Multiple myeloma (MM) is a unique cancer paradigm for investigating the mechanisms involved in the transition from a premalignant condition (monoclonal gammopathy of undetermined significance) into a malignant disease (MM). In the pathogenesis of myeloma, the dialogue between plasma cells and their microenvironment is as important as the genotypic characteristics of the tumor clone. MM is genetically highly complex, with almost all patients displaying cytogenetic abnormalities and frequent intrachromosomal heterogeneity that play a critical role in the outcome of the disease. In fact, it is likely that myeloma will soon no longer be considered as a single entity. This, along with the availability of an unexpected number of new treatment possibilities, has reinforced the need for better tools for prognosis and for monitoring treatment efficacy through minimal residual disease techniques. The outcome of MM patients has significantly improved in the last 2 decades, first through the introduction of high-dose therapy followed by autologous stem cell transplantation and, more recently, due to the use of proteasome inhibitors (bortezomib and carfilzomib) and immunomodulatory agents (thalidomide, lenalidomide, and pomalidomide). Moreover, the need to reexamine the diagnostic criteria of early MM and the possibility of early intervention opens up new therapeutic avenues. New drugs are also emerging, including second- and third-generation proteasome inhibitors and immunomodulators, monoclonal antibodies, histone deacetylase inhibitors, and kinesin spindle protein inhibitors, among others. Our goal is to find a balance among efficacy, toxicity, and cost, with the ultimate aim of achieving a cure for this disease.

Learning Objectives
- To understand that myeloma should no longer be considered as a single entity
- To understand that better tools for diagnosis and monitoring treatment efficacy are being implemented
- To understand that the treatment goal is to find the best possible balance among efficacy, toxicity, and cost

Introduction
Multiple myeloma (MM) is the second most common hematological malignancy, with an annual incidence of 4 new cases per 100 000 people. It accounts for ~1% of all malignant diseases and 15% of all hematological malignancies. In the pathogenesis of MM, the mechanisms responsible for the interaction between malignant plasma cells (PCs) and their microenvironment are as important as the genetic changes involved in the development of the malignant clone because these play an important role in bone destruction; tumor cell growth, survival, and migration; and drug resistance.

Genomic characteristics of myeloma cells
Genome instability is a prominent feature of myeloma cells and, in fact, almost all patients with MM are cytogenetically abnormal.1 Genetic abnormalities include chromosomal translocations, mainly involving the IGH locus on chromosome 14q32, copy number abnormalities, mutations, methylation modifications, and gene and miRNA dysregulation.2 Unlike other B-cell tumors, MM exhibits a marked diversity of chromosomal loci involved in IGH translocations. Approximately 40% of MM tumors have IGH translocations involving 5 recurrent chromosomal patterns: 11q13 (CCND1), 4p16 (FGFR/MMSET), 16q23 (MAF), 6p21 (CCND3), and 20q11 (MAFB), corresponding to an incidence of ~15%–20%, 15%, 5%–10%, and <3% for the latter 2 patterns, respectively.3 Although

IGH translocations induce up-regulation of different oncogenes, it is possible that all IGH translocations involved in MM converge on a common pathway that is essential in the pathogenesis of the disease and cause the inhibition of differentiation and an increase in cell survival and proliferation. Gene expression profiling (GEP) analysis has demonstrated that expression of the cyclin proteins (CCND1, CCND2, and CCND3) is increased in almost all MM patients, supporting the hypothesis that there is a potential unifying event in its pathogenesis.4 In addition to these structural changes, numerical chromosomal abnormalities are frequently observed in MM; in fact, almost all MM cases are aneuploid. The nonhyperdiploid patients are characterized by a very high prevalence of IGH translocations, monosomy/deletion 13, and gains on 1q. In contrast, the hyperdiploid group is associated with recurrent trisomies involving odd chromosomes (3, 5, 7, 9, 11, 15, and 19) and with a low incidence of structural chromosomal abnormalities.2 Lesions on chromosome 1 are the most common abnormalities in MM; these are mostly 1q gains that result from tandem and jumping segmental duplications of the chromosome 1q band, as well as 1p losses. Deletion of chromosome 13 is present in 40%–50% of MM patients and is strongly associated with t(4;14) and t(14;16), deletion of 17p, and gains on 1q. The chromosome 17p deletion, which includes loss of TP53, occurs at a lower frequency in newly diagnosed MM (5%–10%), although the proportion is higher in advanced stages of the disease. Furthermore, 17p deletion is associated with extramedullary MM.

