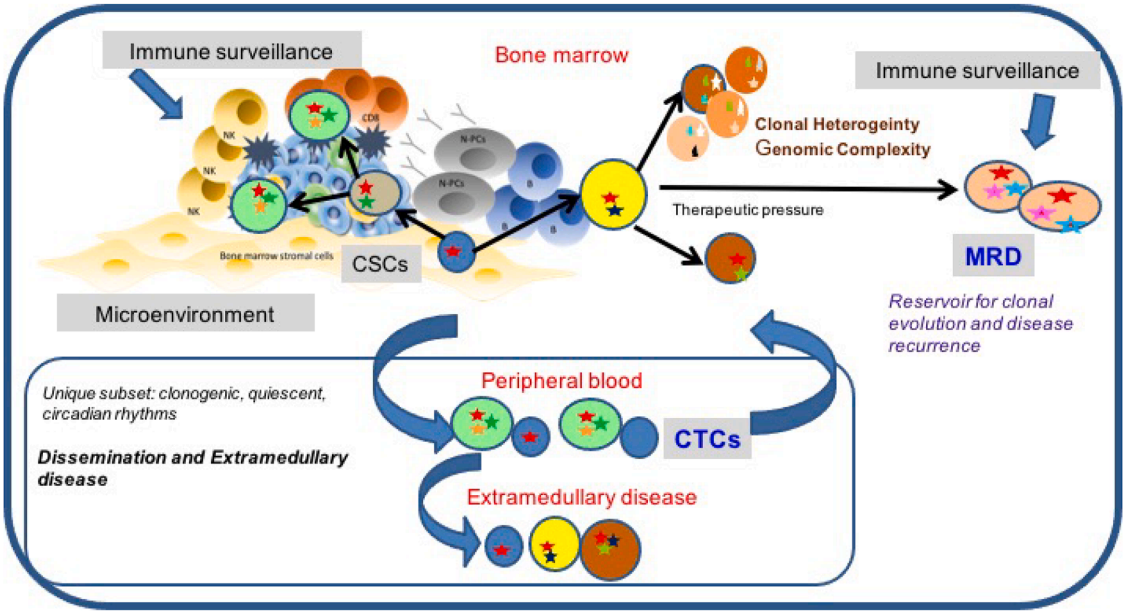

Fig. 1. Pathogenies of Multiple Myeloma: Circulating tumor cells (CTC) and minimal residual disease (MRD) clones represent aggressive clones driving disease dissemination and resistance. *(CTCs: circulating tumor cells, N-PC: normal plasma cells, NK: NK- cells, B: B-lymphocytes, CD8: CD8 + T-cells, MRD: minimal residual disease, CSCs: cancer stem cells).*

