How is patient care for multiple myeloma advancing?

Review

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Abstract

Introduction. Treatment of multiple myeloma has undergone profound changes in the past years thanks to the increased understanding of the biology of the disease and the new treatment options. New drugs and effective approaches are currently available for the treatment of multiple myeloma, including immunomodulatory agents, proteasome inhibitors and autologous stem cell transplantation.

Areas covered. We have described the recent updated criteria to start treatment in multiple myeloma and summarized clinical data from major studies including most recent agents. Particularly, results with pomalidomide, carfilzomib, ixazomib, monoclonal antibodies such as elotuzumab, daratumumab, and checkpoint inhibitors have been reported. Both transplant and non-transplant settings have been covered.

Expert commentary. Despite the successful improvement in overall survival and time to relapse, multiple myeloma still remains incurable. Therefore, there is still an unmet need for new treatment strategies with novel mechanisms of action, like monoclonal antibodies, novel immunomodulators, and novel proteasome inhibitors. Implementation of these novel drugs in rationally designed therapies with a good balance of efficacy and safety should be carefully considered in order to improve outcome.

Keywords: multiple myeloma, immunomodulatory agents, pomalidomide, proteasome inhibitors, carfilzomib, monoclonal antibody, elotuzumab, daratumumab, panobinostat, izoxamib, check point inhibitors.

1. INTRODUCTION

Multiple myeloma (MM) is a malignant plasma cell disorder characterized by the uncontrolled proliferation of monoclonal plasma cells in the bone marrow and aberrant production of monoclonal immunoglobulins or light chains in the blood and/or urine.[1]

MM accounts for approximately 10% of hematological malignant and 1.8% of all new cancer cases. In the USA, between 2009 and 2013, the number of new cases of myeloma was 6.5 per 100,000 men and women per year. The number of deaths was 3.3 per 100,000 men and women per year.[2] The median age at the diagnosis is 70 years, and two-thirds of myeloma patients are over 65 years of age when first diagnosed.[1]

In the last 15 years, considerable progress has been made in the treatment of myeloma with the introduction of novel diagnostic and prognostic assessment tools, and more selective agents that have replaced the older chemotherapy. [3]

In clinical trials, first-line treatment regimens with bortezomib or lenalidomide obtained at least a partial response in nearly all patients, with a complete response in approximately one third of patients,[4,5] thus determining an increased overall survival (OS) from 2.5 years in patients diagnosed before 2001, to 4.6 years and to 6.1 years in those diagnosed between 2001 and 2005 and between 2006 to 2010.

Despite these encouraging results, myeloma patients eventually relapse, thus indicating an ongoing need for new therapeutic approaches. Almost all patients develop acquired resistance to available treatments, leading to relapses with progressively shorter remission times after each treatment regimen. Therefore patients who are dual refractory to bortezomib and lenalidomide have a very poor prognosis, with an OS estimated to be less than 1 year.[6,7]

More recently, a better understanding of the biology of the disease has led to the development of newer, effective, agents that are able to overcome resistance to conventional therapies, and therefore to prolong survival. New treatment strategies with novel mechanisms of action, such as monoclonal

antibodies, histone deacetylase inhibitors, cell signaling inhibitors, selective therapies targeting the bone marrow micro-enviroment, novel immunomodulatory drugs and proteasome inhibitors are under development. The implementation of these novel agents in rationally designed therapies with a good balance of efficacy and safety will further improve the efficacy of anti-myeloma regimens.[8,9]

In the future, risk-adapted therapy with the identification of more sensitive prognostic factors able to predict response to treatments and assessment tools to prevent toxicity will play a central role to improve patients' outcome.

This review highlights the therapeutic options available and under development that will be part of the future treatment paradigms.

2. ADVANCES IN THE GENERAL MANAGEMENT OF MULTIPLE MYELOMA PATIENTS

2.1 Criteria to start treatment

Smoldering MM (SMM) is an asymptomatic clonal plasma cell disorder characterized by the presence of a serum M protein of at least 3 g/dL and/or by clonal plasma cells in the bone marrow encompassing 10% to 60% of overall cellularity, without evidence of myeloma related symptoms.[10] SMM has traditionally been considered as a homogeneous biological entity, with a risk of progression to symptomatic disease of 10%/year for the first 5 years, 5%/year for the following 5 years and 1%/year thereafter.[11] To date, the standard of care is observation, with periodical follow up until the development of symptoms. The recent advances in the understanding of myeloma biology, the identification of new prognostic factors, and the availability of novel effective drugs have questioned the traditional observation approach in this setting. In fact, recent studies found that SMM is not an uniform disease, and it is characterized by different risk of progression to symptomatic disease. In particular, two risk models - one developed by the Spanish team and one by the Mayo Clinic - identified a group of SMM with a high risk (approximately 50%) of progression in 2 years. [12–14] In the Mayo Clinic model the size of the serum M protein (≥3g/dL) and the extent of bone marrow

involvement (≥10% bone marrow plasma cells) and free light chain ratio >0.125 or >8 identifies patients at high risk of disease progression. The model developed by the Spanish Myeloma Group uses the presence of an aberrant plasma cell immunophenotype in >95% of clonal plasma cells and immune paresis to define high-risk patients.