Some genetic changes in MM, such as secondary translocations, mutations, deletions, and epigenetic abnormalities, are considered to be late oncogenic events and are associated with disease progression. Most karyotypic abnormalities involving MYC correspond to complex translocations and insertions that are often nonreciprocal and frequently involve 3 different chromosomes. Activating RAS mutations are considered to be molecular markers
of disease progression. Therefore, the prevalence of activating KRAS and NRAS mutations is >70% in MM cases at relapse. TP53 inactivation via deletion or mutation also seems to be more frequently associated with disease progression.

New insights into MM genetics

GEP analysis has confirmed the huge genetic diversity of MM cases, and several genomic classification models have been proposed by the Arkansas, French, and Dutch groups. The most widely accepted is the Arkansas TC model, which connects genetic abnormalities, cell transcriptome, and clinical features of patients and classifies MM patients into 7 different groups. Each group displays a specific genetic signature, some of which are associated with a particular IGH translocation or ploidy status and with a characteristic clinical behavior. However, so far, the reproducibility of these GEP models has not been optimal and they have not been implemented in the clinical milieu except in selected centers.

In a recent large study including 203 MM patients, whole-genome sequencing strategies have shown that 65% had evidence of mutations in 1 or more of the 11 recurrently mutated genes: K and N-RAS, BRAF, FAM46C, TP53, DIS3, TRAF3, CYLD, RB1, PRDM1, and ACTG1. Interestingly, mutations were often present in subclonal populations and multiple mutations within the same pathway (eg, RAS and BRAF) were observed in the same patient. This pattern is consistent with other hematological malignancies such as acute myeloid leukemia, but is in contrast to hairy cell leukemia and Waldenstrom’s macroglobulinemia, which feature the single unifying mutations BRAF and MYD88, respectively.

Although the role of epigenetics in cancer has been demonstrated, there is limited evidence of its role in the pathogenesis of MM. Silencing of certain tumor-suppressor genes (GPX3, RB1, SPARC, CDKN2A, SOCS, and TGFBR2), overexpression of the histone methyltransferase MMSET, and the presence of mutations of UTX (histone demethylase) have been described. Furthermore, genomewide methylation studies have shown both global DNA hypomethylation and gene-specific DNA hypermethylation in MM, with certain epigenetic signatures being associated with prognostic cytogenetic groups. Another area of emerging interest in cancer pathogenesis concerns miRNAs, small, noncoding RNAs that regulate gene expression at the posttranscriptional level and are involved in critical biological processes including cellular growth and differentiation. Various studies have shown that miRNA expression is deregulated in myeloma cells compared with normal plasma cells and that their GEP profile is associated with genetic abnormalities. Moreover, several miRNAs are known to be involved in MM pathogenesis. Indeed, a mechanism has been identified by which miRNAs act on MDM2 expression to regulate p53; therefore, miR-192, miR-194, and miR-215 reexpression in myeloma cell lines induces degradation of MDM2, with subsequent up-regulation of p53 and inhibition of cell growth.

