Published in final edited form as:

Expert Rev Hematol. 2014 February ; 7(1): 21–31. doi:10.1586/17474086.2014.882224.

Staging and prognostication of multiple myeloma

Rafael Fonseca^{*,1,2}, Jorge Monge², and Meletios A Dimopoulos³

¹Department of Medicine, Mayo Clinic in Arizona, Scottsdale, AZ 85259-5494, USA

²Division of Hematology and Oncology, Mayo Clinic in Arizona, Scottsdale, AZ 85259-5494, USA

³Department of Clinical Therapeutics, University of Athens School of Medicine, Athens, Greece

Abstract

Multiple myeloma (MM) is a heterogeneous disease that, over the past 15 years, has seen an increased understanding of its biology and of novel therapeutic options. Distinctive subtypes of the disease have been described, each with different outcomes and clinic-pathological features. Even though a detailed classification of MM into at least seven or eight major subtypes is possible, a more practical clinical approach can classify the disease into high-risk and non-high-risk MM. Such classification has permitted a more personalized approach to the management of the disease. Additionally, risk stratification should be included in outcome discussions with patients, as survival differs significantly by high-risk status. Nowadays, test for risk stratification are widely available and can be routinely used in the clinic. A greater understanding of the genetic abnormalities underlying the biology of MM will allow for the development of novel targeted therapies and better prognostic markers of the disease.

Keywords

cytogenetics; gene expression profiling; genetics; induction; maintenance; multiple myeloma; prognosis; risk stratification; stem cell transplant

Multiple myeloma (MM) is a plasma cell neoplasm that results from the progression of a monoclonal gammopathy of undetermined significance (MGUS) [1–4]. For over a decade, we have witnessed several breakthroughs that have helped clarify the biology of MM. Some genetic abnormalities have been shown to result from abnormal plasma cell development, driving the pathogenesis of MM [5]. Chromosomal translocations involving the IgH chain

© 2014 Informa UK Ltd

*Author for correspondence: fonseca.rafael@mayo.edu.

Financial & competing interests disclosure

R Fonseca is a Clinical Investigator of the Damon Runyon Cancer Research Fund. This work is supported by grants R01 CA83724, ECOG CA 21115T, Predolin Foundation and the Mayo Clinic. R Fonseca has received a patent for the prognostication of multiple myeloma based on genetic categorization of the disease. He has also received consulting fees from Medtronic, Otsuka, Celgene, Genzyme, BMS, Lilly, Onyx, Binding Site, Millennium and AMGEN; and has sponsored research from Celgene and Onyx. MA Dimopoulos has received honoraria from Celgene and Ortho Biotech. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

genes account for nearly half of MM cases [6–8], while the other half are hyperdiploid MM, whose genetic drivers remain elusive despite considerable advances [7–10].

Clinical staging

The first stage of plasma cell disorders (Table 1) that can be identified in the clinic is MGUS [11]. In order to detect MGUS in a patient, the amount of monoclonal protein must reach a measurable threshold on protein electrophoresis, be detectable by immunofixation or can also be seen as an abnormality in a serum-free light-chain assay. This leaves the possibility for an earlier stage of plasma cell proliferation (pre-MGUS) with undetectable disease in the clinic. By definition, patients with MGUS lack the complications associated with MM [11] while sharing the same genetic abnormalities [12–16], albeit with a lower prevalence of abnormalities thought to be indicators of clonal progression (e.g., deletion of chromosome 17) [12–16].

Smoldering MM is an intermediate stage between MGUS and active MM [17]. There is a lower prevalence, in smoldering MM, of genetic abnormalities thought to be associated with progression; as well as, according to unpublished data, a lower frequency of genomic instability in the earlier stages of plasma cell disorders.

Progression of these earlier stages to MM is thought to arise from secondary genetic changes, although microenvironment changes and deregulation of the immune system, among other factors, might contribute to it [18,19]. Even though the specific genetic abnormalities have not been fully described, some gene mutations (e.g., *RAS*) have been found in higher prevalence in MM than MGUS [20–22].

Incidence of MM is twice as high in patients of African descent [23–25]. Attempts to unravel the biology of the disease in African-Americans [26–28] have found a lower frequency of IgH translocations in MM [26] along with a higher prevalence of MGUS in patients of African origin [24]. These differences are likely secondary to genetic susceptibility factors, even though the exact mechanisms are not yet known [26,27].

The International Staging System has been developed as a simple and objective method, using serum β -2-microglobulin and serum albumin, to define three stages with distinct prognostic significance [29]. However, the power of these systems is not sufficient for most centers to classify patients with stage III as being truly high-risk MM.

Cytogenetic & molecular classifications

In MM, two cytogenetic subgroups can be identified based on their numerical chromosomal abnormalities: hyperdiploid and non-hyperdiploid MM, the second having a higher prevalence of chromosomal translocations [6–8].

Hyperdiploid MM

When analyzed by FISH, hyperdiploidy is observed in about 50% of patients [6–8], including several trisomies of the odd-numbered chromosomes, except chromosome 13 [7,8]. Even though its pathogenesis remains unclear, hyperdiploidy is considered an

oncogenic event [9,10,30], being present at the earliest stages of the disease (e.g., MGUS) [15,31]. Hyperdiploid MM, when detected by FISH, has a better prognosis and longer overall survival (OS) than non-hyperdiploid MM [32], although the benefit in survival is lost when associated with other genetic markers of progression or aggressiveness (e.g., del17p13) [10]. It is uncertain whether hyperdiploidy detected by conventional cytogenetics has a good prognostic effect, since abnormal meta-phases are themselves an indicator of poor prognosis [33].

Non-hyperdiploid MM

Non-hyperdiploid MM is characterized by a prevalence of over 85% of IgH chromosome translocations [6,8]. The majority of patients with non-hyperdiploid MM have very aggressive disease, marked by a decreased OS and shorter time to relapse, with the exception of patients with t(11;14)(q13;q32) [34–41]. Patients with non-hyperdiploid MM have a higher frequency of genetic events linked with progression, which include chromosome 13 and 14 deletion, chromosome 17 abnormalities, chromosome 1q amplification and 1p deletion, making high-risk MM more common in these patients [34–40].

The translocations t(11;14)(q13;q32), t(4;14)(p16;q32) and t(14;16)(q32;q23) represent the three major chromosomal abnormalities in these patients.

t(11;14)(q13;q32)—One of the most common genetic abnormalities in MM [36,42–44], t(11;14)(q13;q32) results in increased expression of the cyclin D1 gene (*CCND1*), and is also present in MGUS [16,45]. With the help of gene expression profiling (GEP), these patients can be subdivided into a disease with a rather indolent course and another one associated with more aggressive features [46]. This chromosomal abnormality is also quite common in patients with primary plasma cell leukemia and light chain amyloidosis [47–49]. Interestingly, several of these patients have a very stable genome, as suggested by fewer copy number aberrations and interstitial breakpoints, which might explain their favorable prognosis.

High-risk translocations—The translocations t(4;14)(p16;q32) and t(14;16)(q32;q23), seen in 15 and 5% of cases, respectively, are associated with high-risk MM [34,36]. The t(4;14)(p16;q32) is associated with FGFR3 and MMSET dysregulation [50], while t(14;16)(q32;q23) is associated with increased c-maf expression [51]. Several studies have shown a more aggressive disease in patients with any of these chromosomal abnormalities, even though the addition of proteasome inhibitors has nearly eliminated their prognostic impact [52]. Some authors have questioned the utility of t(14;16)(q32;q23) as a predictor [53], nevertheless it remains a significant prognostic factor [54].