The Spanish Myeloma Group conducted a phase III trial where high-risk SMM patients were randomized either to lenalidomide and dexamethasone induction plus lenalidomide maintenance or to observation. After a median follow up of 40 months the median time to progression (TTP) to symptomatic disease was significantly longer in the early treatment than in the observation group (not reached vs 20 months, P<0.001), with an advantage also in the 3-year survival rate.[15,16] However, such results should be interpreted with caution and there are some concerns regarding the generalizability of this study. Patients were included in the trial according to flow cytometry criteria, which are not widely available, and the results were not stratified according to the risk status of the patients. In addition, asymptomatic biochemical progression was differently handled in both arms (waiting for end-organ damage in the control arm versus the addition of dexamethasone during maintenance in the treatment arm), thus determining a potential bias in favor of early therapy. However, despite such considerations, the trial showed that the traditional "watch and wait" approach is not optimal for high-risk SMM patients and it paved the way to going beyond the classical CRAB criteria (hypercalcemia, renal failure, anemia, bone lesion) as a requirement to start therapy.

In addition, also the recent IMWG updated diagnostic criteria include some features previously considered as typical of SMM – in particular those identifying high-risk SMM – as parameters of symptomatic MM, thus requiring active treatment.[10] The proportion of patients upstaged from SMM to symptomatic MM on the basis of the new criteria is relatively small (10-15%).

Treatment of MM should be started based not only on the presence of end-organ damage according to the CRAB criteria, but also when new biomarkers considered high predictors of the development of symptomatic disease are present. These include bone marrow plasma cells ≥ 60%, serum free light

chain ratio ≥100, and >1 focal lesion on magnetic resonance imaging. Before the implementation of these new diagnostic criteria, patients with one or more of these characteristics were considered as SMM patients and therefore managed with periodical follow-up, despite a risk of progression to symptomatic myeloma greater than 80% in 2 years. Conversely, the introduction of the above, new parameters allowed physicians to intervene before the development of end-organ damage, thus decreasing the risk of related long-term morbidity and possibly increasing patients' survival.[10,17]

A better stratification within SMM patients is fundamental and high-risk SMM patients should be possibly enrolled in clinical trials testing early intervention. Several studies with lenalidomide or with novel agents such as elotuzumab or siltuximab are currently ongoing in high-risk SMM.

For low or intermediate risk SMM patients the watch and wait approach is still considered the standard of care, with follow-up every 3-4 months at least in the initial years after diagnosis and then the frequency may be decreased if the parameters remain stable.[18]

2.2 Criteria to choose the appropriate therapy

2.2.1 Characteristics of patients

Since many new effective therapies are currently available, a personalized approach is becoming essential for the management of MM. Determinants of therapy in the era of individualized medicine are reported in Table 1. MM predominantly affects elderly patients; median age at diagnosis is 70 years, and almost one third of patients are older than 75 years of age. In this scenario, the evaluation of patients' fitness is a key element when choosing the appropriate treatment for elderly MM patients.

Newly diagnosed myeloma patients are traditionally defined as transplant-eligible or -ineligible according to age and comorbidities.[19] Patients older than 65 years of age are highly heterogeneous with different levels of vulnerability. Based on this important concept, in 2015, the International Myeloma Working Group (IMWG) developed a frailty score including age, functional status and comorbidities, in order to determine the frailty status of patients and the feasibility of treatment.

According to this score, elderly patients are defined as fit, intermediate and frail. The assessment of frailty is helpful to choose the most appropriate therapeutic approach and to define treatment goal for each patient subgroup. Fit patients can be eligible for full-dose triplet-therapies, whereas intermediate patients need less-intensive triplet-regimens or doublet-regimens, and frail patients may benefit from dose-reduced doublet-therapies or even palliative or supportive care. Consistently, the goal of therapy is different in these groups: the goal of therapy for fit patients is to achieve a complete remission and improve survival, while in frail patients it is more important to improve and preserve the quality of life as long as possible.[20–22]

2.2.2 Characteristics of the disease

MM is a heterogeneous biological entity, and its prognosis is related not only to host factors, but also to the disease characteristics such as stage, cytogenetics and genomic features. Different patients may not respond to the same treatment due to the genetic variability and cancer complexity of the disease, as well as for the genetic characteristics of the patient. Thank to our increased understanding of myeloma biology, myeloma staging systems and risk stratification models are becoming more accurate.

Chromosomal abnormalities detected by interphase Fluorescence In Situ Hybridization (FISH) are a key element to define the biological features of MM. In newly diagnosed MM, standard risk disease is characterized by the absence of any of del(17p), t(4;14)(p16;q32) or t(14;16)(q32;q23) abnormalities and is associated with a median OS of 50.5 months, high-risk disease is characterized by the presence of at least one of the above mentioned abnormalities and is associated with a median OS of 24.5 months. Gene expression profiling (GEP) of an individual patient measures the activity of specific genes and represents the biology of the disease. It has been found that GEP fingerprint can be used to identify high-risk disease and guide therapeutic interventions for MM patients, but due to the higher costs and the lack of a standardized technique, GEP is not yet widely used.

