Risk Stratification in Multiple Myeloma, Part 2: The Significance of Genetic Risk Factors in the Era of Currently Available Therapies

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Abstract: Multiple myeloma (MM) is a heterogeneous disease, and a variety of risk factors at the time of initial diagnosis can be used to stratify patients. In the first part of this 2-part series, we reviewed the currently identified prognostic factors, characterized by disease burden, host factors, tumor biology, and depth of response to therapy. However, these risk factors cannot be interpreted independently of therapies. Novel therapies have the potential to worsen or improve outcomes compared with conventional therapy in high-risk patients, or actually overcome the high-risk status, thereby resulting in reclassification as standard risk. For example, thalidomide (Thalomid, Celgene) is associated with worse outcomes in patients with high-risk cytogenetic abnormalities, such as deletion of chromosomes 13 and 17p, whereas proteasome inhibitors appear to overcome t(4;14). The second part of this series reviews the significance of various genetic risks in the era of novel therapies for MM.

Introduction

In part 1 of this series on the risk stratification of multiple myeloma (MM), we reviewed the currently identified prognostic factors, categorized by disease burden, host factors, tumor biology, and depth of response to therapy. These prognostic factors, however, are not static. Rather, their prognostic value is dependent on the therapies used at the time a particular risk factor is validated.

Fortunately, with the emergence of novel therapies over the past decade, overall survival (OS) in MM has improved significantly. Immunomodulatory agents such as lenalidomide (Revlimid, Celgene) and pomalidomide (Pomalyst, Celgene), and proteasome inhibitors such as bortezomib (Velcade, Millennium) and carfilzomib (Kyprolis, Onyx), have improved the prognosis for MM patients.[1] An important consideration in evaluating the ability of novel agents to overcome high-risk disease is not simply achieving a response but more importantly, achieving a durable response that results in improved progression-free survival (PFS) and OS.

In this second part of the series, we review the significance of various genetic risks, which are the MM risk factors most studied in the era of novel therapies. We distinguish between treatments that only *improve* the outcomes of high-risk patients when compared with previous therapies vs those that *overcome* high-risk status, thereby reclassifying these patients as standard risk.[2]

Improving vs Overcoming High Risk

It is essential to make a distinction between strategies that *overcome* adverse prognosis and those that result in *improved* outcomes in high-risk patients. To *overcome* adverse prognosis implies that with use of specific treatments, the survival of high-risk patients becomes similar to that of standard-risk patients. *Improving* outcome signifies that a new treatment strategy is able to improve outcome compared with standard treatments in the same high-risk patient subgroup. The Figure illustrates the difference between improving vs overcoming risk in patients with high-risk vs standard-risk cytogenetics.

Studies that evaluate the effects of specific novel therapies on adverse prognosis are usually single-arm, phase 2 studies. In these studies, the high-risk group is not addressed independently of the standard-risk group. The larger sample size of the standard-risk group can help the analysis achieve statistical significance. However, the high-risk group, which is usually addressed in a post-hoc, subgroup analysis, is not powered to achieve statistical significance because of the small number of patients and short follow-up. It is difficult to make the conclusion that novel therapy overcomes or even improves risk in these single-arm studies with subgroup analyses. Therefore, a lack of statistical power may misleadingly favor the novel therapy in such studies.

In contrast, a double-arm, randomized controlled clinical trial specifically looking at outcomes with a given therapy for patients with high-risk genetic features compared with those at standard risk can help to evaluate whether a specific strategy improves outcomes. These types of studies are limited because high-risk groups tend to be small, reducing the power of the analysis and making it more difficult to achieve statistical significance. As a result, randomized controlled trials tend to favor conventional therapy rather than novel therapy in improving outcomes.[2]

Thalidomide

Current data indicate that thalidomide (Thalomid, Celgene) not only is unable to improve the adverse prognosis of high-risk cytogenetics, but in certain settings—such as maintenance therapy—may actually lead to worse outcomes in this population. Beginning with the pivotal trial done by the University of Arkansas group in 84