Genetic events associated with progression

Chromosome 17 deletions—Chromosome 17 deletions are a hallmark of high-risk MM [34,55,56]. Most of the deletions involve the short arm of chromosome 17, regularly including TP53 [57,58]. Of note, TP53 mutations have not been routinely detected in these patients, as opposed to what is seen in chronic lymphocytic leukemia [59]. Patients with

chromosome 17 deletions have a more aggressive disease, characterized by a shorter time to relapse, extramedullary disease and central nervous system involvement [34,60]. As part of disease progression, any primary genetic subtype can acquire chromosome 17 deletions, conferring a worse prognosis, and deletion of 17p13 is the single most powerful genetic marker for risk stratification.

Others—Other noteworthy genetic abnormalities associated with outcome are chromosome 1p deletions and 1q duplications or amplification [61,62], which often coexist and are both associated with a more aggressive disease. Chromosome 14 deletions are more common in hypodiploid MM, and have therefore been associated with a more aggressive clinical course [57,63]. The role of MYC abnormalities as prognostic factors has not been established [64,65], although one study has shown no effect [66]. Hypodiploidy detected by karyotype has also been identified as an adverse prognostic factor [67–72].

Gene expression profiling

GEP has been broadly researched as a tool to assess risk in MM [10,40,46,73–76]. The team at the University of Arkansas Medical Sciences (UAMS) has been able to accurately identify patients with high-risk MM (15%) by using RNA-based micro-arrays [40,46], as well as using GEP to detect important clinical outcomes, like response to bortezomib [74,77–79]. Other GEP signatures that can be used for MM prognosis have been developed by other centers [10,40,46,73–76]. It is not clear whether any of these signatures can outperform the 70-gene signature developed by UAMS in the clinical setting, even though most of them are not overlapping. Novel genetic signatures [76,80], array-based comparative hybridization [81] and a centrosome-based index [75] have also been used to try to identify high-risk MM (Table 2).

Next-generation sequencing & clonal evolution

Using next-generation sequencing (NGS), previously known as genetic mutations were confirmed, while new recurrent mutations and altered pathways were discovered that would not have been rationally sought after [63]. In a similar way, tyrosine kinase mutations have also been investigated [82]. However, despite today's technological advancements, no significant new insights into the biology of MM have been made, and further investigation is ongoing. Nevertheless, these studies have contributed to a better understanding of the subclonal nature of the disease.

Others and we have been able to identify multiple clones within a single patient with MM by combining high-throughput genomic tools, like NGS, with single cell analysis, such as FISH [83–85]. Even though these clones are all related and share a common origin, the evolving diversity may favor clonal selection and drug resistance [83–85]. It seems logical to think that patients with a greater number of clones will have a higher capacity to adapt, inherently conferring a higher risk; therefore, further studies should be done to determine its role as a prognostic marker.

Genomic instability

Why certain genetic markers are associated with aggressive MM has not quite been demonstrated. However, Chung *et al.* have shown that genetic markers of high-risk MM correlate with a higher degree of genomic instability, by measuring surrogate markers of genomic complexity and demonstrated their prognostic significance in MM [86]. Our group found that patients with higher genomic instability tend to have an aggressive disease course and shorter survival [86]. Probably the most determinant factor of clonal aggressiveness, genomic instability may allow clonal evolution and selection of drug-resistant subclones, providing a permissive environment that could prove more significant than their specific genetic abnormality, and should perhaps be considered the most important prognostic factor in MM.

Predictive biomarkers

As expected, any number of genetic mutations could grant resistance to MM drug treatments. The discovery of cereblon (CRBN) as a target for immunomodulatory agents (IMiDs), led to finding that its lack of expression has a high correlation with resistance to IMiDs [87,88]. Using CRBN as a biomarker in MM, accurately predicts response rate and survival in patients treated with IMiDs [87,88].

Risk stratification & recommended testing

The International Myeloma Working Group stated in its recommendations that genetic testing should be integrated into the adequate management of a patient with MM [54]. Either FISH or GEP should be implemented to identify patients with high-risk MM, as shown in Table 3. At a minimum, FISH analysis should be performed at baseline and include probes for the detection of t(4;14)(p16;q32), t(14;16)(q32;q23) and -17p13 [54]. Samples tested should only include those in which plasma cells have been selected for scoring, either by magnetic beads purification or co-staining with antibodies that detect the MM cells (cIg-FISH). Otherwise, the assay's sensitivity will diminish, yielding undesirably high false-negative results, especially for deletions. Frequently, samples submitted for FISH analysis may be hemodiluted, and the number of deletions present may fall under the normal range for a given probe, even if all cells present the anomaly. Appropriately collected samples may then be submitted for analysis to a central laboratory. GEP is an alternative to FISH. Sample collection and submission must be done following laboratory recommendations closely, but if done properly these samples can then be submitted to a centralized reference laboratory for analysis.

Through the course of the disease, testing may be repeated, although the major genetic subtypes will not vary over time. New abnormalities might be detected for the high-risk genetic markers (e.g., -17), as well as a change in signatures (high-risk GEP), or the acquisition of secondary genetic factors associated with progression (1p/1q abnormalities). Finally, it is paramount to consider risk stratification as an integral part of the management of patients with MM, which will provide useful information for treatment planning as well as for patient counseling. The management of MM will improve as new bio-markers, predictive of resistance (such as CRBN deletions), and novel therapies are developed.

Risk stratification for treatment outcome & prognosis

Current prognostic markers mainly estimate OS, but are limited in their ability to establish the best treatment strategy and to predict the response duration to specific therapies. Adding to the complexity, the majority of MM patients are now managed with combinatorial strategies. These strategies have resulted in improved responses, and it is likely that an increased complete response will also increase OS [39,89]. For added complexity, new agents seem to improve survival and outcome in patients regardless of baseline risk status [90,91].

Importantly, it has been shown that high-risk patients fare better when they are treated with proteasome inhibitors [52,91–94]. Due to these data, the first recommendations for risk stratification-guided therapy advocated for earlier treatment with proteasome inhibitors during induction therapy in high-risk patients [95]. Currently, most patients will receive proteasome inhibitors as first-line therapy, regardless of risk; therefore, limiting risk stratification role in drug selection. We recommend the use of risk stratification to guide post-stem cell transplantation (SCT) therapy and for patient counseling. Noteworthy, obtaining a complete response is of critical importance in patients with high-risk MM [96].

As previously stated, risk stratification is highly recommended as part of patient counseling. The arrival of novel drugs has led some to believe in a chronic MM, however, patients with high-risk MM face an increased risk of mortality within the first 3 years after diagnosis [39,78]. Even though some of the previously mentioned studies favor abrogating genetic classification in lieu of proteasome inhibitor therapy, larger studies with long-term follow-up suggest that high-risk MM patients still have worse outcomes [90,93,94]. Even though the introduction of proteasome inhibitors has improved outcomes for many high-risk MM patients [39,91], others still present shorter response duration and survival [90,93,94]. Longer follow-up studies usually refute early reports of novel combinations' victory over high-risk MM when used only as induction therapy [93,94]. The use of proteasome inhibitors as consolidation therapy may suggest, however, that this is partially true, particularly for patients with t(4;14)(p16;q32) [39,91].

It should be noted that patients with high-risk MM already present at diagnosis features of a more aggressive disease, have a higher likelihood of relapsing [34,37,40] and a higher degree of clonal evolution. High-risk MM remains a challenge, as well as a greater threat to patients than standard-risk MM.