In 2013 Mayo Clinic updated its risk stratification model (mSMART) including gene expression

profiling (GEP) and patients were classified as standard, intermediate or high-risk accordingly.[23] In 2015, the IMWG presented a new prognostic staging system, the R-ISS, which combines the International Staging System (ISS) with chromosomal abnormalities detected by FISH and serum lactate dehydrogenase levels, and this new model was able to identify three different myeloma entities with different survival.[24] Both the mSMART and the R-ISS are detailed in Table 2.

According to 2016 Mayo Clinic guidelines, [25] the aim of a risk-adapted approach is to provide the optimal therapy to patients, ensuring intense therapy for aggressive disease, providing sufficient but less intense therapy for low-risk disease, while minimizing toxic effects. The Mayo Clinic consensus statement reflects recommendations for a practical approach for newly diagnosed patients with myeloma. Patients with del(17p), t(14;16), and t(14;20) are defined high-risk; patients with t(4;14) translocation and gain(1q) have intermediate-risk and all others are considered standard-risk. In high-risk patients, the triplet carfilzomib, lenalidomide, dexamethasone (KRD) is proposed as an alternative to bortezomib-based induction, since it seems more active and results in deeper and more prolonged responses. Nevertheless, there is no consensus on selecting an intensive therapy for high-risk and a less intensive approach for low-risk patients; this risk-adapted approach may not be beneficial for the latter group, who may be undertreated, negatively affecting their outcome.

There is an urgent unmet medical need for a more precise risk stratification of patients. A more precise – and at the same time simple – stratification will help physicians in treatment decision-making and will allow patients to receive personalized treatments, with the highest efficacy and lowest toxicity.

In the future, the main goal for the physicians will be to select the optimal treatment method for each patient (risk-adapted approach) through a comprehensive and systematic approach that uses genomic information.

3. ROLE OF AUTOLOGOUS STEM CELL TRANSPLANTATION

High-dose chemotherapy followed by ASCT is considered the standard of care for NDMM patients aged 65 years old or younger.[26][27] Of note, consolidation with upfront ASCT prolongs progression-free and overall survival by deepening response, and improves quality of life. Therefore, this strategy showed to be cost-effective and a valuable option.

However, the introduction of novel agents questioned the role of ASCT as front-line therapy for young NDMM patients due to substantial toxic side effects and the prolonged hospitalization associated with ASCT. Different phase III trials therefore compared consolidation strategies with conventional ASCT and less toxic drug combinations containing PIs or IMiDs.

One study compared consolidation with melphalan 200mg/m^2 followed by ASCT versus 6 cycles of melphalan, prednisone and lenalidomide (MPR) following 4 cycles of lenalidomide-dexamethasone (Rd) as induction in NDMM patients younger than 65 years old. Patients were subsequently randomized to lenalidomide maintenance or no maintenance. After a median follow-up of 51 months, PFS was significantly longer in the ASCT arm (43 months vs 22 months) and the 4-year OS was 82% versus 65%.[28]

These results were comparable with another phase III trial comparing high-dose melphalan followed by ASCT and 6 cycles of cyclophosphamide-dexamethasone-lenalidomide (CRD). Patients were subsequently randomized to lenalidomide or lenalidomide-prednisone maintenance. The ASCT arm showed an advantage in terms of both PFS (43 vs 29 months) and 4-year OS (86% vs 73%) compared to the CRD arm. [29]

In both studies, patients receiving high-dose melphalan plus ASCT experienced a greater rate of grade 3-4 adverse events. Nevertheless, such toxicities were easily manageable and did not increase significantly the rate of treatment discontinuation or early death.

An ongoing clinical trial is comparing high-dose melphalan followed by ASCT to 4 cycles of bortezomib-melphalan-prednisone (VMP) after induction therapy with bortezomib-cyclophosphamide-

dexamethasone. Patients were then randomized to consolidation with bortezomib-lenalidomide-dexamethasone versus no consolidation before lenalidomide maintenance. Preliminary data after a median follow-up of 26 months showed a median PFS of 44 months for the VMP arm while median PFS was not reached in the ASCT arm (3-year estimated PFS: 58% vs 66%). [30]

In another study, the Intergroupe Francophone Du Myelome/Dana Farber Cancer Institute (IFM/DFCI) trial, patients were randomized to ASCT or no ASCT after induction therapy including lenalidomide-bortezomib-dexamethasone (RVD). Patients treated with ASCT received subsequent RVD consolidation, and all patients received 12 months of maintenance therapy with lenalidomide. Initial results showed a 3-year PFS in favor of early transplant, 61% versus 48% ($p<0.0002$), and OS was similar in both groups [31].

Based on the results of the major phase III clinical trials conducted so far, upfront ASCT as consolidation provides a significant clinical benefit compared to combination therapies with novel agents. In addition, upfront ASCT showed to have a good impact on quality of life and to be an appropriate cost-effective strategy. Therefore, ASCT is still the preferable option as first-line treatment for NDMM patients younger than 65 years.