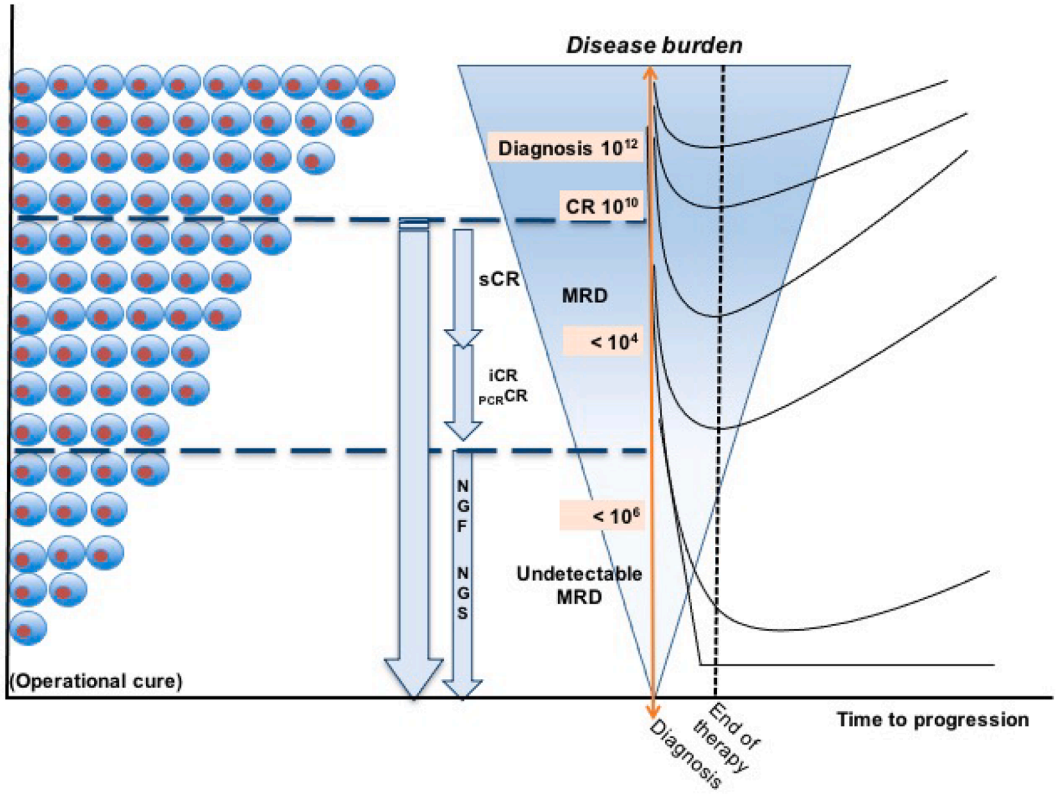

Fig. 2. Representation that illustrates the correlation between depth of response and survival in multiple myeloma. This highlights the need for more sensitive techniques to evaluate response beyond the conventional criteria. *(CR: complete response, MRD: minimal residual disease, sCR: stringent complete response, iCR: immunophenotipyc response (sensitivity level $\langle 10^{-6}$), $_{PCR}$CR: complete response assessed by PCR (sensitivity level $\langle 10^{-6}$), NGF: next-generation flow cytometry, NGS: next generation sequencing).*

in the past, next generation sequencing (NGS) is now the gold standard molecular method to monitor MRD, which also affords a sensitivity of 10^{-6}.

Patients that achieve a negative MRD status at the level of 10^{-5} or 10^{-6}, display significantly longer progression-free (PFS) and overall survival (OS) when compared to those with positive MRD. Using either NGS or NGF it has been shown that the deepest the definition of undetectable MRD, the longer the survival [17]. The prognostic impact of MRD apply to newly-diagnosed transplant eligible and ineligible MM as well as relapsed/refractory patients [18]. After decades or research, methodological improvement and reproducible findings, there is growing consensus that MRD is the most relevant prognostic factor in MM. That notwithstanding, an MRD negative result should be confirmed and sustained for 12 or more months to minimize the risk of false-negative results. This is very important since both hemodiluted samples and patchy BM infiltration hurdle the specificity of a negative MRD result. For this reason, additional MRD assessment outside of the BM is mandatory to define the deepest response possible. PET-CT is the current optimal technique and it has been shown that patients that achieve both imaging and MRD negativity have longer survival [19]. *Accordingly, high-sensitive and imaging techniques should help in avoiding over and under treatment and may become a surrogate biomarker for accelerated drug development and operational cure.*

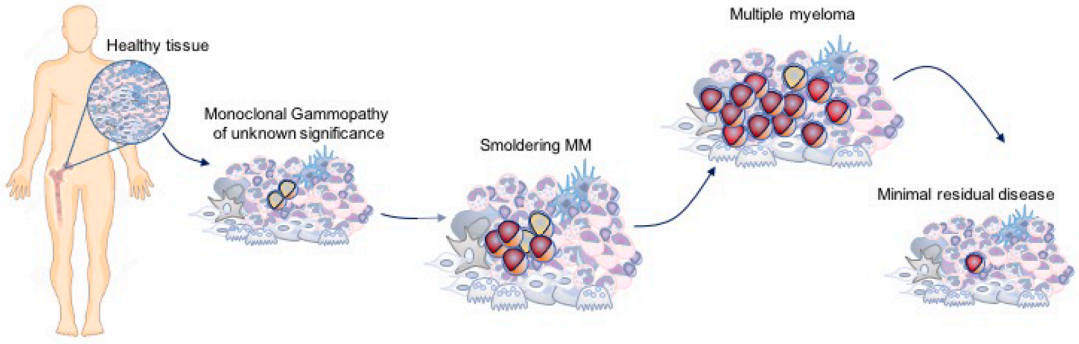

Fig. 3. The figure illustrates the evolution of multiple myeloma from a premalignant condition (MGUS), through smoldering myeloma, until the development of overt symptomatic disease. Early detection and early intervention in the phase of SMM with preventing or curative strategies may be the way to increase the cure rates in this complex disease.