Melphalan & auto-SCT after simple induction

Genetic factors that are associated with high-risk MM are able to predict outcomes in patients treated either with conventional chemotherapy (e.g., melphalan-based therapy) or with induction therapy (e.g., vincristine + doxorubicin + dexamethasone or bortezomib + dexamethasone) followed by SCT [37,38,97]. Patients with high-risk MM treated with these agents had a shorter progression-free survival (PFS) as well as shorter OS [37,38,97]. It has been recently shown that a 4-month induction with bortezomib and dexamethasone improves the outcome of MM patients with t(4;14)(p16;q32), but not for those with -17p13 [52]. Previous studies indicated that induction with either thalidomide + dexamethasone or

vincristine + doxorubicin + dexamethasone, followed by a single auto-SCT in patients with t(4;14)(p16;q32), resulted in relapse within the first 12 months after auto-SCT in nearly all patients [37,38,97]. Therefore, simple inductions (doublets) and auto-SCT seem unable to nullify the effect of genetic factors associated with high-risk MM.

Modern combinatorial induction regimens

As previously mentioned, combinatorial strategies have increased the proportion of patients achieving deep responses [96], and have been suggested to improve long-term outcomes in certain patients, including OS [89,94]. Current practice is based on combining bortezomib, dexamethasone and cyclophosphamide [98] or bortezomib, dexamethasone and lenalidomide [99]. In high-risk MM populations, cyclophosphamide, bortezomib and dexamethasone achieved an overall response rate of 83 and 75% in patients with t(4;14) and deletion 17, respectively [98], while bortezomib, dexamethasone and lenalidomide achieved at least a very good partial response in 100 and 60% of patients with t(4;14) and deletion 17, respectively [99]. At the same time, efforts are on their way to study the role of carfilzomib as part of induction regimens [100]. Recently, a first-line regimen including carfilzomib, lenalidomide and dexamethasone showed a dramatic rate of deep responses among newly diagnosed MM patients, and an overall response rate of 94% in high-risk MM [100]. Even though both strategies (i.e., adding cyclophosphamide or lenalidomide to proteasome inhibitors and dexamethasone) are similarly effective, several authors favor the use of cyclophosphamide-based combinations due to lower cost, availability, side-effect profile and no need for renal dosage adjustment. Hypothetically, adding lenalidomide may be superior to adding cyclophosphamide in patients with high-risk MM (i.e., higher genomic instability), since introduction of alkylating agents when tumor burden is high might favor the creation of drug-resistant clones. Although the reasoning for this is mainly hypothetical, favoring non-alkylating-based therapies, such as lenalidomide-based combinations, for the induction of high-risk MM seems reasonable; even after the fact that lenalidomide may also be genotoxic (based on the reported second primary malignancies).

Maintenance & consolidation therapy

Autologous-SCT remains the mainstay treatment for eligible MM patients. As discussed above, risk stratification seems to have a greater influence on patient counseling and guiding post-SCT therapy. However, in cases of high-risk MM, it may be reasonable to pursue maximum tumor bulk reduction, due to the likely genotoxic effects of high-dose melphalan therapy on tumor cells.

Based on large clinical trials, therapy duration appears to be important for optimal outcomes. This has been studied in different settings, including maintenance therapy post-SCT [101,102], consolidation post-SCT [39,91] and maintenance after induction therapy in non-SCT-eligible patients [93,103]. The terms ‘consolidation’ and ‘maintenance’ represent semantic variations for continuation of therapy, used to define the temporal characteristics of a treatment. It is still unclear whether there are any biological differences between consolidation and maintenance, primarily reflecting the physician’s perception of treatment toxicity (i.e., maintenance being less toxic). Recent studies have suggested that longer therapy duration may be important [104,105]. The rationale behind this being that, MM,

being a low proliferation rate neoplasm, might be better targeted the more opportunity there is for tumor cells undergoing mitosis to be exposed to anti-myeloma treatment.

Of two clinical trials evaluating lenalidomide as maintenance after SCT, one showed an increase in OS [102], while the other study (Intergroupe Francophone du Myelome [IFM]) did not, although it did show a significant increase in PFS (Table 4) [101]. The study by the IFM had a greater proportion of high-risk MM patients in the lenalidomide group, which undoubtedly had an impact on the results [101]. The use of thalidomide as maintenance therapy appears to be deleterious in patients with high-risk MM [106]. It is possible that low-dose maintenance therapy, or other incomplete therapeutic interventions, might stimulate sub-clone selection in high-risk MM patients, resulting in greater disease aggressiveness. Maintenance therapy appears to be a commendable effort, but its role among the various risk categories needs further investigation. Post-SCT disease burden (i.e., none to minimal to measurable) and risk category could help identify which patients would benefit from maintenance therapy.

Recently, new combinatorial strategies in the post-SCT setting have shown deeper responses as well as improvements in survival (Table 5). Patients with high-risk MM, particularly those with t(4;14)(p16;q32), appear to benefit from consolidation therapy with bortezomib [90]. A large study in Germany showed that bortezomib therapy improved both PFSI and OS in all cytogenetic subtypes, especially patients with -17p13 [90]. Although these data contradict what was found in the IFM study [52], it could indeed be due to the longer therapy duration. In another study, it was found that two cycles of consolidation post-SCT with bortezomib, thalidomide and dexamethasone improved the quality and duration of responses [91]. Of note, it was shown that bortezomib therapy eliminated the prognostic effect of t(4;14)(p16;q32), while no specific analysis was obtained for patients with -17p13 due to the small number of cases [91]. The UAMS group had previously shown, in the context of their Total Therapy 3 protocol, the benefit of adding bortezomib [39].

Allogeneic-SCT

The role of allogeneic-SCT in the treatment of MM has been limited due to the high rate of treatment-related mortality and because the increase in response rate does not appear to translate into a survival benefit compared with auto-SCT [107–110]. Recently, Kröger *et al.* showed no difference in PFS between high-risk and standard-risk MM, likely due to achieving molecular remission after auto-allo tandem SCT [111]. While it is tempting to recommend allogeneic-SCT in young patients with high-risk MM, there is a paucity of data to recommend such approach.

Minimal residual disease

Multiple studies have shown the importance of accurately estimating residual disease, by either molecular methods or flow cytometry, after SCT or similar strategies, in order to predict outcome and possibly the need for additional therapy [112–118]. Even though it is still technically challenging, flow cytometry is preferred since it appears to be as sensitive and more widely available [112–116]. The indication for additional treatment will be better

answered by incorporating these assays into large clinical trials that also determine risk stratification.

Expert commentary

Genetic stratification for MM is a necessity for optimal and modern care of MM patients. Identification of these factors allows a more tailored approach to the care of patients including timing and selection of therapies, duration of therapy and patient counseling. The classification of myeloma into various distinct genetic subtypes is of paramount importance to discuss the nuances of prognosis with patients; patients with high-risk MM will not have MM be a 'chronic disease'. Selection of post-SCT therapies will likely be dictated by this risk stratification: emerging evidence suggests that maintenance with proteasome inhibitors will be essential, particularly for those with -17p13 and t(4;14)(p16;q32).