4.CLINICAL RESULTS WITH NEW GENERATION AGENTS

4.1 Pomalidomide

Pomalidomide is a new generation oral anti-myeloma agent belonging to the immunomodulatory class. It has a strong direct tumoricidal activity; it is also able to interfere with the stromal cell-support system of the bone marrow, inhibiting both intracellular and extracellular myeloma growth mediators. Moreover, pomalidomide has an immunomodulatory action based on the activation of natural killer cells and inhibition of regulatory T cells, which lowers the immune system tolerance to myeloma cells.

The high efficacy and the favorable toxicity profile of pomalidomide, led to its approval by the Food and Drug Administration and by the European Medical Agency in 2013 for its use alone or in

combination with dexamethasone in relapsed/refractory myeloma patients who have received at least two prior lines of therapy including lenalidomide and bortezomib and have demonstrated disease progression within 60 days of their most recent treatment.[32–35]

Pomalidomide starting-dose has been established to be 4 mg daily for the first 21 days of 28-day cycles, followed by 7 days of rest. Therapy has to be continued until disease progression or unacceptable toxicity.

The pivotal phase III trial MM-003 compared pomalidomide and low-dose dexamethasone with high-dose dexamethasone in patients who had received prior bortezomib- and lenalidomide-based therapies (Table 3). After an updated median follow-up of 15 months, patients in the pomalidomide and low-dose dexamethasone arm showed significantly longer PFS (4 vs 1.9 months) and OS (13.1 vs 8.1 months). A sub-group analysis showed that these benefits are generally maintained regardless of the number or the type of prior treatments, or the refractory status.[36–38]

The high efficacy of this regimen has been confirmed in the STRATUS trial, the largest phase IIIb study evaluating pomalidomide plus low-dose dexamethasone in patients relapsed/refractory to bortezomib- and lenalidomide-based therapies. This study reported a median PFS of 4.6 months and a median OS of 12.9 months.[39]

Several clinical trials – some are still ongoing – evaluated the role of pomalidomide-based combinations in relapsed/refractory myeloma patients. Pomalidomide-cyclophosphamide-prednisone (PCP) demonstrated to be a very effective and promising regimen, with an overall response rate (ORR) of 51% and a median PFS of 10.4 months.[40]

A recent phase II trial compared the combination pomalidomide-cyclophosphamide-dexamethasone (PomCyDex) with pomalidomide-dexhametasone (PomDex) alone, showing a better ORR (38.9% vs 64.7%) and PFS (4.4 vs 9.5 months) in the PomCyDex arm.[41]

Encouraging results are emerging also from the first phase I trial of carfilzomib-pomalidomide-dexamethasone, with an ORR of 50% and a median PFS of 7.2 months.[42]

The most frequent pomalidomide-related adverse events are myelosuppression, fatigue and infection. Peripheral neuropathy, rash, gastrointestinal disorders and muscle cramps are rare. Thromboembolic events are rare as well, but, similarly to other immunomodulators, patients require deep-vein thrombosis prophylaxis with aspirin or low-molecular weight heparin, based on individual risk factors.

4.2 NEW PROTEASOME INHIBITORS.

4.2.1 Carfilzomib

Carfilzomib is a second-generation proteasome inhibitor structurally different from bortezomib. Carfilzomib is an epoxy-ketone able to irreversibly and selectively inhibit the chymotrypsin-like site of the proteasome. Thus Carfilzomib exerts a more sustained proteasome inhibition compared to bortezomib, which is a reversible and less selective inhibitor. Carfilzomib has shown activity against cell lines resistant to conventional and novel agents, including bortezomib.[43,44]

Carfilzomib was initially approved by FDA in 2012 as monotherapy for patients with relapsed and refractory MM who received at least two prior treatments including bortezomib and an immunomodulatory agent, and demonstrated disease progression within 60 days of their most recent therapy. In 2015 FDA approved the use of carfilzomib in combination with lenalidomide and dexamethasone and in 2016 with dexamethasone alone for patients who previously received one to three lines of therapy.[45]

Carfilzomib is administered intravenously twice-weekly for three consecutive weeks followed by one week of rest. The starting dose for the first two infusions is 20 mg/m^2. If well tolerated, the dose can be increased to 27 mg/m^2, if carfilzomib is administered in combination with lenalidomide and dexamethasone; or to 56 mg/m^2 if it is used in combination with dexamethasone or as monotherapy.[46]

Several clinical trials tested carfilzomib both in relapsed/refractory and newly diagnosed patients, either as monotherapy or in combination with different agents.

Carfilzomib as monotherapy demonstrated significant efficacy in relapsed/refractory myeloma patients. In 266 MM patient, mainly refractory to their most recent therapy and 80% dual refractory to bortezomib and lenalidomide, carfilzomib induced an ORR of 23.7%, with a median duration of response of 7.8 months and a median OS of 15.6 months.[43]

In the ASPIRE trial, 792 patients with relapsed/refractory MM were randomized to either a carfilzomib-lenalidomide-dexamethasone or to lenalidomide-dexamethasone. The addition of carfilzomib to lenalidomide-dexamethasone resulted in an ORR of 87.1% versus 66.7% and in a better PFS compared to the control group (26.3 months versus 17.6 months).[44]

The ENDEAVOR study was the first that directly compared carfilzomib-dexamethasone with bortezomib-dexamethasone. This study included 929 patients with relapsed/refractory MM with one to three prior lines of therapy. Carfilzomib demonstrated a higher response rate and a longer PFS (18.7 vs 9.4 months).[47]

Champion study is the first clinical trial that investigated carfilzomib in a once-weekly dosing schedule in association with dexamethasone in 116 patients with relapsed/refractory myeloma patients. Results of this phase I-II trial suggest that once-weekly administration of carfilzomib is feasible, generally well-tolerated and active for patients with relapsed/refractory MM.[48] Other ongoing trials are currently investigating the once-weekly strategy.