Multistep pathogenesis and drug resistance

MM is a unique cancer paradigm for investigating the mechanisms involved in the emergence of a premalignant condition and its transition to a malignant disease; in other words, from an “early/benign phase” known as monoclonal gammopathy of undetermined significance (MGUS), to an “intermediate/indolent phase” [smoldering MM (SMM)] and a final “advanced stage” (symptomatic and ultimately resistant/refractory MM). Unfortunately, the key questions in this process are yet to be answered: why does a quiescent clone become aggressive in some patients but remains stable in others? and what are the mechanisms responsible for primary and acquired chemoresistance? Is this dictated only by the genotypic characteristics of the tumor clone or is the dialogue between myeloma PCs and their microenvironment also significant in this process? Until recently, the pathogenic models assumed that MM develops through a multistep transformation from normal PCs to MGUS (implying PC immortalization) and subsequent transformation into active MM, in which clonal PCs are responsible for end-organ damage. However, studies based on FISH, single-nucleotide polymorphism arrays, and whole-genome sequencing have demonstrated that most genetic lesions typically observed in MM are already present in MGUS patients and that the progression from MGUS to SMM, and eventually to MM, would involve a clonal expansion of genetically abnormal PCs, implying a complex evolutionary process with intraclonal heterogeneity. Three distinct patterns of genomic evolution have been proposed based on data generated by new genomic approaches: (1) stable genomes, without differences between diagnosis and relapse clones; (2) linear evolution, in which the relapse clone apparently derives from the major subclone at diagnosis, but continues to diversify through additionally acquired lesions; (3) and branching (nonlinear) models, in which the relapse clone clearly derives from a minor subclone that is barely present at diagnosis. Patients with high-risk cytogenetics usually follow the last 2 evolutionary models. These findings are also relevant for the treatment of MM, because the presence of intraclonal heterogeneity with clonal tides supposes a significant obstacle for targeted therapy. For example, even though patients harboring the BRAF mutation might respond to BRAF inhibitors, this effect would be suboptimal if the mutation were not present in a major PC subclone; in fact, BRAF-negative clones could even become stimulated. Therefore, mutations are often present in subclonal populations, and drug combinations targeting coexisting subclones will probably be a more efficient approach.

Mechanism of resistance

The final step in this continuous transformation process from MGUS into symptomatic MM is illustrated by those MM patients who are refractory to treatment. Two major types of chemoresistance have been identified: intrinsic and acquired. Intrinsic resistance has mainly been associated with gene deregulation driven by specific genetic abnormalities such as the t(4;14), t(14;16), del(17p), and TP53 abnormalities. Nevertheless, we still lack a complete understanding of the precise mechanisms responsible for drug resistance driven by these genetic hits. Moreover, patients without these abnormalities also show primary resistance to therapy, indicating that other alterations are also involved. For example, after seminal work identifying cereblon (CRBN) as the binding protein of immunomodulatory drugs (IMiDs) [which, in PCs, leads to the ubiquitination of substrates such as Ikaros (IKZF1) and Aiolos (IKZF2)], more recent studies have already shown that CRBN and IKZF1 levels correlate with survival in MM patients treated with pomalidomide and dexamethasone. To fully describe this intrinsic resistance, we need to consider the contribution of the interaction of malignant PCs with the BM microenvironment, which provides a sanctuary for myeloma cells by promoting proliferation and blocking apoptosis, thereby enabling tumor progression and the eventual emergence of drug resistance. Therefore, down-regulating the interaction between tumor cells and the microenvironment can potentially halt cell growth and proliferation and be of benefit to patients. The second type of resistance, acquired resistance, is easily recognized in the clinical setting when patients’ tumor cells become refractory to the treatment strategies used. We can consider 2
bortezomib in patients with t(4;14).17 Pomalidomide in the relapse prognosis identifies an ultra-high-risk population.16 Novel in Table 1, the association between genetic lesions and the other because of its impact on disease outcome.15 Moreover, as indicated on purified PCs is essential in all patients with newly diagnosed MM discontinuation, and shorter survival. Cytogenetic/FISH evaluation clearly affect treatment options and cause a risk of toxicity, drug paid to performance status (frailty) and comorbidities because they tumor burden and disease complications). Particular interest is being paid to performance status (frailty) and comorbidities because they clearly affect treatment options and cause a risk of toxicity, drug discontinuation, and shorter survival. Cytogenetic/FISH evaluation on purified PCs is essential in all patients with newly diagnosed MM because of its impact on disease outcome.15 Moreover, as indicated in Table 1, the association between genetic lesions and the other prognostic features identifies an ultra-high-risk population.16 Novel drugs can improve but not overcome the adverse prognosis of high-risk patients. The most positive results are being reported for bortezomib in patients with t(4;14).17 Pomalidomide in the relapse setting has been effective in patients with del(17p), whereas carfilzomib appears to be more useful for t(4;14). However, the signficance of cytogenetic abnormalities at relapse is not so well established. Finally, the recently reported positive results for tandem autologous stem cell transplantation (ASCT), particularly in patients with t(4;14), should be highlighted.18