Five-year view

During the last 5 years, we have witnessed affirmation of the value of risk stratification in MM. Developments in novel methodologies have allowed the introduction of high-throughput tools such as GEP and soon NGS. Early studies also indicate that the predictive markers such as CRBN mutations will be useful in the clinic. It is quite likely that the advent of NGS will become standard and through this technology various aspects of the genetic makeup will be incorporated into standard clinical practice. For instance, evidence of genetic heterogeneity and ongoing genomic instability will be thought of as one of the main drivers of poor prognosis. This information will also be used to seek for additional therapeutic targets, including introduction of small molecules in combination with standard therapies. Furthermore, these authors believe that the continued refinement in our understanding of the genetic and subclonal nature of MM will ultimately lead to the perpetuation of combinatorial, intense and prolonged treatment strategies.

References

Papers of special note have been highlighted as:

- of interest
- of considerable interest

1. Rajkumar SV, Kyle RA. Multiple myeloma: diagnosis and treatment. *Mayo Clin Proc.* 2005; 80(10):1371–82. [PubMed: 16212152]
2. Rajkumar SV, Lacy MQ, Kyle RA. Monoclonal gammopathy of undetermined significance and smoldering multiple myeloma. *Blood Rev.* 2007; 21(5):255–65. [PubMed: 17367905]
3. Landgren O, Kyle RA, Pfeiffer RM, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. *Blood.* 2009; 113(22):5412–17. [PubMed: 19179464]
4. Weiss BM, Abadie J, Verma P, et al. A monoclonal gammopathy precedes multiple myeloma in most patients. *Blood.* 2009; 113(22):5418–22. [PubMed: 19234139]
5. Bergsagel PL, Kuehl WM, Zhan F, et al. Cyclin D dysregulation: an early and unifying pathogenic event in multiple myeloma. *Blood.* 2005; 106(1):296–303. [PubMed: 15755896]

6. Fonseca R, Debes-Marun CS, Picken EB, et al. The recurrent IgH translocations are highly associated with nonhyperdiploid variant multiple myeloma. *Blood*. 2003; 102(7):2562–7. [PubMed: 12805059]
7. Debes-Marun C, Dewald G, Bryant S, et al. Chromosome abnormalities clustering and its implications for pathogenesis and prognosis in myeloma. *Leukemia*. 2003; 17(2):427–36. [PubMed: 12592343]
8. Smadja NV, Leroux D, Soulier J, et al. Further cytogenetic characterization of multiple myeloma confirms that 14q32 translocations are a very rare event in hyperdiploid cases. *Genes Chromosomes Cancer*. 2003; 38(3):234–9. [PubMed: 14506697]
9. Rio-Machin A, Ferreira BI, Henry T, et al. Downregulation of specific miRNAs in hyperdiploid multiple myeloma mimics the oncogenic effect of IgH translocations occurring in the non-hyperdiploid subtype. *Leukemia*. 2013; 27(4):925–31. [PubMed: 23174883]
10. Chng WJ, Kumar S, Vanwier S, et al. Molecular dissection of hyperdiploid multiple myeloma by gene expression profiling. *Cancer Res*. 2007; 67(7):2982–9. The authors describe four different subclasses of H-multiple myeloma (MM) with distinct prognostic and response characteristics. [PubMed: 17409404]
11. Kyle RA, Therneau TM, Rajkumar SV, et al. Long-term follow-up of 241 patients with monoclonal gammopathy of undetermined significance: the original Mayo Clinic series 25 years later [see comment]. *Mayo Clin Proc*. 2004; 79(7):859–66. [PubMed: 15244381]
12. Ackermann J, Meidlinger P, Zojer N, et al. Absence of p53 deletions in bone marrow plasma cells of patients with monoclonal gammopathy of undetermined significance. *Br J Haematol*. 1998; 103(4):1161–3. [PubMed: 9886335]
13. Kaufmann H, Ackermann J, Baldia C, et al. Both IGH translocations and chromosome 13q deletions are early events in monoclonal gammopathy of undetermined significance and do not evolve during transition to multiple myeloma. *Leukemia*. 2004; 18(11):1879–82. [PubMed: 15385925]
14. Konigsberg R, Ackermann J, Kaufmann H, et al. Deletions of chromosome 13q in monoclonal gammopathy of undetermined significance. *Leukemia*. 2000; 14(11):1975–9. [PubMed: 11069034]
15. Chng WJ, Van Wier SA, Ahmann GJ, et al. A validated FISH trisomy index demonstrates the hyperdiploid and nonhyperdiploid dichotomy in MGUS. *Blood*. 2005; 106(6):2156–61. [PubMed: 15920009]
16. Fonseca R, Bailey RJ, Ahmann GJ, et al. Genomic abnormalities in monoclonal gammopathy of undetermined significance. *Blood*. 2002; 100(4):1417–24. [PubMed: 12149226]
17. Kyle RA, Remstein ED, Therneau TM, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. *N Engl J Med*. 2007; 356(25):2582–90. [PubMed: 17582068]
18. Dhodapkar KM, Barbuti S, Matthews P, et al. Dendritic cells mediate the induction of polyfunctional human IL17-producing cells (Th17–1 cells) enriched in the bone marrow of patients with myeloma. *Blood*. 2008; 112(7):2878–85. [PubMed: 18669891]
19. Dhodapkar MV. Myeloid neighborhood in myeloma: cancer's underbelly? *Am J Hematol*. 2009; 84(7):395–6. [PubMed: 19507213]
20. Rasmussen T, Kuehl M, Lodahl M, et al. Possible roles for activating RAS mutations in the MGUS to MM transition and in the intramedullary to extramedullary transition some plasma cell tumors. *Blood*. 2005; 105(1):317–23. [PubMed: 15339850]
21. Chng WJ, Gonzalez-Paz N, Price-Troska T, et al. Clinical and biological significance of RAS mutations in multiple myeloma. *Leukemia*. 2008; 22(12):2280–4. [PubMed: 18528420]
22. Billadeau D, Jelinek DF, Shah N, et al. Introduction of an activated N-ras oncogene alters the growth characteristics of the interleukin 6-dependent myeloma cell line ANBL6. *Cancer Res*. 1995; 55(16):3640–6. [PubMed: 7627974]
23. Landgren O, Gridley G, Turesson I, et al. Risk of monoclonal gammopathy of undetermined significance (MGUS) and subsequent multiple myeloma among African American and white veterans in the United States. *Blood*. 2006; 107(3):904–6. [PubMed: 16210333]