Carfilzomib has also been evaluated also in newly diagnosed myeloma patients. In elderly patients carfilzomib-cyclophosphamide-dexamethasone induced a high complete response rate with a good toxicity profile.[49] Moreover, in transplant-ineligible patients, carfilzomib was evaluated in combination with melphalan and prednisone as induction strategy.[50]

As for toxicity, carfilzomib has a lower risk of neurotoxicity compared to bortezomib, probably due to its more selective action on the proteasome. On the other hand, a small proportion of patients may experience serious cardiac adverse events such as dyspnea, heart failure and hypertension. Investigation is underway to better understand the biological basis of carfilzomib-related cardiotoxicity and to

develop global guidelines for an appropriate prevention and management.

4.2.2 Ixazomib

Ixazomib is the first oral proteasome inhibitor with demonstrated activity in relapsed/refractory MM. In 2015, FDA - and more recently also EMA - approved ixazomib in combination with lenalidomide and dexamethasone for the treatment of relapsed MM patients who had received at least one prior therapy. This combination is the first all oral, triplet therapy for relapsed/refractory myeloma patients. The recommended starting dose of ixazomib is 4 mg once-weekly for three consecutive weeks in a 28-day cycle.

TOURMALINE MM1 is a phase III trial that enrolled 722 patients with relapsed/refractory MM, demonstrating that the combination of ixazomib, lenalidomide and dexamethasone is superior to lenalidomide and dexamethasone. Indeed, median PFS was 20.6 months in the ixazomib group compared with 14.7 months in the control group.[51]

An ongoing phase III trial, TOURMALINE MM2, is currently evaluating the efficacy of ixazomib, lenalidomide and dexamethasone in newly diagnosed myeloma patients, whereas two other phase III trials are testing ixazomib as maintenance therapy after standard induction therapy in elderly patients and after ASCT in young patients.

Of note, ixazomib is associated with a lower risk of neurotoxicity in comparison to bortezomib, despite a higher rate of gastrointestinal adverse events.

4.2.3 Other proteasome inhibitors.

Marizomib and oprozomib are new proteasome inhibitors that are currently being investigated in preclinical models and in phase I-II clinical trials.

Marizomib is structurally and functionally different from the other proteasome inhibitors, since it inhibits all the three proteolytic sites of the enzyme, showing a greater activity on myeloma cells

compared with bortezomib in preclinical models. In the first phase I clinical trial in relapsed refractory myeloma patients, this agent proved to be active and relatively well tolerated.[52,53]

Oprozomib is structurally related to carfilzomib, with the advantage of the oral administration. Preliminary results from phase I-II clinical trials are encouraging.[54]

4.3 MONOCLONAL ANTIBODIES.

4.3.1 Elotuzumab

Elotuzumab is a humanized IgG1 monoclonal antibody that targets CS1 and activates host natural killer cells to release perforin granules resulting in targeted myeloma cell death.[55]

CS1 is a cell surface glycoprotein and member of the signaling lymphocyte-activating molecule-related receptor family 7 (SLAMF 7). It is highly expressed in most patients with MM, regardless of previous therapy or cytogenetic profile. Although the role of CS1 in the pathogenesis of myeloma remains unclear, it is considered a promising target with a favorable therapeutic index because it has little expression in normal tissues.

Elotuzumab does not appear to have high activity as single agent, differently from other monoclonal antibodies such as anti-CD38. Nevertheless it seems to have synergistic activity when combined with other anti-myeloma drugs like bortezomib or lenalidomide.

Based on this, elotuzumab was approved by FDA in 2015 in combination with lenalidomide and dexamethasone for patients with relapsed MM who had been previously treated with one to three lines of therapy. The recommended dose is 10 mg/kg weekly for the first two 28-days cycles and every two weeks thereafter. Therapy with elotuzumab should be continued until disease progression or unacceptable toxicity.[56]

In the phase III, ELOQUENT2 trial, 646 patients with relapsed/refractory MM were randomized to either elotuzumab, lenalidomide and low-dose dexamethasone or to lenalidomide and dexamethasone. The elotuzumab group proved to be superior in terms of ORR (79% vs 66%) and PFS (median 19.4 vs

14.9 months).[57]

A recent phase II clinical trial compared the combination of elotuzumab, bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed/refractory myeloma patients, and showed a 2 year PFS rate of 18% versus 11% in the three-drug combination group.[58]

Elotuzumab is currently under investigation also in newly diagnosed patients in combination with lenalidomide and dexamethasone (ELOQUENT1). Overall, elotuzumab is well tolerated, and the most common treatment-related adverse events included infusion reactions and pyrexia, generally limited to grade 1 or 2.