Early detection and early intervention: Treating disease causation instead of symptomatology

Early detection and intervention are a pre-requisite to cure most malignancies. (Fig. 3). Therefore, we should ask why, until recently, the standard of care in MM was no treatment until the development of CRAB symptoms (hypercalcemia, renal insufficiency, anemia or bone disease). The reasons were the lack of benefit of early intervention based on drugs such as melphalan or thalidomide and due to study design, that have not prioritized high-risk SMM patients, together with concerns about clonal selection and unacceptable toxicity with treatment. The possibility of identifying SMM patients with high risk of progression to active MM raised new opportunities for early intervention [20]. In line with this, the Mayo Clinic and the Spanish group, among others, had previously created different risk stratification models that identified patients with a 2-year risk of progression to active disease $\geq$ 50%, identified as high-risk SMM [21]. Also recently, the IMWG have published a new and easy-to-implement model, the so-called 2/20/20 risk stratification model including M−spike concentration (g/dl), FLC ratio and percent of bone marrow plasma cells, respectively. This model segregates three different risk groups. Patients with 2–3 risk factors represent the high-risk SMM population with a 48% risk of progression to active MM in 2 years [21]. These high-risk SMM patients have been the focus of early intervention trials in the recent years. The Spanish myeloma group pioneered this idea through a randomized study conducted in high risk SMM with the aim of delaying disease progression. The results (now with more than 10 years of follow-up) show that patients treated with lenalidomide and dexamethasone (Rd) displayed significantly longer time to progression to symptomatic MM (not reached vs 23 months in the control arm, [HR 0.24; 95% CI 0.14 – 0.41]). Importantly, this was associated with a significant benefit in overall survival; early treatment reduced the risk of death in 46% [22]. These results were confirmed in another phase 3 study using single agent lenalidomide, which showed a HR of 0.28 (95% CI, 0.12 – 0.62) in favor of the early treatment intervention arm [23].

Another approach for early intervention that warrants consideration is to use intensive schemes to eradicate all tumor cells at earlier disease stages (a curative approach). Accordingly, the Spanish myeloma group initiated the CESAR trial in high-risk SMM patients who were transplant candidates, and received six induction cycles of carfilzomib, lenalidomide and dexamethasone (KRD) followed by high-dose melphalan and autologous stem cell transplantation (ASCT), consolidation with two KRD courses and maintenance with Rd for two years [24]. The primary endpoint of this study was to achieve a negative MRD status sustained for five years in $\geq$ 50% of patients. A similar study is being conducted in the United States (ASCENT) with the incorporation of daratumumab, [25]. *Collectively, we envision that early detection and intervention in high risk SMM may not only contribute to delay disease progression into active MM, but also to increase cure rates.*

Use the most active treatments in standard risk patients

We will discuss separately the treatment options for transplant eligible and ineligible patients.

The current treatment approach of **transplant eligible patients** commonly includes four stages: induction, ASCT, consolidation and maintenance [26] (Fig. 4).

What is the optimal induction therapy?: With three-drug regiments based on proteasome inhibitors (PI) such as bortezomib (Btz) or carfilzomib (Cfz) plus immunomodulatory drugs (IMiDs) (thalidomide (thal) or lenalidomide (len)) and dexamethasone, overall response rates beyond 90% can be achieved. Almost one-third of patients may achieve CR and around 20% MRD negativity [27–32]. One retrospective and two prospective studies have shown that these approaches (using Btz-Thal-Dex or Cfz-Len-dex) are superior to the combination of PI with cyclophosphamide-dex [30]. Moreover, the Spanish group has shown in two consecutive studies that Btz-len-Dex is superior to Btz-thal-Dex in terms of depth of response and tolerability (less peripheral neuropathy) [27,29]. For the comparison between Btz-len-Dex versus Cfz-len-Dex, there are not appropriate studies since the Endurance trial was not designed for transplant candidate patients and excluded the high-risk population, showing equivalent efficacy [33].