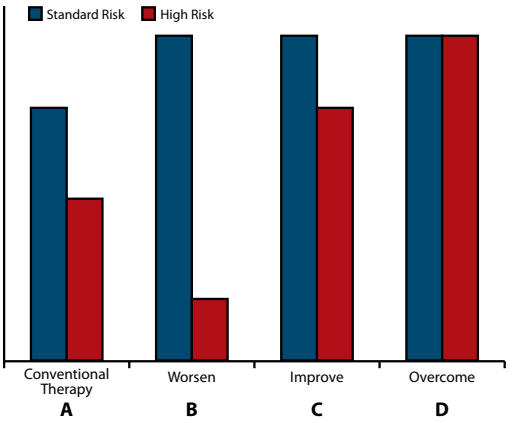

Figure. In this example, myeloma patients in a hypothetical randomized phase 3 clinical trial are treated with either conventional therapy or a novel agent, *X*. In this ideal trial, patient enrollment is also stratified by risk status in order to achieve adequate statistical power to detect differences between the 2 risk groups. Panel (A) shows the superior outcomes (ideally, overall survival) with conventional therapy in standard-risk patients compared with high-risk patients. Panels (B) through (D) all show further improvement in the outcomes of the standard-risk patients treated with agent *X* when compared with standard-risk patients treated with conventional therapy. However, in panel (B), not only does drug *X* not improve the outcomes of the high-risk patients relative to the standard-risk patients, the outcomes of the high-risk patients are actually *worse* than those with conventional therapy. In panel (C), the outcomes of the high-risk patients treated with drug *X* are improved relative to conventional therapy, but are still inferior to those with standard-risk disease, meeting the definition for *improving* outcome. In panel (D), outcomes are equivalent between standard-risk and high-risk patients who receive drug *X*, indicating that high risk has been truly *overcome*. This example also illustrates the potential difficulty in interpreting results from underpowered subgroup analyses of a single-arm, phase 2 study, where there would be no available results from a comparator group (eg, panel A).

relapsed or refractory patients treated with single-agent thalidomide, the 42% of patients who had del(13q) by cytogenetics had statistically inferior OS.[3]

In 238 newly diagnosed MM patients who received thalidomide and dexamethasone (TD) induction therapy before double autologous stem-cell transplant (ASCT) and also as consolidation after ASCT, those with t(4;14) had significantly worse 3-year PFS (20% vs 48%) compared with those without the translocation.[4]

In terms of del(17p), there is no improvement in outcomes with thalidomide maintenance, as shown in the HOVON 65/GMMG-HD4 (Dutch-Belgian Hemato-Oncology Cooperative Group/German Multicenter Myeloma Group) trial. Those who were in the standard-

treatment arm received induction therapy with vincristine, doxorubicin, and dexamethasone (VAD), followed by 1 or 2 rounds of ASCT and thalidomide maintenance without bortezomib. Those with del(17p) had a 3-year OS of 17%, compared with 79% in the same arm if the chromosomal abnormality was not present.[5]

Thalidomide maintenance may actually be associated with worse outcomes in patients with high-risk cytogenetic abnormalities. A recently published trial by the Medical Research Council showed a much worse 3-year OS for those with poor fluorescence in situ hybridization (FISH)—defined as 1q, del(1p32), del(17p), t(4;14), t(14;16), and t(14;20)—randomized to thalidomide maintenance compared with those randomized to placebo.[6]

Lenalidomide

The benefit of lenalidomide in high-risk patients is less clear. In a study of patients with newly diagnosed MM who were treated with induction lenalidomide and dexamethasone (RD), those with high-risk MM had a statistically significant shorter PFS (18.5 vs 36.5 months) and achieved less durable responses compared with the standard-risk group. High-risk MM was defined by the presence of hypodiploidy, del(13q) by cytogenetics, del(17p), t(4;14), or t(14;16), or plasma-cell labeling index (PCLI) of 3% or greater. OS, however, was comparable between high- and standard-risk groups.[7] In contrast, in the phase 3 E4A03 study comparing lenalidomide with either high- or low-dose dexamethasone in patients with newly diagnosed MM, the 2-year OS in patients with high-risk vs standard-risk FISH was 76% vs 91% (P=.004).[8]

In the maintenance setting, the Intergroupe Francophone du Myélome (IFM) found that lenalidomide maintenance was associated with an increase in PFS from 24 to 42 months (P<.0001). In patients with del(17p), lenalidomide maintenance was associated with an improvement in PFS from 14 to 29 months (P<.02) but it did not overcome this risk. In patients with t(4;14), the improvement in PFS was a more modest increase, from 24 to 28 months (P<.04).[9] In a randomized study of 460 patients who received lenalidomide or placebo 100 days after undergoing ASCT, cytogenetic analysis was not required for enrollment, but a review of available data is ongoing in order to determine the effect of maintenance lenalidomide on high-risk patients.[10]