4.3.2 Daratumumab

CD 38 is highly expressed on myeloma cells, whereas low levels are found on normal lymphoid and myeloid cells. This molecule plays a role in receptor-mediated signaling events regulating cell adhesion and it also contributes to the intra cellular mobilization of calcium. There are currently three anti CD38 monoclonal antibodies under clinical development for MM patients: daratumumab, SAR650984, and MOR202.

Daratumumab is a humanized IgG1k monoclonal antibody that interacts with myeloma cells through different mechanisms of action, expressing direct and indirect anti-tumor activity. It can elicit antibody-dependent cell mediated cytotoxicity (ADCC), activate complement-dependent cytotoxicity (CDC) and antibody dependent cellular phagocytosis (ADCP), and it can directly induce tumor cell apoptosis. Moreover daratumumab has immunomodulatory functions since it targets and depletes CD38 positive regulator immune suppressor cells, leading to T-cell expansion and activation. Alternatively, binding of daratumumab to CD38 showed to mediate phagocytosis of myeloma cells by macrophages.

FDA in 2015 - and subsequently EMA in 2016 - approved daratumumab as monotherapy for the treatment of MM in patients who previously received at least three therapies, including a proteasome inhibitor and an immunomodulatory agent or who were double refractory to them.

The recommended dose is 16 mg/kg administered intravenously every week for the first 8 weeks and then every two weeks from week 9 to 24 and every 4 week thereafter until disease progression.[9,59]

The approval of this agent was based on the results of the pivotal GEN 501 and SIRIUS trials which demonstrated that daratumumab is active as monotherapy in heavily pretreated patients with relapsed/refractory MM. Indeed, the ORR in patients refractory to both immunomodulatory drugs and proteasome inhibitors was 36% in GEN501 and 29.7 % in SIRIUS, the respective PFS was 5.6 months and 3.7 months. In a combined analysis of both studies including 148 heavily pre-treated patients with relapsed or relapsed and refractory MM, after 5 prior lines of treatment, single agent daratumumab was associated with an ORR of 31% and a median OS of 20.1 months.[60–62]

Daratumumab is currently being investigated in combination with proteasome inhibitors and immunomodulatory agents. In the phase III CASTOR trial, the combination of daratumumab, bortezomib, and dexamethasone resulted in significantly longer PFS than bortezomib and dexamethasone alone in relapsed/refractory myeloma patients (1-year PFS rate 60.7% vs 26.9%).[63]

Daratumumab is under evaluation also in combination with lenalidomide and dexamethasone in the phase III POLLUX trial, showing advantages in term of ORR (93% vs 76%) and PFS (1-year PFS 85.7% vs 63.2%).[64]

Daratumumab is being tested also in patients with newly diagnosed MM in combination with bortezomib-based regimens. The phase III trial ALCYONE is comparing bortezomib, melphalan, prednisone (VMP) with daratumumab-VMP in myeloma patients ineligible for autologous stem-cell transplantation. In the phase III trial CASSIOPEIA, transplant-eligible patients are randomized to VTD or daratumumab-VTD as induction followed by VTD with/or without daratumumab as consolidation. Patients will be subsequently randomized to daratumumab maintenance therapy vs observation.[65]

As far as safety profile is concerned, daratumumab appears to be well tolerated, and the main adverse events are infusion related reactions.

4.3.3 Programmed death-1 immune checkpoint blockade.

Nivolumab (BMS- 936558) and Pembrolizumab (MK-3475) are humanized monoclonal antibodies targeting the programmed cell death receptor (PD-1) expressed on the surface of activated T cells, including tumor-infiltrating lymphocytes (TILs). When one of the PD-1 ligands (PD-L1 and PD-L2) binds to PD-1, TILs become inactive, allowing cancer immune escape. Many tumor cells overproduce PD-L1 and induce the upregulation of PD-1 on TILs surface, preventing T cells from targeting the tumor[66].

Nivolumab and pembrolizumab have been approved by FDA for the treatment of different solid tumors. In vitro studies demonstrated that also myeloma cells show an increased expression of PD-L1, supporting the initiation of clinical trials with checkpoint inhibitors in MM.[67]

In a phase Ib trial in patients with relapsed and/or refractory hematological malignancies, 27 MM patients were treated with single agent nivolumab without any objective response (stable disease was the best response achieved in 63% of patients).[68]

Preliminary results from ongoing clinical trials with pembrolizumab in MM are promising. In the phase I KEYNOTE 023 trial, patients with relapsed/refractory MM were treated with pembrolizumab, lenalidomide and low-dose dexamethasone. The most frequent treatment related toxicities were thrombocytopenia (47%), neutropenia (41%), anemia, hyperglycemia and muscle spasms (23% each). Preliminary data showed an ORR of 76%, with responses observed also in IMIDs refractory and double refractory patients.[69] The rationale of this combination therapy derives from the evidence in preclinical models that the activity of anti PD-1 checkpoint inhibitors is enhanced by lenalidomide.[70]

Pembrolizumab is being tested also in association with pomalidomide and dexamethasone in a phase II study in relapsed/refractory MM, showing an acceptable safety profile and a good therapeutic activity (ORR 56%). Most frequent grade ≥3 adverse events are hematological (mainly neutropenia, 40%), hyperglycemia (25%), upper respiratory tract infections(21%) and rash (10%). [71]

5. Expert commentary

In the last few years, significant progresses have been made in the understanding of MM biology. It is now clear clonal heterogeneity plays a fundamental role and the disease can be characterized by different patterns of clonal evolution, partially influenced by the selective pressure of the therapy administered.[72,73]

In addition, new targeted drugs with new mechanisms of action have been recently approved or are under evaluation, and they will gradually increase the available therapeutic options.