Can the addition of a monoclonal antibody (MoAb) increase the efficacy of three-drug regimens?. Two randomized studies have addressed this question. The first one compared one standard of care (Btz-thal-Dex) versus the same combination plus daratumumab (CASSIOPEIA). The experimental arm showed higher CR and MRD rates both after induction and after consolidation and this was associated with significantly prolonged PFS (93% vs 85% at 18 months; [HR 0.47, 95% CI 0.33–0.67])

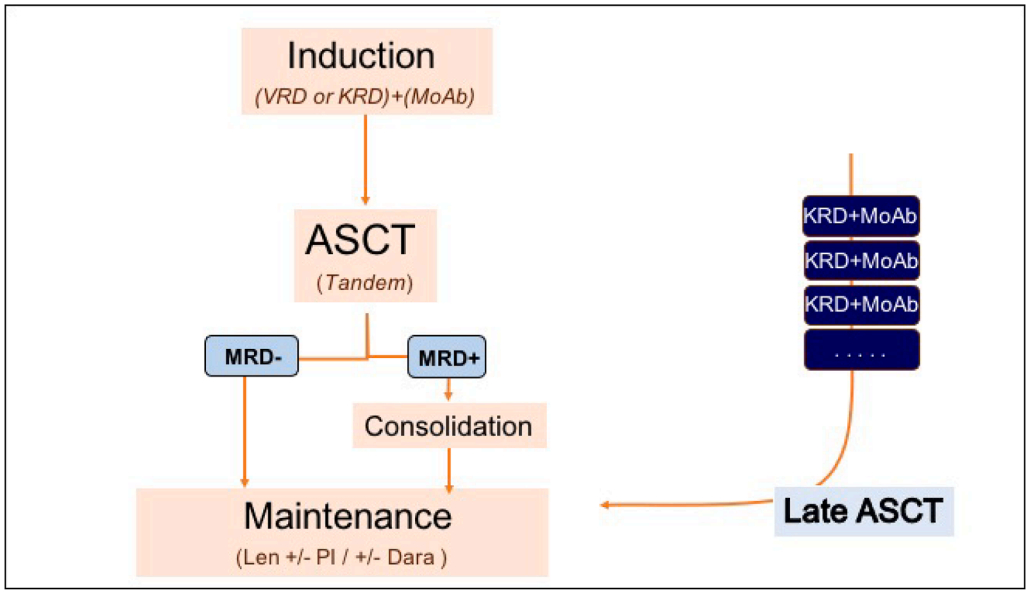

Fig. 4. Schematic representation of our current approach in the treatment of newly diagnosed transplant eligible MM patients. *(V: bortezomib, K: carfilzomib, R: lenalidomide, D: dexamethasone, MoAb: anti-CD38 monoclonal antibody, ASCT: autologous stem cell transplantation, MRD: minimal residual disease, PI: proteasome inhibitor).*

[34]. The Griffin Study investigated the standard of care BTz-len-Dex with or without daratumumab; the addition of the MoAb resulted in higher CR (51% vs 42%) and MRD negative rates (62% vs 32%) after consolidation. Differences in PFS are yet to be observed [35].

Early versus *late transplant?* Intensification with ASCT remains the standard of care since it increases response rates achieved after induction. However, the efficacy of novel combinations is challenging the role of early ASCT, and some patients and doctors may favor continuous treatment with optimal combinations, with the aim of controlling the disease for as long as possible, and to reserve ASCT for relapse. Four randomized studies have addressed this question, one of them including a pooled analysis of two Italian trials [36]. PFS was significantly superior for early vs late transplant in all studies, which favors the use of ASCT upfront [36–38]. However, so far, differences in OS are unclear. In fact, in the IFM/DFCI trial the 8-years OS was equivalent (62% vs 60%) [39]. Moreover, none of these comparisons included MoAb in the trial design.