**Table 1. Factors prognostic of high-risk disease**

<table>
<thead>
<tr>
<th>Patient-specific factors</th>
<th>Tumor-specific factors</th>
<th>Tumor burden</th>
<th>Tumor resistance (failure to respond)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Adverse cytogenetics tumor†: t(4;14); t (14;16), del 17p, 1q gains, 1p del</td>
<td>High LDH</td>
<td>Circulating plasma cells</td>
</tr>
<tr>
<td>Comorbidities*</td>
<td></td>
<td>ISS III (high B2M and low albumin)</td>
<td>Extramedullary disease</td>
</tr>
<tr>
<td>Frailty</td>
<td></td>
<td></td>
<td>Tumor resistance (failure to respond)</td>
</tr>
</tbody>
</table>

* | † There is a strong association among adverse genetic factors: the cooccurrence of 2 or 3 of them [particularly t(4;14) and del 17p] identifies an ultra-high-risk subset (OS: <2 y). Ultra-high risk can also be defined by the coexistence of adverse cytogenetics, ISS III, and either high lactate dehydrogenase (LDH) or failure to achieve CR (OS: <2 y).


cumulative mechanisms by which acquired or secondary resistance arises: self-altered genomic/transcriptomic cell machinery in response to chemotherapy and the presence of substantial clonal heterogeneity within the initial MM tumor clone. The latter mechanism requires several clones to coexist and compete with one another within the myelomatous population in such a way that treatment eradicates the major clone (chemosensitive) and a minor, resistant, and initially dormant clone subsequently proliferates, giving rise to a resistant disease (clonal selection). Our group has shown that even in patients who achieve complete hematological remission, a small chemoresistant clone [minimal residual disease (MRD)] can be detected using highly sensitive techniques.14 Ultimately, this MRD clone represents a very small fraction of tumor cells that are chemoresistant, potentially quiescent (not producing M-protein), and able to recapitulate the initial tumor burden at relapse. The MRD clone may be a unique model, the analysis of which can help us to understand chemoresistance and the characteristics of eventual MM clonogenic cells and ultimately to design therapeutic strategies to overcome resistance. The understanding of the molecular, biological, and functional characteristics of these MRD cells, along with the investigation of whether these cells were detectable before treatment (treatment resistant cells) or not (acquired resistant cells) will provide insight into this field.

**Prognostic factors and tools for monitoring treatment efficacy**

Table 1 summarizes the most important prognostic factors for identifying high-risk MM based on the tumor clone, the host, and the interaction between the tumor and the host (represented by tumor burden and disease complications). Particular interest is being paid to performance status (frailty) and comorbidities because they clearly affect treatment options and cause a risk of toxicity, drug discontinuation, and shorter survival. Cytogenetic/FISH evaluation on purified PCs is essential in all patients with newly diagnosed MM because of its impact on disease outcome.15 Moreover, as indicated in Table 1, the association between genetic lesions and the other prognostic features identifies an ultra-high-risk population.16 Novel drugs can improve but not overcome the adverse prognosis of high-risk patients. The most positive results are being reported for bortezomib in patients with t(4;14).17 Pomalidomide in the relapse setting has been effective in patients with del(17p), whereas carfilzomib appears to be more useful for t(4;14). However, the

**Treatment monitoring**

Response to frontline therapy is one of the most important prognostic factors in most hematological malignancies, myeloma being no exception, whereby the better the quality of the response the longer the survival. However, the definition of complete response (CR) is far from optimal and more sensitive techniques for evaluating MRD both outside the BM (eg, imaging techniques such as MRI or PET) and inside the BM [eg, immunophenotyping by multiparametric flow cytometry (MFC) or molecular analysis by allele-specific oligonucleotide-PCR or next-generation sequencing] are needed. The Italian and Arkansas groups have shown that failure to achieve complete fludeoxyglucose-PET suppression after transplantation is associated with shorter survival.19 Using MFC, the Spanish and UK groups have both shown that, in transplanted and elderly MM patients, persistence of MRD is associated with significantly poorer outcome and this parameter is of significantly more prognostic power than negative immunofixation16,20; however, further standardization of MFC is still required. Allele-specific oligonucleotide-PCR also predicts outcome and is probably one log more sensitive than MFC, but is significantly less applicable (50% vs 95%). Preliminary data from next-generation sequencing indicate higher applicability and sensitivity (90%), making the technique a possible alternative to MFC.21 It should be noted that, due to the patchy pattern of myeloma BM infiltration, a negative MRD result may not be indicative of disease eradication, but rather the result of a nonrepresentative BM sample.