24. Landgren O, Katzmann JA, Hsing AW, et al. Prevalence of monoclonal gammopathy of undetermined significance among men in Ghana. *Mayo Clin Proc.* 2007; 82(12):1468–73. [PubMed: 18053453]
25. Landgren O, Weiss BM. Patterns of monoclonal gammopathy of undetermined significance and multiple myeloma in various ethnic/racial groups: support for genetic factors in pathogenesis. *Leukemia.* 2009; 23(10):1691–7. [PubMed: 19587704]
26. Baker A, Braggio E, Jacobus S, et al. Uncovering the biology of multiple myeloma among African Americans: a comprehensive genomics approach. *Blood.* 2013; 121(16):3147–52. [PubMed: 23422747]
27. Greenberg AJ, Vachon CM, Rajkumar SV. Disparities in the prevalence, pathogenesis and progression of monoclonal gammopathy of undetermined significance and multiple myeloma between blacks and whites. *Leukemia.* 2012; 26(4):609–14. [PubMed: 22193966]
28. Weiss BM, Minter A, Abadie J, et al. Patterns of monoclonal immunoglobulins and serum free light chains are significantly different in black compared to white monoclonal gammopathy of undetermined significance (MGUS) patients. *Am J Hematol.* 2011; 86(6):475–8. [PubMed: 21544856]
29. Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. *J Clin Oncol.* 2005; 23(15):3412–20. [PubMed: 15809451]
30. Agnelli L, Fabris S, Biccato S, et al. Upregulation of translational machinery and distinct genetic subgroups characterise hyperdiploidy in multiple myeloma. *Br J Haematol.* 2007; 136(4):565–73. [PubMed: 17367409]
31. Brousseau M, Leleu X, Gerard J, et al. Hyperdiploidy is a common finding in monoclonal gammopathy of undetermined significance and monosomy 13 is restricted to these hyperdiploid patients. *Clin Cancer Res.* 2007; 13(20):6026–31. [PubMed: 17947464]
32. Trendle MC, Greipp PR, Leong T, et al. Prognostic significance of the S-phase fraction of light chain restricted cytoplasmic immunoglobulin (cIg) positive plasma cells in patients with newly diagnosed multiple myeloma (Meeting abstract). *Proc Annu Meet Am Soc Clin Oncol.* 1996; 15
33. Dewald GW, Kyle RA, Hicks GA, Greipp PR. The Clinical Significance of Cytogenetic Studies in 100 Patients With Multiple Myeloma, Plasma Cell Leukemia, or Amyloidosis. *Blood.* 1985; 66(2):380–90. [PubMed: 3926026]
34. Fonseca R, Blood E, Rue M, et al. Clinical and biologic implications of recurrent genomic aberrations in myeloma. *Blood.* 2003; 101(11):4569–75. This review provides a molecular cytogenetic classification of MM. [PubMed: 12576322]
35. Keats JJ, Reiman T, Maxwell CA, et al. In multiple myeloma, t(4;14)(p16;q32) is an adverse prognostic factor irrespective of FGFR3 expression. *Blood.* 2003; 101(4):1520–9. [PubMed: 12393535]
36. Avet-Loiseau H, Facon T, Grosbois B, et al. Oncogenesis of multiple myeloma: 14q32 and 13q chromosomal abnormalities are not randomly distributed, but correlate with natural history, immunological features, and clinical presentation. *Blood.* 2002; 99(6):2185–91. [PubMed: 11877296]
37. Avet-Loiseau H, Attal M, Moreau P, et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myelome. *Blood.* 2007; 109(8):3489–95. [PubMed: 17209057]
38. Chang H, Sloan S, Li D, et al. The t(4;14) is associated with poor prognosis in myeloma patients undergoing autologous stem cell transplant. *Br J Haematol.* 2004; 125(1):64–8. [PubMed: 15015970]
39. Pineda-Roman M, Zangari M, van Rhee F, et al. VTD combination therapy with bortezomib-thalidomide-dexamethasone is highly effective in advanced and refractory multiple myeloma. *Leukemia.* 2008; 22(7):1419–27. [PubMed: 18432260]
40. Shaughnessy JD Jr, Zhan F, Burington BE, et al. A validated gene expression model of high-risk multiple myeloma is defined by deregulated expression of genes mapping to chromosome 1. *Blood.* 2007; 109(6):2276–84. The authors elaborated a gene expression profiling model to molecularly define high-risk MM. [PubMed: 17105813]

41. Avet-Loiseau H, Durie BG, Cavo M, et al. Combining fluorescent in situ hybridization data with ISS staging improves risk assessment in myeloma: an International Myeloma Working Group collaborative project. *Leukemia*. 2013; 27(3):711–17. [PubMed: 23032723]
42. Fonseca R, Harrington D, Oken MM, et al. Prognostic Significance Of 13q-Deletions and the t(11;14)(q13;q32) in Myeloma (MM); An Interphase Fish Study of 351 Patients Entered into the Eastern Cooperative Oncology Group E9487 Clinical Trial. *Blood*. 2000; 96(11):547a.
43. Nishida K, Taniwaki M, Misawa S, Abe T. Nonrandom rearrangement of chromosome 14 at band q32. 33 in human lymphoid malignancies with mature B-cell phenotype. *Cancer Res*. 1989; 49(5): 1275–81. [PubMed: 2492904]
44. Chesi M, Bergsagel PL, Brents LA, et al. Dysregulation of cyclin D1 by translocation into an IgH gamma switch region in two multiple myeloma cell lines. *Blood*. 1996; 88(2):674–81. [PubMed: 8695815]
45. Avet-Loiseau H, Facon T, Daviet A, et al. 14q32 translocations and monosomy 13 observed in monoclonal gammopathy of undetermined significance delineate a multistep process for the oncogenesis of multiple myeloma. *Intergroupe Francophone du Myelome Cancer Res*. 1999; 59(18):4546–50.
46. Zhan F, Huang Y, Colla S, et al. The molecular classification of multiple myeloma. *Blood*. 2006; 108(6):2020–8. Zhan and colleagues provide a gene expression profiling-defined classification of MM. [PubMed: 16728703]
47. Tiedemann RE, Gonzalez-Paz N, Kyle RA, et al. Genetic aberrations and survival in plasma cell leukemia. *Leukemia*. 2008; 22(5):1044–52. [PubMed: 18216867]
48. Hayman SR, Bailey RJ, Jalal SM, et al. Translocations involving heavy-chain locus are possible early genetic events in patients with primary systemic amyloidosis. *Blood*. 2001; 98:2266–8. [PubMed: 11568015]
49. Harrison, C.; Mazullo, H.; Cheung, K., et al. Chromosomal abnormalities in systemic amyloidosis. *Proceedings of the VIII International Myeloma Workshop; Banff, Alberta, Canada*. 2001; p. P18
50. Chesi M, Nardini E, Brents LA, et al. Frequent translocation t(4;14)(p16.3;q32. 3) in multiple myeloma is associated with increased expression and activating mutations of fibroblast growth factor receptor 3. *Nat Genet*. 1997; 16(3):260–4. [PubMed: 9207791]
51. Chesi M, Bergsagel PL, Shonukan OO, et al. Frequent dysregulation of the c-maf proto-oncogene at 16q23 by translocation to an Ig locus in multiple myeloma. *Blood*. 1998; 91(12):4457–63. [PubMed: 9616139]
52. Avet-Loiseau H, Leleu X, Roussel M, et al. Bortezomib plus dexamethasone induction improves outcome of patients with t(4;14) myeloma but not outcome of patients with del(17p). *J Clin Oncol*. 2010; 28(30):4630–4. [PubMed: 20644101]
53. Avet-Loiseau H, Malard F, Campion L, et al. Translocation t(14;16) and multiple myeloma: is it really an independent prognostic factor? *Blood*. 2010; 117(6):2009–11. [PubMed: 20962323]
54. Fonseca R, Bergsagel PL, Drach J, et al. International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. *Leukemia*. 2009; 23(12):2210–21. [PubMed: 19798094]
55. Xiong W, Wu X, Starnes S, et al. An analysis of the clinical and biologic significance of TP53 loss and the identification of potential novel transcriptional targets of TP53 in multiple myeloma. *Blood*. 2008; 112(10):4235–46. [PubMed: 18337559]
56. Drach J, Ackermann J, Fritz E, et al. Presence of a p53 gene deletion in patients with multiple myeloma predicts for short survival after conventional-dose chemotherapy. *Blood*. 1998; 92(3): 802–9. [PubMed: 9680348]
57. Keats JJ, Fonseca R, Chesi M, et al. Promiscuous mutations activate the noncanonical NF-kappaB pathway in multiple myeloma. *Cancer Cell*. 2007; 12(2):131–44. [PubMed: 17692805]
58. Carrasco DR, Tonon G, Huang Y, et al. High-resolution genomic profiles define distinct clinico-pathogenetic subgroups of multiple myeloma patients. *Cancer Cell*. 2006; 9(4):313–25. [PubMed: 16616336]
59. Chng WJ, Price-Troska T, Gonzalez-Paz N, et al. Clinical significance of TP53 mutation in myeloma. *Leukemia*. 2007; 21(3):582–4. [PubMed: 17215851]