One or Two transplants? The EMN-02 trial reported that tandem ASCT is superior to single ASCT, both in terms of 3-years PFS (75% vs 64%, p-value 0.04) and OS (89% vs 81%, p-value 0.001), although this benefit was mainly observed in patients with high risk cytogenetics [40]. The STaMINA trial conducted in US showed no superiority for tandem ASCT in the intention-to-treat analysis, however benefit was found in the population of patients indeed treated per protocol (6-years PFS: 49% vs 39%, p-value = 0.01; with statistical differences for high-risk patients (6-year PFS 43.6% tandem vs 26% single ASCT, p-value 0.03) but not for standard risk patients. No differences in OS were observed in the STaMINA trial [41].

Is there a role for consolidation? Consolidation is a short treatment of 2–3 cycles given after ASCT to improve depth of response. There is evidence that CR rates may improve with consolidation but the question is if this translates into significant differences in PFS. In the EMN02 trial patients underwent a second randomization after ASCT to evaluate the role of consolidation with Btz-Len-Dex. A significant benefit was observed with a HR of 0.81 (p-value: 0.04) and this appeared to be more evident in standard than in high risk patients [42]. However, the induction treatment in the EMN02 was short (4 cycles) and did not included any immunomodulatory drug, which may explain these results. Indeed, the value of consolidation was not evident in the STaMINA trial even after the subanalysis based on the type of treatment that patients received [41,43]. In our current practice, we offer consolidation only to those patients that were highly sensitive to the induction therapy but remain MRD positive after ASCT. In patients with high-risk cytogenetics, we change the type of drugs to consolidate with the aim of eradicating MRD before maintenance (Fig. 4).

Maintenance: What drugs and for how long? Four large randomized studies have unequivocally shown that maintenance treatment with lenalidomide (until progression or at least for 2 years) is associated with a marked prolongation of PFS (median increase of 24 months), and an estimated 2.5-year increase in median OS according to a *meta*-analysis [44]. Although the recommendation is to give maintenance until progression, many investigators stop after two years, particularly in MRD negative patients. This statement is not evidence-based, and in fact it could be that the patients that benefit more from maintenance are those that were already in CR. Our policy is to prolong maintenance till the achievement of sustained MRD negativity for at least 2-years. A recent Italian study (FORTE) showed that the addition of carfilzomib to lenalidomide during maintenance increases the rate of conversion from positive into negative MRD (46% vs 32%, p-value = 0.04) and this is associated with significantly longer PFS (81% vs 68% at 30 months, HR 0.63 and p-value 0.026, for Cfz + len vs len, respectively) [38]. The Spanish group randomized patients to receive lenalidomide-dexamethasone plus minus ixazomib but results are still pending. In patients that are intolerant to lenalidomide, there is the alternative of maintenance with ixazomib, that has shown a significant increase in PFS post-transplant although differences are modest as compared to the above reported for lenalidomide (median PFS 26.5 months for ixazomib vs 21.3 months in the placebo groups, HR 0.72 [95 % Ci 0.58–0.89, p-value = 0.0023]), [45].

The initial treatment of **transplant ineligible patients** is particularly relevant since some may have no chances to receive a second or a third line of therapy. The current standard of care are triplets based on the combinations of PI and IMiDs (BTz-len-dex, Cfz-Len-dex; Ixa-len-dex) that yield a PFS of approximately three years. A similar PFS was reported with the combination of daratumumab plus Btz-melphalan-Pred in the ALCYONE study [46]. Nonetheless, these results could have been further improved if bortezomib would have been added to the monoclonal antibody during maintenance. Currently, one of the most appealing combinations for the treatment of newly diagnosed transplant ineligible patients is daratumumab-Len-Dex with a median PFS not yet reached at a median follow-up of 47.9 months and PFS rate at 4 years of 60% observed in the MAIA study [47]. Interestingly, median PFS reported for this combination in patients with high-risk cytogenetic abnormalities was 45.3 months, which is the longest reported so far with a Lenalidomide-based combination for the initial treatment of MM [47].