**Treatment**

Since the introduction of melphalan–prednisone (MP) in the late 1960s, the only significant innovation in the subsequent 30 years was the use of high-dose melphalan followed by stem cell support (ASCT) for young myeloma patients, whereas for elderly patients, MP remained the standard treatment. In contrast, since 2000, a revolution in the treatment of MM has been made possible by the availability of new agents with distinct mechanisms of action: the IMiDs thalidomide and lenalidomide and the proteasome inhibitor bortezomib.22

**Should all myeloma patients be treated?**

Currently, only myeloma patients with symptomatic disease (defined by CRAB criteria) are recommended for treatment.23 Attempts at early intervention in SMM patients with alkylating agents, bisphosphonates, antagonists of the receptor of IL-1β, or thalidomide failed to produce any significant benefit, although none of the studies discriminated among high- and low-risk SMM patients. The Spanish group has conducted a phase 3 randomized trial on high-risk SMM comparing early treatment with lenalidomide–dexamethasone versus observation. The results showed that the experimental arm is associated with a significant delay in progression to symptomatic myeloma [3-year progression-free survival (PFS) 77% vs 30%; P < .001, and overall survival (OS) benefit (94% and 80% at 3 years; P = .03).24 Although these data indicate a benefit of early intervention in high-risk SMM patients, improved criteria for defining this population and other confirmatory trials are needed before this could be accepted as a new standard of care. Nevertheless, the possibility of early treatment has stimulated the myeloma research community to reexamine the diagnostic criteria for myeloma, leading to the proposal that patients with focal lesions...
detected by MRI or low-dose CT, >60% PCs in BM, or an free light chain ratio >100 should already be considered as early myeloma patients requiring immediate treatment.25

Treatment of newly diagnosed transplantation candidate patients
Currently, treatment of young patients usually includes 3-6 cycles of induction therapy, intensification with ASCT, and the possibility of consolidation and maintenance therapy.

Induction
With VAD (vincristine, doxorubicin, and dexamethasone) or T-Dex (thalidomide–dexamethasone) combinations, only 2/3 of patients achieve a partial response (PR) and <$10% achieve CR. In contrast, after induction with bortezomib (Bz)-based triplet combinations with either alkylators or IMiDs [bortezomib-cyclophosphamide-dexamethasone (Bz-Cyclo-Dex), bortezomib-thalidomide-dexamethasone (BzTDex), or bortezomib-lenalidomide-dexamethasone (BzLenDex)], >90% of patients respond with >30% CR.23 These schemes are also associated with longer PFS than with VAD or T-Dex.26 New proteasome inhibitors such as carfilzomib and ixazomib are being investigated in combination with Len-Dex; both schemes show high predictive activity: immunophenotypic responses with the former while the second is very attractive due to its oral formulation.

ASCT
Prospective randomized trials of high-dose therapy (usually melphalan 200 mg/m²) followed by ASCT compared with chemotherapy showed a significant improvement in CR and PFS and have provided evidence for >10-year survivorship in at least a subset of patients.27 In the setting of novel agents, ASCT also enhances the response rates obtained with these new induction regimens, suggesting that induction with novel agents and ASCT are complementary rather than alternative treatment approaches. Moreover, this strategy favors the upfront exposure to all active antimyeloma agents (proteasome inhibitors, IMiDs, corticosteroids, and high-dose melphalan) to minimize the risk of subclonal escape. Nevertheless, some investigators argue that this approach is challenged by the need to control the residual tumor clone. The Italian group has proposed evidence for a partial response (PR) and <10% achieve CR. In contrast, after induction with bortezomib (Bz)-based triplet combinations with either alkylators or IMiDs [bortezomib-cyclophosphamide-dexamethasone (Bz-Cyclo-Dex), bortezomib-thalidomide-dexamethasone (BzTDex), or bortezomib-lenalidomide-dexamethasone (BzLenDex)], >90% of patients respond with >30% CR.23 These schemes are also associated with longer PFS than with VAD or T-Dex.26 New proteasome inhibitors such as carfilzomib and ixazomib are being investigated in combination with Len-Dex; both schemes show high predictive activity: immunophenotypic responses with the former while the second is very attractive due to its oral formulation.