The data are even more complex in the relapsed and refractory setting. In a subanalysis of a large study, Reece and colleagues investigated the effects of lenalidomide and dexamethasone on patients with t(4;14) and del(17p) detected by FISH in 130 patients. Patients with t(4;14) experienced a median time to progression (TTP) and OS comparable to those without the translocation.[11] However, in the same study, those with del(17p) had a significantly worse outcome, with a median TTP of 2.22 months and OS of 4.67 months.[11] Two other retrospective studies in patients with relapsed or refractory MM have also found shorter TTP in these patients with lenalidomide; one also found inferior OS.[12,13]

Therefore, although lenalidomide—unlike thalidomide—does not appear to be associated with any worsening of outcomes in high-risk patients, there is also no clear and consistent evidence to date of an improvement in OS, let alone PFS.

Pomalidomide

Pomalidomide is an immunomodulatory derivative of thalidomide and is similar in structure to it. Pomalidomide has a mechanism of action that is similar to that of lenalidomide, with dual induction of caspase 8–dependent apoptotic signaling and sensitization of MM cells to apoptosis induced by Fas cross-linking.[14] Given that it was only recently approved by the US Food and Drug Administration, the data on pomalidomide overcoming high-risk cytogenetics are very preliminary.

In the first phase 2 trial of pomalidomide plus low-dose dexamethasone, 60 patients who were refractory to lenalidomide, thalidomide, or bortezomib had a 63% response rate. Seventy-four percent of those with high-risk cytogenetics—defined as del(13) by cytogenetics, t(4;14), t(14;16), del(17p), or PCLI of 3 or greater—had a response. The median PFS of 11.6 months was not significantly different in patients with high-risk disease compared with patients with standard-risk disease.[15] However, only 50% of these patients had FISH results available. Preliminary data from a total of 345 patients treated at the Mayo Clinic also did not appear to find inferior outcomes in high-risk patients.

However, in the IFM 2009-02 phase 2 open-label study of pomalidomide plus low-dose dexamethasone, all survival endpoints for patients with t(4;14) and del(17p) were inferior to those without these abnormalities. The PFS was 44% vs 95%, respectively (P=.0005); OS was 27% vs 67% at 1 year, respectively (P=.0002).[16] Preliminary data from the MM 002 phase 2 study of pomalidomide in genomically defined high-risk relapsed/refractory MM appears to confirm inferior outcomes in high-risk disease.[17,18]

To resolve these apparently conflicting results, data are needed from larger, phase 3 trials and from trials that use a standardized definition of high risk (eg, excluding patients with only deletion 13).

Bortezomib

Retrospective analyses of prospective trials of bortezomib suggest that this agent may overcome high-risk disease

Table. Effect of Bortezomib, Thalidomide, Lenalidomide, Carfilzomib, and Pomalidomide on High-Risk Multiple Myeloma by Cytogenetic Finding

Drug	High-Risk Cytogenetic Finding	Effect of Therapy on High-Risk MM	Reference
Thalidomide	t(4;14)	No change	Cavo, 2012[4]
	del(17p)	Worsened	Neben, 2012[5]
	Monosomy 13 by cytogenetics	Worsened	Singhal, 1999[3]
	Poor fluorescence in situ hybridization: 1q, del (1p32), del(17p), t(4;14), t(14;16), t(14;20)	Worsened	Morgan, 2012[6]
Lenalidomide	t(4;14)	Overcame (in relapsed/refractory)	Reece, 2009[11,*]
	del(17p)	No change	Reece, 2009[11,*] Chang, 2010[13] Avet-Loiseau, 2007[12]
Pomalidomide	t(4;14)	No change	Leleu, 2013[32,*]
	del(17p)	No change	Leleu, 2013[32,*]
	t(4;14), t(14;16), del(17), del(13) by cytogenetics	Appeared to overcome	Lacy, 2009[15,*]
	High-risk GEP	No change	Siegel, 2012[18,*] Usmani, 2012[17,*]
Bortezomib	t(4;14)	Improved and overcame	Cavo, 2010[22] Pineda-Roman, 2008[33] Barlogie, 2007[23] San Miguel, 2008[29]
	t(14;16)	Improved	San Miguel, 2008[34] Rosinol, 2012[26]
	del(17p)	Improved and possibly overcame	Neben, 2012[5] Avet-Louiseau, 2010[25] Harousseau JL, 2010[30] San Miguel, 2008[29] Shaughnessy, 2009[28]
	Monosomy 13 by cytogenetics	Overcame	Richardson, 2003[20] Richardson, 2005[19] Jagannath, 2007[21]
Carfilzomib	t(4;14), t(14;16), del(13) by cytogenetics; del(17p)	No change	Jakubowiak, 2013[31,*]
	t(4;14)	Improved	Jakubowiak, 2013[31,*]