Altogether, offering intensive scheme to high-risk patients and a gentle approach to standard risk patients may be a wrong philosophy if cure is the aim of treatment. We should give the best possible treatment to standard risk patients up-front. In transplant-candidates, this may include a quadruplet induction, intensification with ASCT, and consolidation if the patient remains MRD positive (but the scheme should be different from that used in induction if the response was suboptimal), maintenance (at least two years in patients with sustained MRD negative) based on lenalidomide +/- PI. In elderly patients, a MoAb + len-dex or BTz-len-dex should be standards of care.

To investigate experimental therapies upfront in high-risk patients

High-risk patients are those with adverse cytogenetics [e.g. del (17p13), t(4;14), t(14;16)], but also patients with early relapse or with suboptimal response to effective induction therapies as well as those with extramedullary disease [48]. In this setting, effective treatment may not be a matter of dose intensity but density, and short sequential therapies, including the novel immunotherapeutic drugs, may be the pathway to follow to avoid early tumor re-growth.

A direct way to overcome the poor prognosis of patients with high-risk genetics, is to achieve a sustained MRD negative status [49]. Data from our group showed that patients with R-ISS 3 remaining MRD-positive after ASCT have dismal outcome with less than 2 years PFS; by contrast, outcomes were significantly improved in those achieving undetectable MRD [16,49]. Although the addition of a monoclonal antibody upfront improves the outcome in these patients (CASSIOPEIA) (30), it does not completely overcome their adverse prognosis, and the only way to make real progress would be to eradicate all residual cells carrying the adverse genetic signature, because otherwise we will face an impending early relapse [34]. Hence, our proposal for high-risk patients is drived by two strategies: 1. An adapted treatment approach upfront in order to eradicate residual disease inside and outside the bone marrow, and 2. Early Rescue intervention (ERI) in case of biochemical or even MRD relapse.

How can we implement treatment-adaptation upfront, with the aim to eradicate MRD? First, to modify the original treatment strategy as soon as we observe suboptimal outcomes. In high risk patients, these would include a sub-optimal response or response stagnation, eg, achieving less than a VGPR after induction or persistent MRD after ASCT [49,50]. In such scenarios, we favor using second generation PI and IMiDs such as carfilzomib or pomalidomide in combination with a CD38, particularly if it was not used upfront, instead of consolidation with the same drugs used during induction. If the new combination is able to eradicate MRD, a prolonged consolidation would be reasonable.

How to implement ERI? There are already data suggesting that patients treated at biochemical relapse have superior outcomes than those in whom treatment was initiated after clinical relapse [51]. The next

step is why not to introduce ERI, particularly in high risk patients, as soon as we detect and confirm, in a subsequent BM exam, an MRD conversion from negative into positive, with a significant increase in the tumor load, e.g by 2 logs?. It could be envisioned that the efficacy and tolerability of salvage therapies may be greater in patients with early biochemical relapse or progressively increasing MRD levels, because the tumor would be rechallenged at a time of controlled rather than uncontrolled disease. Furthermore, it could be hypothesized that in a context of minimal emerging tumor volume, it would be possible to fully rescue patients and to recover their prognosis using alternative therapy embedded within the first-line setting [51]. Although the use of continuous treatment with lenalidomide and anti-CD38 represent a challenge for ERI, several new immunotherapeutic approaches targeting different antigens have emerged. Thus, BCMA, GPRC5D, FcHR5 or SLAMF-7 are antigens present in plasma cells and there is solid evidence that these can be targeted using conjugated antibodies, bispecific T-cell engagers antibodies or CAR-T cells. Moreover, new CellMods as well as other drugs with singular mechanism of action such as selinexor (exportin-1 inhibitor), venetoclax (bcl2 inhibitor) and melflufen (peptide-drug conjugate) will be available.