60. Chang H, Qi C, Yi QL, et al. p53 gene deletion detected by fluorescence in situ hybridization is an adverse prognostic factor for patients with multiple myeloma following autologous stem cell transplantation. *Blood*. 2005; 105(1):358–60. [PubMed: 15339849]
61. Hanamura I, Stewart JP, Huang Y, et al. Frequent gain of chromosome band 1q21 in plasma-cell dyscrasias detected by fluorescence in situ hybridization: incidence increases from MGUS to relapsed myeloma and is related to prognosis and disease progression following tandem stem-cell transplantation. *Blood*. 2006; 108(5):1724–32. [PubMed: 16705089]
62. Fonseca R, Van Wier SA, Chng WJ, et al. Prognostic value of chromosome 1q21 gain by fluorescent in situ hybridization and increase CKS1B expression in myeloma. *Leukemia*. 2006; 20(11):2034–40. [PubMed: 17024118]
63. Chapman MA, Lawrence MS, Keats JJ, et al. Initial genome sequencing and analysis of multiple myeloma. *Nature*. 2011; 471(7339):467–72. [PubMed: 21430775]
64. Chng WJ, Huang GF, Chung TH, et al. Clinical and biological implications of MYC activation: a common difference between MGUS and newly diagnosed multiple myeloma. *Leukemia*. 2011; 25(6):1026–35. [PubMed: 21468039]
65. Gabrea A, Martelli ML, Qi Y, et al. Secondary genomic rearrangements involving immunoglobulin or MYC loci show similar prevalences in hyperdiploid and nonhyperdiploid myeloma tumors. *Genes Chromosomes Cancer*. 2008; 47(7):573–90. [PubMed: 18381641]
66. Avet-Loiseau H, Gerson F, Magrangeas F, et al. Rearrangements of the c-myc oncogene are present in 15% of primary human multiple myeloma tumors. *Blood*. 2001; 98(10):3082–6. [PubMed: 11698294]
67. Smadja NV, Bastard C, Brigaudeau C, et al. Hypodiploidy is a major prognostic factor in multiple myeloma. *Blood*. 2001; 98(7):2229–38. [PubMed: 11568011]
68. Barlogie B, Alexanian R, Dixon D, et al. Prognostic implications of tumor cell DNA and RNA content in multiple myeloma. *Blood*. 1985; 66(2):338–41. [PubMed: 2410065]
69. Calasanz MJ, Cigudosa JC, Otero MD, et al. Hypodiploidy and 22q11 rearrangements at diagnosis are associated with poor prognosis in patients with multiple myeloma. *Br J Haematol*. 1997; 98(2):418–25. [PubMed: 9266942]
70. Fassas AB, Spencer T, Sawyer J, et al. Both hypodiploidy and deletion of chromosome 13 independently confer poor prognosis in multiple myeloma. *Br J Haematol*. 2002; 118(4):1041–7. [PubMed: 12199783]
71. Morgan RJ Jr, Gonchoroff NJ, Katzmman JA, et al. Detection of hypodiploidy using multi-parameter flow cytometric analysis: a prognostic indicator in multiple myeloma. *Am J Hematol*. 1989; 30(4):195–200. [PubMed: 2929579]
72. Van Wier S, Braggio E, Baker A, et al. Hypodiploid multiple myeloma is characterized by more aggressive molecular markers than non-hyperdiploid multiple myeloma. *Haematologica*. 2013; 98:1586–92. [PubMed: 23716545]
73. Chng WJ, Braggio E, Mulligan G, et al. The centrosome index is a powerful prognostic marker in myeloma and identifies a cohort of patients that might benefit from aurora kinase inhibition. *Blood*. 2008; 111(3):1603–9. [PubMed: 18006703]
74. Decaux O, Lode L, Magrangeas F, et al. Prediction of survival in multiple myeloma based on gene expression profiles reveals cell cycle and chromosomal instability signatures in high-risk patients and hyperdiploid signatures in low-risk patients: a study of the Intergroupe Francophone du Myelome. *J Clin Oncol*. 2008; 26(29):4798–805. [PubMed: 18591550]
75. Anguiano A, Tuchman SA, Acharya C, et al. Gene expression profiles of tumor biology provide a novel approach to prognosis and may guide the selection of therapeutic targets in multiple myeloma. *J Clin Oncol*. 2009; 27(25):4197–203. [PubMed: 19636021]
76. Broyl A, Hose D, Lokhorst H, et al. Gene expression profiling for molecular classification of multiple myeloma in newly diagnosed patients. *Blood*. 2010; 116(14):2543–53. [PubMed: 20574050]
77. Mulligan G, Mitsiades C, Bryant B, et al. Gene expression profiling and correlation with outcome in clinical trials of the proteasome inhibitor bortezomib. *Blood*. 2007; 109(8):3177–88. [PubMed: 17185464]