* Not a prospective phase 3 clinical trial.

from del(13). In matched-pairs analyses of 2 large phase 2 and 3 trials, SUMMIT (Study of Uncontrolled Myeloma Managed With Proteasome Inhibition Therapy) and APEX (Assessment of Proteasome Inhibition for Extending Remissions),[19,20] response and survival appeared comparable in bortezomib-treated patients with or without del(13) by cytogenetics as an independent prognostic factor.[21] Indeed, this study is in part the reason why del(13) is no longer considered a high-risk finding.

The most evidence for bortezomib improving and overcoming high-risk cytogenetics is in t(4;14). In 1 randomized study, where newly diagnosed patients in 1 arm received induction with bortezomib, thalidomide, and dexamethasone (VTD), tandem ASCT, and bortezomib consolidation, 3-year PFS was 65% vs 61% for patients with and without t(4;14), respectively. In contrast, the arm that received TD as induction therapy before and consolidation therapy after tandem ASCT showed a statistically inferior PFS in patients with t(4;14).[22] Similarly, with the University of Arkansas Total Therapy 2 regimen, patients with t(4;14) had significantly shorter event-free survival (EFS) and OS vs those without the translocation. This difference disappeared in the bortezomib-containing Total Therapy 3 (TT3) regimen.[23,24]

Of note, a comparison of these favorable results with those of 2 other studies suggests an important caveat. In both the IFM 2005 and the Spanish GEM05 study, where patients randomized to the bortezomib-containing arms received only bortezomib-based induction therapy

(ie, no maintenance), the survival of patients with t(4;14) remained inferior to that of those without t(4;14).[25,26] This suggests that the duration of bortezomib treatment may be important in overcoming the risk of t(4;14).

Bortezomib in combination with melphalan, prednisone, and thalidomide (VMPT) was evaluated in transplant-ineligible patients.[27] A total of 511 newly diagnosed patients who were not eligible for high-dose chemotherapy plus ASCT were randomly assigned to receive 9 cycles of VMPT followed by maintenance with bortezomib-thalidomide (VMPT-VT), or 9 cycles of bortezomib, melphalan, and prednisone (VMP) at the same doses with no additional therapy. The high-risk patients were defined by an International Staging System score of 3 or by the presence of t(4;14), t(14;16), or del(17p). The outcome of high-risk patients was similar in patients receiving VMPT-VT or VMP. In contrast, the outcome of standard-risk patients was superior with VMPT-VT. At first glance, this study implies that in the high-risk transplant ineligible population, more bortezomib may not necessarily improve outcome, as has been shown in the standard-risk patients. However, a potential detrimental effect of thalidomide cannot be ruled out.

The data with bortezomib and del(17p) are conflicting. Some, but not all, studies have shown that the negative prognostic implications of del(17p) can be at least improved with bortezomib. In a phase 3 trial by the HOVON group, of 354 patients treated with either bortezomib, doxorubicin, and dexamethasone (PAD) or VAD, a subgroup analysis of 37 patients with del(17p) demonstrated significantly longer PFS (26 vs 12 months) and higher 3-year OS (69% vs 17%) than those assigned to PAD.[5] However, compared with patients without the abnormality, the 3-year OS rate was significantly higher, 85%, indicating that bortezomib does not completely overcome the adverse prognosis of del(17p).