Consolidation and maintenance
Consolidation consists of 2-3 courses of combination therapy (generally a triplet similar to induction) with the aim of reducing residual disease after ASCT, whereas maintenance involves a prolonged treatment (until progression or at least 1-2 years) that aims to control the residual tumor clone. The Italian group has demonstrated the value of BzTDex consolidation both in terms of improving the CR rate, including molecular responses, and prolonging PFS.29 With respect to maintenance therapy, 6 randomized trials have explored the value of thalidomide. Although, all 6 studies showed prolonged PFS (by a median of 6 months), only 3 of them showed a similar improvement in OS.30 The situation is clearly different for lenalidomide, for which 3 trials found a marked prolongation in PFS (median 18 months), one of which also noted a beneficial effect on OS.31,32 Although lenalidomide maintenance is associated with increased incidence of second primary malignancies, this risk is outweighed by the survival benefit. Bortezomib has also been tested as a single agent or in combination with thalidomide, giving positive results for PFS in both trials and for OS in one of them.33 Overall, these studies indicate that maintenance significantly prolongs PFS and probably OS, although the duration of maintenance remains to be determined. We need to establish the benefit of treatment until progression over a fixed period (eg, 2 years), because continuous treatment could theoretically favor the emergence of more resistant clones, would reduce the possibility of retreatment after a treatment-free interval, and might be associated with unnecessary costs and toxicity. In addition, we need to establish the benefit in specific cohorts such as CR and high-risk patients. MRD techniques may help to monitor treatment efficacy, particularly during consolidation and maintenance therapy, so that undertreatment and overtreatment can be prevented.

Allogeneic SCT
Allogeneic SCT is a potentially curative therapeutic approach in MM. However, it is associated with a high transplantation-related mortality (up to 30%) and high morbidity, mainly due to chronic GVHD. Six randomized trials have compared double ASCT with ASCT followed by allogeneic-reduced-intensity conditioning regimens; only in 2 of them did the allogeneic approach prove to be superior, so we do not recommend this treatment in newly diagnosed patients.34 However, the role of allogeneic SCT should be reexamined in the era of novel drugs using “integrated programs” in the context of clinical trials designed for high-risk patients.

Treatment of newly diagnosed elderly and non-transplantation candidate patients
MP has been the gold standard treatment for >40 years, although the scenario has completely changed with the introduction of novel agents such as thalidomide or bortezomib and lenalidomide. Six randomized trials have compared thalidomide plus MP (MPT) with MP, showing significant prolongation in PFS and OS (median 6-month benefit), although the difference in OS was only statistically different in 3 of the trials.35 Based on these results, MPT has been approved as a standard of care. The toxicity associated with thalidomide—asthenia, peripheral thrombosis, and particularly peripheral neuropathy (PN)—are shortcomings of prolonged treatment. Lenalidomide has also been combined with MP (Len+MP). A randomized trial comparing MP and Len+MP, using lenalidomide either only as part of the induction or also as maintenance, showed a significantly longer PFS for the maintenance approach (31, 14, and 12 months, respectively), but no significant differences in OS.36 A recent large clinical trial involving 1600 patients has compared Len-Dex (low-dose dexamethasone, 40 mg weekly) until progression with fixed-time Len-Dex (18 cycles) and with MPT (9 cycles). Results show a significant advantage for continuous Len-Dex treatment both in terms of PFS (25.5, 20.7, and 21.2 months, respectively) and OS (59.4%, 55.7%, and 51.4% OS at 4 years, respectively; P = .01).37 Based on these findings, continuous Len-Dex could become a new (alkylator-free) standard for newly diagnosed nontransplantation candidate patients. Interestingly, the greater incidence of second primary
malignancies observed with Len+MP was not detected with Len-Dex; this could be attributed to the lack of melphalan or to a protective effect of dexamethasone. Bz in combination with MP (BzMP) has been compared with MP (9 cycles in each arm). The BzMP treatment was associated with a longer time to progression (24.0 vs 16.6 months) and 1-year prolongation of OS (56 vs 43 months) and has been approved as another standard of care. In an attempt to reduce the high incidence of PN (12%–15%), the Spanish and Italian myeloma groups explored the administration of bortezomib only once weekly instead of the standard twice weekly schedule. Results showed a reduction in PN of 5%–7% and the efficacy was maintained (probably due to the better tolerability with fewer treatment discontinuations). In addition, the French group reported that when bortezomib is administered subcutaneously, the rate of grade 3/4 PN drops from 16% to 6%. New proteasome inhibitors such as carfilzomib and ixazomib are being investigated in combination with Len-Dex or MPR, yielding encouraging results, particularly for the first combination. Different strategies for treatment individualization are summarized in Table 2.