Regarding antibody-drug conjugates targeting BCMA, belantamab mafodotin was recently approved by the Food and Drug Administration (FDA) and by the European Medicine Agencies (EMA) for the treatment of adult patients with relapse and refractory MM (RRMM) who have received at least 4 prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody. This approval was based on the results of the phase 2 pivotal DREAMM-2 study that evaluated two different doses of belantamab mafodotin in 196 patients. ORR at the approved dose of 2.5 mg/kg was 31% with a median duration of response (DoR) of 11 months (4.2 – NR), median PFS 2.8 months (1.6 – 3.6) and median OS 13.7 months (9.8 – NR). Safety profile was manageable with keratopathy and thrombocytopenia being the two most frequent treatment-related adverse events [52].

Biespecific T-cell engagers (TCE) are another important group of drugs with promising efficacy. Several studies evaluating different BCMA-directed bispecific TCE are ongoing showing ORR between 60 and 80%. Teclistamab, a BCMA-CD3 duobody type TCE, has the most mature data as of today. In the phase 1 dose-escalation study a total of 149 were treated with different doses of Teclistamab and two formulations (intravenous -IV- and subcutaneous -SC-). At the most active doses (270–720 μg/kg IV and 720–3000 μg/kg SC), ORR was 69% (47/68 patients) with very good partial response (VGPR) or better 59% and CR or better in 26%. At the recommended phase two dose (R2PD), stablished at 1500 μg/kg SC, ORR was 73% with $\geq$ VGPR of 55% [53].

Importantly, other targets are also being investigated using the TCE platform. Talquetamab is a GPRC5d-CD3 duobody with comparable efficacy. Thus, in the phase 1 dose escalation study, 157 patients were treated with different doses of Talquetamab either IV or SC. Eleven patients were treated at the RP2D (800 μg/kg SC) with an ORR of 69% and a $\geq$ VGPR rate of 39% [54]. Cevostamab is a FcHR5-CD3 TCE also evaluated in a phase 1 study. In 29 out of 51 patients treated with the active dose levels, ORR was 53% and CR was 18% [55].

Overall, safety profile of the different TCE was acceptable. Cytopenia, specially neutropenia, and cytokine release syndrome (CRS) were the most frequent treatment related adverse events across the different trials. Interestingly, CRS is generally grade 1–2 with very few cases reported being grade 3 (i.e. 0% with Teclistamab or 3% with Talquetamab) due to different mitigation strategies such as step-up doses or steroid premedication.

Adoptive cell therapy with BCMA-directed autologous CAR T-cells is showing very encouraging results in end-stage relapse and refractory multiple myeloma (MM). The largest series of patients so far reported (n = 128) correspond to the KarMMA study based on ide-cel (idecabtagene autoleucel,) with ORR of 73% (33% CR and MRD negativity in 50%) across the three dose levels (150, 300 and 450 $\times$ 10^6 CAR T cells) and ORR 81% and CR/sCR 39% at the target dose level (450 $\times$ 10^6). Median PFS with ide-cel was 8.8 months (95% CI, 5.6 – 11.6) among all 128 patients infused, and increased to 12.1 months (95% CI, 8.8 – 12.3) among patients receiving the highest dose (450 $\times$ 10^6 CAR + T cells) and to 20.2 months (95% CI, 12.3 – NE) in those achieving a CR. Unfortunately, duration of response is usually short and there is no apparent survival plateau. Toxicity profile was manageable. Cytopenia, especially neutropenia and thrombocytopenia, were the most frequent treatment-related adverse events. Median time to recovery of grade $\geq$ 3 neutropenia and thrombocytopenia was 1.9 months (95% CI, 1.9–2.1) and 2.1 months (95% CI, 2.1–5.5), respectively. Any grade CRS was present in 84% of patients, 96% at the highest dose level, and was generally grade 1 or 2. Neurotoxicity was uncommon (20%) and mostly grade 1 or 2. Ide-cel has received FDA approval for the treatment of RRMM [56].