78. Nair B, van Rhee F, Shaughnessy JD Jr, et al. Superior results of Total Therapy 3 (2003–33) in gene expression profiling-defined low-risk multiple myeloma confirmed in subsequent trial 2006–66 with VRD maintenance. *Blood*. 2010; 115(21):4168–73. [PubMed: 20124509]
79. Shi J, Tricot GJ, Garg TK, et al. Bortezomib down-regulates the cell-surface expression of HLA class I and enhances natural killer cell-mediated lysis of myeloma. *Blood*. 2008; 111(3):1309–17. [PubMed: 17947507]
80. Kuiper R, Broyl A, de Knecht Y, et al. A gene expression signature for high-risk multiple myeloma. *Leukemia*. 2012; 26(11):2406–13. [PubMed: 22722715]
81. Avet-Loiseau H, Li C, Magrangeas F, et al. Prognostic significance of copy-number alterations in multiple myeloma. *J Clin Oncol*. 2009; 27(27):4585–90. [PubMed: 19687334]
82. Huchtagowder V, Meyer R, Mullins C, et al. Resequencing analysis of the candidate tyrosine kinase and RAS pathway gene families in multiple myeloma. *Cancer Genet*. 2012; 205(9):474–8. [PubMed: 22939401]
83. Keats JJ, Chesi M, Egan JB, et al. Clonal competition with alternating dominance in multiple myeloma. *Blood*. 2012; 120(5):1067–76. [PubMed: 22498740]
84. Walker BA, Wardell CP, Melchor L, et al. Intracлонаl heterogeneity and distinct molecular mechanisms characterize the development of t(4;14) and t(11;14) myeloma. *Blood*. 2012; 120(5):1077–86. [PubMed: 22573403]
85. Morgan GJ, Walker BA, Davies FE. The genetic architecture of multiple myeloma. *Nat Rev Cancer*. 2012; 12(5):335–48. [PubMed: 22495321]
86. Chung T-H, Mulligan G, Fonseca R, Chng W-J. A Novel measure of chromosome instability can account for prognostic difference in multiple myeloma. *PLoS One*. 2013; 8(6):e66361. [PubMed: 23840451]
87. Broyl A, Kuiper R, van Duin M, et al. High cereblon expression is associated with better survival in patients with newly diagnosed multiple myeloma treated with thalidomide maintenance. *Blood*. 2013; 121(4):624–7. [PubMed: 23233657]
88. Egan JB, Kortuem KM, Kurdoglu A, et al. Extramedullary myeloma whole genome sequencing reveals novel mutations in Cereblon, proteasome subunit G2 and the glucocorticoid receptor in multi drug resistant disease. *Br J Haematol*. 2013; 161(5):748–51. [PubMed: 23480694]
89. Sonneveld P, Schmidt-Wolf IG, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/GMMG-HD4 trial. *J Clin Oncol*. 2012; 30(24):2946–55. [PubMed: 22802322]
90. Neben K, Lokhorst HM, Jauch A, et al. Administration of bortezomib before and after autologous stem cell transplantation improves outcome in multiple myeloma patients with deletion 17p. *Blood*. 2012; 119(4):940–8. [PubMed: 22160383]
91. Cavo M, Pantani L, Petrucci MT, et al. Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma. *Blood*. 2012; 120(1):9–19. [PubMed: 22498745]
92. San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N Engl J Med*. 2008; 359(9):906–17. [PubMed: 18753647]
93. Mateos MV, Oriol A, Martinez-Lopez J, et al. Maintenance therapy with bortezomib plus thalidomide or bortezomib plus prednisone in elderly multiple myeloma patients included in the GEM2005MAS65 trial. *Blood*. 2012; 120(13):2581–8. [PubMed: 22889759]
94. Rosinol L, Oriol A, Teruel AI, et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. *Blood*. 2012; 120(8):1589–96. [PubMed: 22791289]
95. Stewart AK, Bergsagel PL, Greipp PR, et al. A practical guide to defining high-risk myeloma for clinical trials, patient counseling and choice of therapy. *Leukemia*. 2007; 21(3):529–34. [PubMed: 17230230]
96. Haessler J, Shaughnessy JD Jr, Zhan F, et al. Benefit of complete response in multiple myeloma limited to high-risk subgroup identified by gene expression profiling. *Clin Cancer Res*. 2007; 13(23):7073–9. [PubMed: 18056185]

97. Gertz MA, Lacy MQ, Dispenzieri A, et al. Clinical implications of t(11;14)(q13;q32), t (4;14)(p16.3;q32), and -17p13 in myeloma patients treated with high-dose therapy. *Blood*. 2005; 106(8): 2837–40. [PubMed: 15976175]
98. Reeder CB, Reece DE, Kukreti V, et al. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. *Leukemia*. 2009; 23(7):1337–41. [PubMed: 19225538]
99. Richardson PG, Weller E, Lonial S, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. *Blood*. 2010; 116(5): 679–86. [PubMed: 20385792]
100. Jakubowiak AJ, Dytfield D, Griffith KA, et al. A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. *Blood*. 2012; 120(9):1801–9. [PubMed: 22665938]
101. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012; 366(19):1782–91. [PubMed: 22571202]
102. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012; 366(19):1770–81. [PubMed: 22571201]
103. Palumbo A, Sezer O, Kyle R, et al. International Myeloma Working Group guidelines for the management of multiple myeloma patients ineligible for standard high-dose chemotherapy with autologous stem cell transplantation. *Leukemia*. 2009; 23(10):1716–30. [PubMed: 19494840]
104. Dimopoulos MA, Delforge M, Hajek R, et al. Lenalidomide, melphalan, and prednisone, followed by lenalidomide maintenance, improves health-related quality of life in newly diagnosed multiple myeloma patients aged 65 years or older: results of a randomized phase III trial. *Haematologica*. 2013; 98(5):784–8. [PubMed: 23242595]
105. Falco P, Cavallo F, Larocca A, et al. Lenalidomide-prednisone induction followed by lenalidomide-melphalan-prednisone consolidation and lenalidomide-prednisone maintenance in newly diagnosed elderly unfit myeloma patients. *Leukemia*. 2013; 27(3):695–701. [PubMed: 22996335]
106. Morgan GJ, Gregory WM, Davies FE, et al. The role of maintenance thalidomide therapy in multiple myeloma: MRC Myeloma IX results and meta-analysis. *Blood*. 2012; 119(1):7–15. [PubMed: 22021371]
107. Krishnan A, Pasquini MC, Logan B, et al. Autologous haemopoietic stem-cell transplantation followed by allogeneic or autologous haemopoietic stem-cell transplantation in patients with multiple myeloma (BMT CTN 0102): a phase 3 biological assignment trial. *Lancet Oncol*. 2011; 12(13):1195–203. [PubMed: 21962393]
108. Lokhorst HM, van der Holt B, Cornelissen JJ, et al. Donor versus no-donor comparison of newly diagnosed myeloma patients included in the HOVON-50 multiple myeloma study. *Blood*. 2012; 119(26):6219–25. quiz 6399. [PubMed: 22442350]
109. Garban F, Attal M, Michallet M, et al. Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma. *Blood*. 2006; 107(9):3474–80. [PubMed: 16397129]
110. Rosinol L, Perez-Simon JA, Sureda A, et al. A prospective PETHEMA study of tandem autologous transplantation versus autograft followed by reduced-intensity conditioning allogeneic transplantation in newly diagnosed multiple myeloma. *Blood*. 2008; 112(9):3591–3. [PubMed: 18612103]
111. Kröger N, Badbaran A, Zabelina T, et al. Impact of high-risk cytogenetics and achievement of molecular remission on long-term freedom from disease after autologous-allogeneic tandem transplantation in patients with multiple myeloma. *Biol Blood Marrow Transplant*. 2013; 19(3): 398–404. [PubMed: 23078786]
112. Paiva B, Vidriales MB, Cervero J, et al. Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation. *Blood*. 2008; 112(10):4017–23. [PubMed: 18669875]

113. Paiva B, Vidriales MB, Perez JJ, et al. Multiparameter flow cytometry quantification of bone marrow plasma cells at diagnosis provides more prognostic information than morphological assessment in myeloma patients. *Haematologica*. 2009; 94(11):1599–602. [PubMed: 19880781]
114. Paiva B, Vidriales MB, Mateo G, et al. The persistence of immunophenotypically normal residual bone marrow plasma cells at diagnosis identifies a good prognostic subgroup of symptomatic multiple myeloma patients. *Blood*. 2009; 114(20):4369–72. [PubMed: 19755674]
115. Paiva B, Gutierrez NC, Rosinol L, et al. High-risk cytogenetics and persistent minimal residual disease by multiparameter flow cytometry predict unsustained complete response after autologous stem cell transplantation in multiple myeloma. *Blood*. 2012; 119(3):687–91. [PubMed: 22128143]
116. Paiva B, Vidriales MB, Rosinol L, et al. A multiparameter flow cytometry immunophenotypic algorithm for the identification of newly-diagnosed symptomatic myeloma with an MGUS-like signature and long-term disease control. *Leukemia*. 2013; 27(10):2056–61. [PubMed: 23743858]
117. Ladetto M, Pagliano G, Ferrero S, et al. Correlation between clinical outcome and disease kinetics by quantitative PCR in myeloma patients following post-transplant consolidation with bortezomib, thalidomide and dexamethasone. *Blood (ASH Annual Meeting Abstracts)*. 2009; 114:960.
118. Ladetto M, Pagliano G, Ferrero S, et al. Major tumor shrinking and persistent molecular remissions after consolidation with bortezomib, thalidomide, and dexamethasone in patients with autografted myeloma. *J Clin Oncol*. 2010; 28(12):2077–84. [PubMed: 20308672]
119. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. *Leukemia*. 2009; 23(1):3–9. [PubMed: 18971951]
120. Fonseca R, Monge J. Myeloma: classification and risk assessment. *Semin Oncol*. 2013; 40:554–66. [PubMed: 24135400]
121. Cavo M, Tacchetti P, Patriarca F, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. *Lancet*. 2010; 376(9758):2075–85. [PubMed: 21146205]