Table 2. Strategies for treatment individualization in elderly patients

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Therapy option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fit patients (Karnofsky ≥80%/Charlson = 0)*</td>
<td>Alkylator-based: BzMP × 9 cycles (MPT); alkylator-free: Len-dex until PD</td>
</tr>
<tr>
<td>Unfit patients (Karnofsky 60%–80%/Charlson index ≤2)†</td>
<td>Alkylator-based: BzMP × 9 cycles (MPT); alkylator-free: Len-dex until PD</td>
</tr>
<tr>
<td>Frail patients (Karnofsky &lt;60%/Charlson index &gt;2, age &gt;80 y)‡</td>
<td>Alkylator-based: TCyP × 9 cycles (CyBoR); alkylator-free: Rd or BzP</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>BzMP (Thal or Len can also be used with anticoagulants)</td>
</tr>
<tr>
<td>Recent thromboembolic event</td>
<td>Len-dex</td>
</tr>
<tr>
<td>History of peripheral neuropathy</td>
<td>No definitive information but Bz combinations are preferred for t(4;14)</td>
</tr>
<tr>
<td>High-risk cytogenetics</td>
<td>Oral treatments (Len or Thal)</td>
</tr>
<tr>
<td>Long distance from hospital</td>
<td>Treatment at the hospital visit (Bz SQ)</td>
</tr>
<tr>
<td>Poor compliance</td>
<td>MPT (TCyP)</td>
</tr>
<tr>
<td>Poor economic resources</td>
<td></td>
</tr>
</tbody>
</table>

* For fit patients: Bz subcutaneous (SQ) and biweekly for first cycle and weekly thereafter; thalidomide: up to 200 mg; lenalidomide: full doses; melphalan: 9 mg/m²; dexamethasone: 40 mg weekly.
† For unfit patients: Bz SQ and weekly; thalidomide: 100 mg; melphalan: 7 mg/m²; dexamethasone: 20 mg weekly.
‡ For frail patients: thalidomide: up to 50 mg; lenalidomide: 10–15 mg; cyclophosphamide instead of melphalan: 50 mg daily; bortezomib SQ: 1 mg/m² weekly; prednisone instead of dexamethasone: 30 mg on alternate days.

Should we use maintenance therapy?
Maintenance with thalidomide has been investigated in 3 studies and, although they showed some benefit to PFS (from 2 to 7 months), only 1 showed benefit in OS, so this approach has been abandoned. Continuous treatment with lenalidomide in the MPR and Len-Dex trials were associated with a significant prolongation in PFS (~18 months benefit), which translated into longer OS in the latter but not the former trial. With respect to bortezomib maintenance, the Spanish and Italian groups have investigated the value of maintenance with either Btz-Thal or Btz-Pred and found a median PFS of ~3 years; the Italian trial showed a significant OS benefit compared with no maintenance.

Options for treatment at relapse
Table 3 summarizes the critical decision-making points at the time of relapse and potential options for treating young and elderly patients. Regarding new agents, 2 groups can be distinguished: second- and third-generation IMiDs and proteasome inhibitors and drugs with a novel mechanism of action.

Table 3. Making decisions at relapse or disease progression

### Four critical considerations
- Type of relapse: indolent vs aggressive
- Efficacy of previous treatments: can I retreat with the same drug
- Toxicity of previously used agents
- What alternative drugs are available?