In the TT3 regimen, in which bortezomib was added to the induction, consolidation, and maintenance phases of multidrug treatments, p53 haploinsufficiency based on gene expression profiling (GEP) of purified plasma cells was not associated with inferior EFS or OS in multivariate analysis.[28] Similarly, in the VISTA (Velcade as Initial Standard Therapy in Multiple Myeloma) study, transplant-ineligible patients were randomized to treatment with melphalan and prednisone with or without bortezomib (MP vs VMP). The addition of bortezomib was able to overcome high-risk cytogenetics—including t(4;14), t(14;16), and del(17p)—although present in only 26 of a total of 168 patients.[29]

However, the IFM group recently reported the outcomes of 507 patients treated with bortezomib and dexamethasone induction before high-dose melphalan therapy compared with a cohort of 512 patients treated with VAD. Both EFS and OS were improved for patients with t(4;14) but not for those with del(17p).[25] In another large trial done by the IFM, there was a significant difference in 4-year OS (50% vs 79%) in patients with del(17p) despite bortezomib-based induction plus ASCT.[30]

Among the 5 studies examining bortezomib in patients with del(17p)—HOVON, TT3, 2 IFM trials, and VISTA (Bortezomib Plus Melphalan and Prednisone for Initial Treatment of Multiple Myeloma)—TT3 had the strongest evidence for bortezomib overcoming del(17p). The TT3 trial was the only one that included bortezomib for induction, consolidation, and maintenance phases. The HOVON trial included bortezomib in the induction and maintenance phase, and outcomes were improved yet not overcome. Therefore, randomized, prospective clinical trials are needed to resolve whether prolonged bortezomib treatment can truly improve and/or overcome the high-risk nature of 17p deletions.

Several trials have grouped patients with t(4;14), t(14;16), and del(17p) into the same category. In the VISTA study described above, the 26 patients with t(4;14), t(14;16), and del(17p) who received bortezomib had the same OS as standard-risk patients.[29] However, in the randomized GEM 2005 trial, VTD followed by a single ASCT, the prognosis of patients with del(17p), t(4;14), and t(14;16) was significantly shorter than that of standard-risk patients, with a 3-year OS of 60% vs 88% (P=.001).[26]

Carfilzomib

Carfilzomib is a novel, well-tolerated, irreversible proteasome inhibitor with minimal neurotoxicity that was approved by the US Food and Drug Administration (FDA) in July of 2012 for patients who progressed on bortezomib and an immunomodulatory agent (thalidomide or lenalidomide).

Jakubowiak and colleagues evaluated the PX-171-003-A1 phase 2 study of carfilzomib, for which 229 of the 257 response-evaluable patients had cytogenetics and/or FISH available.[31] Twenty-seven percent of these patients had at least one of the following chromosomal abnormalities: del(17p), t(4;14), or t(14;16) by FISH, or deletion 13 or hypodiploidy by cytogenetics. Although the overall response was comparable with standard risk, the PFS and OS were shorter in high-risk patients: 3.6 vs 4.6 months (P=.06) and 9.3 vs 19 months, respectively (P=.0003). Similar to the data for bortezomib, the outcomes for t(4;14) were superior to those for del(17p). The Table summarizes the effect of each above-mentioned specific therapeutic approach on high-risk cytogenetic abnormalities.

Conclusions

MM is a heterogeneous disease, and a variety of risk factors at the time of initial diagnosis can be used to stratify patients, including disease burden (Durie-Salmon staging system, International Staging System, magnetic resonance imaging,

positron emission tomography, extramedullary disease, plasma cell leukemia), host factors (age, performance status, and renal function), and disease biology (lactate dehydrogenase, PCLI, metaphase karyotype, FISH, cytoplasmic immunoglobulin FISH, CD138-selected FISH, and GEP). Although correlating response with prognosis is fraught with issues, the achievement of an immunophenotypic complete response appears to maintain its prognostic value even with landmark analysis.

Novel therapies have been shown to improve outcomes in patients with these cytogenetic abnormalities and high-risk features, most notably proteasome inhibitors in t(4;14). It is also important to note that certain therapies can worsen outcomes in patients with high-risk cytogenetic abnormalities, such as thalidomide in deletion of chromosomes 13 and 17p. It is hoped that multidrug regimens, or the addition of novel agents such as histone deacetylase inhibitors and monoclonal antibodies, may further overcome high-risk MM.

Although prognostication is important, the ultimate objective of risk stratification and personalized medicine is to provide a given patient who has a particular myeloma subtype with appropriately tailored therapy to improve survival and quality of life. Ideally, this approach also will contain the cost of care. Achieving these goals will require a biologic understanding of sequential genetic events and clonal heterogeneity, standardized and universally available risk criteria, and well-designed, prospective randomized controlled studies with the appropriate clinical endpoints.

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