The CARTITUDE 1 study based on the BCMA-directed CAR T-cell ciltacabtagene autoleucel (cilta-cel) has reported an overall response rates of 97.9%, (80.4% $\geq$ sCR and 91.8% MRD negativity in evaluable patients) in 96 patients infused. The 18-months PFS rate was 66% (95% CI; 63.6 – 84.5) and 18-months OS rate was 80.9% (95% CI 71.4 – 87.6). Safety profile of cilta-cel was overall acceptable. Cytopenia was the most common treatment related adverse event, with 95% and 60% of patients developing grade 4 neutropenia and thrombocytopenia, respectively. Most cytopenia were rapidly recovered. Median time to recover from grade 3–4 neutropenia was 2 weeks and thrombocytopenia was 4 weeks. CRS was present in 95% of patients (4.1% grade $\geq$ 3). Neurotoxicity occurred in 20.6% of patients, in 10% grade it was grade 3 or higher. Late neurotoxicity events including movement or neurocognitive disorders, or peripheral neuropathies were present in 12 patients. The exact mechanism underlying this toxicity is not yet elucidated [57].

Based on this data and suboptimal sustained MRD-negative rates achieved with current standards of care in high-risk patients, we consider that these new modalities should be rapidly moved to the frontline setting or at least to be introduced for ERI in high-risk patients. Once we prove the efficacy in a high-risk myeloma population, the same policy should be implemented for the standard risk patients since they would be the easiest to cure and represent the largest MM population.

Final thoughts

Is curing myeloma a dream or reality? Although there is no consensus on a definition of cure, this would probably require having 40–50% of patients with sustained CR for 10 years (ideally MRD negative and without treatment). Two randomized trials activated in 2005, based on relatively old-fashioned approaches (VTD-ASCT-maintenance with corticosteroids or thalidomide) have shown that 32%-24% of patients remain progression free at 10 years [27,58]. Therefore, the dream of cure may not be so far. Although current myeloma treatment is associated with high economical cost, we should recognize that the cheapest medical care is that associated with a high cure rate. This reinforces the concept of personalized medicine that should leverage on the progress in myeloma cell biology and by accepting that MM should no longer be considered as a single entity, but by several subtypes embedded in the term MM. To be sure that we have selected the best road of our roadmap, we need to use the most sensitive techniques to evaluate treatment efficacy, particularly if complete eradication of tumor cells is the objective. This would contribute to avoid both under and over treatment, which is associated with heavy economic burden and emotional frustration. Moreover, we should learn from other hematological malignancies where early detection and intervention were the roadmap to increase cure rates. This approach is not yet widely accepted in the myeloma community, but there is emerging data showing that it may not only contribute to delay disease progression in high risk SMM, but also to increase OS.

If cure is the objective of treating patients with active MM, offering intensive therapies to high-risk patients and a gentle approach to standard risk patients may be a wrong philosophy. The best possible

treatment should always be offered to standard risk patients upfront. In high-risk patients, current strategies are suboptimal. In these patients, the achievement of MRD negativity is of utmost importance and treatment adaptation to achieve this goal, together with early rescue intervention incorporating novel strategies with bispecific T-cell engagers or CAR T-cell therapies, should be implemented to prolong the survival of these patients and, ultimately, cure high-risk MM.

Authorship

Contribution: J.S.-M. conceived the manuscript. J.S.-M., B.P. and P. R.O. wrote the manuscript and have reviewed and provided final approval of the manuscript.

Declaration of Competing Interest

P.R-O declares honoraria for lectures from and membership on advisory boards with Celgene-BMS, Janssen, Amgen, GSK, Kite Pharma, Oncopeptides, Sanofi, Abbvie and Takeda. Consultancy for Celgene, Janssen and GSK. J.S-M has received honoraria from consulting or Advisory Role: Amgen (Inst), Celgene (Inst), Takeda (Inst), Bristol-Myers Squibb (Inst), MSD (Inst), Novartis (Inst), Sanofi (Inst), Janssen (Inst), Roche (Inst), AbbVie (Inst). B.P reports honoraria for lectures from and membership on advisory boards with Amgen, Bristol-Myers Squibb, Celgene, Janssen, Merck, Novartis, Roche, and Sanofi; unrestricted grants from Celgene, EngMab, Sanofi, and Takeda; and consultancy for Celgene, Janssen, and Sanofi.

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