### Choices

#### Young patients relapsing after HDT-ASCT
- Late relapse: > 2–3 y after HDT-ASCT
- Early relapse: within the first year after HDT-ASCT

#### Elderly patients relapsing after a standard of care
- Step 1
- Step 2
- Step 3
- Step 4
- Step 5

HDT indicates high-dose therapy; VDL-PACE, bortezomib, dexamethasone, lenalidomide, cisplatin, adriamycin, cyclophosphamide, etoposide; DCEP, dexamethasone, cyclophosphamide, etoposide, cisplatin; and RIC-Alo-SCT: reduced-intensity conditioning regimen followed by allogeneic SCT.
Pomalidomide, a third-generation IMiD, in combination with dexamethasone has demonstrated substantial efficacy in phase 1 and 2 trials, with the result being confirmed in a phase 3 randomized trial comparing pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in patients who had failed prior bortezomib and lenalidomide. The combination significantly improved PFS (4 vs 1.9 months, hazard ratio = 0.50; P < .001) and OS (13.1 vs 8.1 months, hazard ratio = 0.72; P = .009).52 Triple combinations of pomalidomide with cyclophosphamide-prednisone or with bortezomib-dexamethasone are also being investigated. The second-generation proteasome inhibitor carfilzomib has also shown encouraging efficacy in heavily pretreated MM patients, with a response rate of 50% (≥PR) and a PFS of >8 months when used as single agent and 16% responses in Bz-refractory patients.43 The incidence of PN is notably very low (<3%). Combinations with lenalidomide, pomalidomide, cyclophosphamide, and panobinostat are also being tested, including a phase 3 trial (CRd versus Rd) that already indicated superiority for the triple (CRd) combination. Ixazomib (MLN9708) has shown ≥PR in 15% of relapse/refractory patients (most of whom had previously been exposed to bortezomib) and is being tested in a phase 3 trial in combination with Rd. Other oral proteasome inhibitors, such as oprozomib, are also in an early phase of development. Bendamustine (a hybrid between an alkylating agent and a purine analogue) as a single agent produced an overall response rate of 31% in relapsing patients, the figure being twice as high in combinations.

There is considerable interest in agents with novel mechanisms of action, particularly monoclonal antibodies. The most clinically developed monoclonal antibody for multiple myeloma is elotuzumab (SLAMF7: Signaling Lymphocytic Activation Molecule F7), a humanized IgG1 antibody targeting the CS1 glycoprotein. Although elotuzumab monotherapy only elicits modest activity in patients with MM, the addition of lenalidomide and low-dose dexamethasone has resulted in an overall response rate of 92% in patients receiving 10 mg/kg elotuzumab, with an impressive PFS of 26.9 months. Phase 2 and 3 trials currently in progress are evaluating elotuzumab in this combination, as well as with bortezomib. The second type of monoclonal antibody under investigation is anti-CD38 (daratumumab, SAR650984). Results from phase 1 and 2 dose escalation studies have demonstrated activity in monotherapy, with 30%–40% responses at the optimized doses and only mild infusion reactions, which were well controlled with steroids. This has prompted the investigation of it in combination with lenalidomide or bortezomib plus dexamethasone.

Deacetylase inhibitors have exhibited only modest activity (minor responses or disease stabilization) as single agents and vorinostat in combination with bortezomib has failed to show any significant clinical benefit compared with bortezomib as a single agent (PFS of 7.63 vs 6.83 months, respectively).44 In contrast, the combination of panobinostat with bortezomib-dexamethasone produces 35% PR in bortezomib-refractory patients;55 moreover, this combination has proved to be superior to bortezomib/dexamethasone in a phase 3 trial (PFS: 12 vs 8 months). More selective deacetylase inhibitors (Hdac6, Acetonyl) with improved tolerability are under investigation. Other novel agents under investigation include the kinase spindle protein inhibitor filanesib (ARRY-520), which has shown 22% ≥PR when combined with low-dose dexamethasone in patients refractory to bortezomib, lenalidomide, and dexamethasone, as well as drugs targeting signaling pathways such as the PI3K/mTOR and the RAS/MEK/ERK pathways or checkpoint inhibition combined with immunotherapy.

Our goal in myeloma treatment is to find a balance among efficacy, toxicity, and cost, with the ultimate aim of achieving a cure for this disease. Integration of new biological insights (MM should no longer be considered as a single disease) with evidence-based drug combinations should place us on the road to success.

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**Disclosures**

Conflict-of-interest disclosure: The author is on the advisory committees for Millennium, Celgene, Novartis, Onyx, Janssen, BMS, and MSD. Off-label drug use: None disclosed.

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