In this scenario, we are moving more and more towards the era of individualized therapy. In particular patient's clinical status and risk stratification will be crucial in determining the most appropriate treatment .

For young and elderly fit patients it is important to obtain a high quality response in order to improve survival, and this can be done by using highly active combinations. Moreover, most effective regimens should be offered in the early phase of the disease, when malignant clones are more drug sensitive, long-lasting remission are more frequent, and serious adverse events are less prominent. [28,29]. On the other hand, the goal of treatment for the frail elderly patients is to maintain the asymptomatic status as long as possible, preserving the quality of life; to achieve this aim, lower dose intensity regimens with a good toxicity profile should be preferred.[74]

The higher efficacy of the new targeted therapies requires the introduction of more sensitive methods to evaluate response. Assessment of minimal residual disease (MRD) seems a valid surrogate biomarker for survival and it is currently used in many clinical trials to further assess its role in therapeutic decisions. In several studies, patients with persistent MRD positivity despite achieving a complete response (CR) had an inferior PFS compared with MRD negative patients. Different methods to detect MRD are currently available, such as multiparametre flow cytometry (MFC), allele-specific oligonucleotide (ASO)-qPCR, next-generation sequencing of VDJ sequences, as well as imaging techniques like PET/TC scans or MRI. Although the most convenient standardized method of MRD

assessment has not been established yet, in 2016 the IMWG defined new response categories of MRD negativity to allow uniform reporting in clinical practice and in trials.[75–77]

Despite these advances in the management of the patients with MM, further investigation is needed to clarify whether treatment should include multidrug highly-active strategies with the goal of curing patients (despite the higher risk of adverse events), or if treatment should consist of less toxic regimens to control a disease considered as chronic and incurable (preserving the quality of life).

These two different philosophies lead to another unsolved issue, namely which treatment strategy should be preferred between sequencing or combination therapy. Indeed, three-drug regimens provide higher response rates and PFS compared to doublet regimens, which on the other hand are less toxic and allow physicians to keep the third agent for subsequent lines of therapy. Currently, the advantage in term of OS is not clear and the question about which approach is better needs to be better addressed.

6. Five-year view

Patient care for myeloma patients is rapidly advancing thanks to new targeted drugs with different but complementary mechanisms of action. New combinations of these drugs are expected to improve PFS and OS. However there are still some dilemmas that need to be clarified in the future, such as the best combination, the optimal sequence and the proper targets of newer agents. The safety profile should guarantee minimal toxicity and a good quality of life. An important challenge will be the identification of patient subsets that will benefit most from a certain combination of novel agents. Today, myeloma patients relapsed or refractory to lenalidomide, bortezomib or both, can be treated with novel immunomodulators, novel proteasome inhibitors and monoclonal antibodies. In the next years, new approaches will emerge in the treatment of myeloma patients. New anti-myeloma drugs will target MM cells in the context of the bone marrow micro environment. A better understanding of the biology of MM will allow us to create precocious treatments for patients, using rationally informed combination therapies with curative potential. These combinations will include monoclonal antibodies, vaccines,

immune checkpoint inhibitors, CAR-T cell.

We expect the additional aberrant signaling pathways in myeloma cells to be discovered and to enable us to identify new molecular targets. Having in mind the genomic heterogeneity and the complexity of MM, there is certainly an urgent need for targeted, combination therapies to prevent genomic evolution and disease progression.

7. Key issues

- Despite the advances in treatment of patients with MM due to the introduction of new agents, including immunomodulatory drugs, proteasome inhibitors and the use of autologous stem cell transplant, patients eventually relapse and may become refractory to previous therapies.
- There is an urgent unmet need for novel anti-myeloma agents, especially for patients who have become refractory to currently available therapeutic options.
- Pomalidomide is more potent and better tolerated than its predecessors, thalidomide and lenalidomide, thus in 2013 FDA approved it either alone or in combination with dexamethasone in relapsed/refractory MM patients who received at least two prior therapies.
- Ixazomib is an oral proteasome inhibitor with advantage of lower incidence of neurotoxicity and once-weekly oral administration for patients with newly diagnosed and relapsed/refractory MM.
- Monoclonal antibodies represent the next step in the treatment of MM. Elotuzumab, a SLAM7-target humanized monoclonal antibody, seems to have synergistic activity when combined with anti-myeloma therapies that stimulate host immunity. Anti – CD 38 antibody - Daratumumab as monotherapy and in combination regimens showed impressive results with favorable safety profile without significant increase in toxicity in relapsed/refractory MM patients.
- Clinical trials with multiple checkpoint inhibitors are underway or are planned in MM, like

pembrolizumab (MK-3475) - monoclonal antibody considered as immune checkpoint inhibitor that target the programmed cell death receptor.