Key issues

- Conventional cytogenetics and FISH, with or without gene expression profiling, should be used to identify patients with high-risk multiple myeloma (MM).
- Genetic testing should be performed at least once during the course of the disease, although repeat testing has the advantage of detecting abnormalities associated with disease progression.
- A number of genetic expression profiling signatures have been developed, and are now available in the clinic, to identify high-risk MM.
- The choice of therapy – and even its outcome – may be guided in part by the results of genetic testing, as seen by the benefit derived from treating patients with high-risk MM, particularly those with t(4;14), with bortezomib.
- The use of risk stratification as part of patient counseling should not be overlooked.

Table 1

Clinical staging of plasma cell disorders.

Disorder [119]	Serum monoclonal protein (g/dl)	Clonal BM plasma cells (%)	End-organ damage
MGUS	<3	<10	Absence of end-organ damage (CRAB)
SMM	>3	>10	Absence of end-organ damage (CRAB)
MM	>3	>10	Presence of end-organ damage (CRAB) attributable to the underlying PC disorder

BM: Bone marrow; CRAB: Hypercalcemia, renal failure, anemia and/or bone lesions; MGUS: Monoclonal gammopathy of undetermined significance; MM: Multiple myeloma; PC: Plasma cell; SMM: Smoldering multiple myeloma.

Table 2

Prognosis of high-risk multiple myeloma by gene expression profiling.

GEP signature	Outcome measured	Outcome measured	Ref.
<i>UAMS 70-gene signature</i>			[40]
Training cohort (high vs low risk)	EFS: HR 4.51 (p < 0.001)	OS: HR 5.16 (p < 0.001)	
Test cohort (high vs low risk)	EFS: HR 3.41 (p = 0.002)	OS: HR 4.75 (p < 0.001)	
<i>H-MM signature</i>			[10]
Cluster 3 vs others	PFS: 253 vs 127 days (p = 0.13)	Response to bortezomib: 70 vs 29% (p = 0.02)	
Cluster 3 vs cluster 1	Median survival: 122 vs 27 months (p = 0.04)		
<i>Centrosome index</i>			[73]
High vs low CI	OS: HR 1.95 (p = 0.04)	OS (patients with PI >2): 30.6 vs 45.6 months (p = 0.04)	
Bortezomib trials (high vs low CI)	PFS: 2.8 vs 4.9 months (p = 0.02)	OS: 11.5 vs 20.9 months (p = 0.0002)	
<i>IFM 15-gene signature</i>			[74]
High vs low risk	Mean 3-year survival: 47.4 vs 90.5%	OS: HR 6.8 (p = 0.001)	
<i>Treatment response by high-risk GEP</i>			[78]
2003–33 trial	EFS: HR 2.57 (p < 0.001)	OS: HR 2.43 (p = 0.001)	
2006–66 trial	EFS: HR 2.77 (p = 0.019)	OS: HR 3.00 (p = 0.016)	
<i>EMC-92-gene signature</i>			[80]
UAMS-TT2 data set	19.4% of patients identified as high risk	OS: HR 3.4 (p < 0.001)	
UAMS-TT3 data set	16.2% of patients identified as high risk	OS: HR 5.23 (p < 0.001)	
MRC-IX data set	20.2% of patients identified as high risk	OS: HR 2.38 (p < 0.001)	

CI: Centrosome index; GEP: Gene expression profiling; H-MM: Hyperdiploid multiple myeloma; HR: Hazard ratio; EFS: Event-free survival; EMC: Erasmus University Medical Center; IFM: Intergroupe Francophone du Myelome; MRC: Medical Research Council; OS: Overall survival; PFS: Progression-free survival; PI: Proliferation index; UAMS: University of Arkansas for Medical Sciences.

Reproduced with permission from [120] © Elsevier (2013).

Table 3

Risk stratification and recommended testing.

High risk	Standard risk
<i>FISH</i>	
<i>t(4;14)(p16;q32)</i>	Hyperdiploidy
<i>t(14;16)(q32;q23)</i>	<i>t(11;14)(q13;q32)</i>
<i>del17p13</i>	Chromosome 13 Other translocations Chromosome 1 abnormalities <i>del12p</i> 5q amplification
<i>GEP</i>	
UAMS 70-gene or 17-gene signature	
IFM 15-gene signature	
Centrosome index	
Proliferation index	

Essential tests in *italics*, as recommended by the International Myeloma Working Group [54].

Table 4

Maintenance therapy after stem cell transplantation.

Regimen	Length of treatment	PFS	3-year OS (%)	Second primary cancers	Adverse events	Ref.
Lenalidomide vs placebo	Until relapse	41 vs 23 months (HR: 0.5; p < 0.001)	80 vs 84 (HR: 1.25; p = 0.29)	3.1 vs 1.2 per 100 patient-years (p = 0.002)	Thromboembolic events: 6 vs 2% (p = 0.01)	[101]
Lenalidomide vs placebo	Until progression	46 vs 27 months (p < 0.001)	88 vs 80 (HR: 0.62; p = 0.053)	7.8 vs 2.6%	Thromboembolic events: 1 vs 0%	[102]
Thalidomide vs no maintenance	Until progression	Overall: 23 vs 15 months (p < 0.001) Adverse iFISH: 9 vs 12 months (p = 0.48)	Overall: no significant difference Adverse iFISH: worse OS (p = 0.009)	NR	Any serious adverse reaction: 9.1 vs 2.6% (p = 0.0001)	[106]
Thalidomide and bortezomib vs thalidomide vs α2-IFN	Up to 3 years, discontinued at disease progression	78 vs 63 vs 49% at 2 years (p = 0.01)	No significant difference	NR	NR	[94]

HR: Hazard ratio; iFISH: Interphase FISH; IFN: Interferon; NR: Not reported; OS: Overall survival; PFS: Progression-free survival.

Table 5

Bortezomib-based consolidation therapy.

Regimen	Chromosomal abnormality	PFS	3-year OS (%)	Ref.
Bortezomib vs thalidomide	del(17p13)	26.2 vs 12 months (p = 0.024)	69 vs 17 (p = 0.028)	[90]
	t(4;14)	25.3 vs 21.7 months (p = 0.12)	66 vs 44 (p = 0.37)	
	+1q21	28.2 vs 23.6 months (p = 0.22)	77 vs 62 (p = 0.10)	
	del(13q14)	27.4 vs 25.2 months (p = 0.27)	81 vs 61 (p = 0.072)	
Bortezomib, thalidomide and dexamethasone vs thalidomide and dexamethasone	All patients	HR 0.63 (p = 0.0061)	86 vs 84 (p = 0.3)	[121]
	del(13q)	HR 0.49 (p = 0.0039)	NR	
	t(4;14)	HR 0.51 (p = 0.0174)	NR	

HR: Hazard ratio; NR: Not reported; OS: Overall survival; PFS: Progression-free survival.

Reproduced with permission from [120] © Elsevier (2013).