- Despite the availability of numerous anti-myeloma drugs, many questions still remain unanswered. The best combination, the optimal sequence and proper target and setting of newer myeloma are relevant issues that need to be clarified in the next future.

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Reference annotations

* Of interest
** Of considerable interest

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TABLE 1. Determinants of therapy in the era of individualized medicine.

CHOICE OF THERAPY			
DISEASE CHARACHTERISTICS • cytogenetic risk • stage • tumor burden • organ function • types and response to eventual previous therapies	PATIENT CHARACHTERISTICS • age • performance status • comorbidities • independence and functional status • social context	GOAL OF CARE • complete remission/MRD • disease control • quality of life	SETTING • availability of clinical trials

TABLE 2. IMWG updated criteria for the diagnosis of SMM and MM and main risk assessment models

	DEFINITION	RISK ASSESMENT MODELS	
SMOLDERING MULTIPLE MYELOMA (SMM)	- serum monoclonal protein ≥ 3 g/dL or urinary monoclonal protein ≥ 500mg/24h and/or bone marrow plasma cells (BMPC) 10-60% -absence of myeloma defining events or amyloidosis	MAYO CLINIC RISK MODEL - ≥10% of BMPC infiltration - ≥3 g/dL serum M-protein - serum FLC[1] ratio <0.125 or >8	SPANISH RISK MODEL -≥95% of aberrant plasma cells at MFC[2] - immune paresis
MULTIPLE MYELOMA (MM)	- clonal BMPC ≥10% or biopsy proven plasmacytoma and - evidence of end organ damage according to CRAB[3] criteria or -≥1 of the following biomarkers of malignancy: - clonal BMPC ≥60% -serum FLC ratio ≥100 -> 1 focal lesion at magnetic resonance imaging	R-ISS -ISS stage -chromosomal abnormalities (CA) detected by FISH[4] -LDH[5] ➢ R-ISS stage I: ISS stage I, standard risk CA and normal LDH ➢ R-ISS II: not R-ISS stage I or III ➢ R-ISS III: ISS stage III and either high risk CA[6] or high LDH	mSMART - chromosomal abnormalities (CA) detected by FISH -gene expression profiling (GEP) ➢ high risk: del 17p, t(14;16), t(14;20), GEP high risk signature ➢ intermediate risk: t(4;14), del13, hypodiploidy, PCLI[7] ≥3% ➢ standard risk: all others CA

1.FLC: free light chain. 2.MFC: multiparametric flow cytometry. 3. CRAB criteria: hyperCalcemia ,Renal insufficiency, Anemia, Bone lesions. 4.FISH: fluorescent in situ hybridization. 5.LDH:lactate dehydrogenase. 6.high risk CA according to R-ISS: del 17p, t(4;14), t(14;16) 7.PCLI: plasma cells labeling index.

TABLE 3. Approved new generation agents for the treatment of multiple myeloma

CATEGORY	AGENT	INDICATION[1]	MAJOR TRIALS (in RRMM[2] patients)
Immunomodulatory drugs (IMIDs)	pomalidomide	RRMM ≥2 prior therapies including lenalidomide and bortezomib Regimen: - monotherapy - with low dose dexamethasone	- MM03: Pom-dex vs DEX ORR[3] 31% vs 10%; PFS[4] 4 vs 1.9 months; OS[5] 13.1 vs 8.1 months -STRATUS: Pom-dex ORR 32.6%; PFS 4.6 months; OS 12.9 months
Proteasome inhibitors (PI)	carfilzomib	RRMM: - ≥2 prior therapies including an IMID and bortezomib (as single agent) - 1-3 prior therapies (in combination) Regimen: - monotherapy -with low dose dexamethasone -with lenalidomide and dexamethasone	-PX171003A1: single-agent carfilzomib ORR 23.7%; PFS 3.7 months ; OS 15.6 months -ENDEAVOR:Kd vs Vd ORR 77% vs 63% PFS 18.7 vs 9.4 months; -ASPIRE: KRd vs Rd ORR 87.1% vs 66,7%; PFS 26.3 vs 17.6 months
	ixazomib	RRMM ≥1 prior therapy Regimen: - with lenalidomide and dexamethasone	- TOURMALINE MM01: IXA-Rd vs Rd ORR 78% vs 72%; PFS 20.6 vs 14.7 months
Monoclonal antibodies	elotuzumab	RRMM 1-3 prior therapies Regimen: - with lenalidomide and dexamethasone	- ELOQUENT2: elo-Rd vs Rd ORR 79% vs 66%; PFS 19.4 vs 14.9 months
	daratumumab	RRMM ≥3 prior therapies or double refractory to PI and IMID Regimen:	-GEN 501 : single-agent daratumumab ORR 36%; PFS 5.6 months; -SIRIUS: single-agent daratumumab

		- monotherapy	ORR 29.7%;PFS 3.7 months

1.Indications according to Food and Drug Administration approval. 2.RRMM: relapsed refractory multiple myeloma. 3. ORR: overall response rate 4. PFS: progression free survival 5. OS: overall survival