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. 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 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
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), response and survival appeared comparable in bortezomib-treated patients with or without del(13) by cytogenetics as an independent prognostic factor. 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). 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.

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>High-Risk Cytogenetic Finding</th>
<th>Effect of Therapy on High-Risk MM</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td>t(4:14)</td>
<td>No change</td>
<td>Cavo, 2012</td>
</tr>
<tr>
<td></td>
<td>del(17p)</td>
<td>Worsened</td>
<td>Neben, 2012</td>
</tr>
<tr>
<td></td>
<td>Monosomy 13 by cytogenetics</td>
<td>Worsened</td>
<td>Singhal, 1999</td>
</tr>
<tr>
<td></td>
<td>Poor fluorescence in situ hybridization: 1q, del(1p32), del(17p), t(4:14), t(14:16), t(14:20)</td>
<td>Worsened</td>
<td>Morgan, 2012</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>t(4:14)</td>
<td>Overcame (in relapsed/refractory)</td>
<td>Reece, 2009</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>t(4:14)</td>
<td>No change</td>
<td>Leleu, 2013</td>
</tr>
<tr>
<td></td>
<td>del(17p)</td>
<td>No change</td>
<td>Leleu, 2013</td>
</tr>
<tr>
<td></td>
<td>t(4:14), t(14:16), del(17), del(13) by cytogenetics</td>
<td>Appeared to overcome</td>
<td>Lacy, 2009</td>
</tr>
<tr>
<td></td>
<td>High-risk GEP</td>
<td>No change</td>
<td>Siegel, 2012, Usmani, 2012</td>
</tr>
<tr>
<td></td>
<td>t(14:16)</td>
<td>Improved</td>
<td>San Miguel, 2008, Rosinol, 2012</td>
</tr>
<tr>
<td></td>
<td>Monosomy 13 by cytogenetics</td>
<td>Overcame</td>
<td>Richardson, 2003, Richardson, 2005, Jagannath, 2007</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>t(4:14), (14:16), del(13) by cytogenetics; del(17p)</td>
<td>No change</td>
<td>Jakubowiak, 2013</td>
</tr>
<tr>
<td></td>
<td>t(4:14)</td>
<td>Improved</td>
<td>Jakubowiak, 2013</td>
</tr>
</tbody>
</table>

* Not a prospective phase 3 clinical trial.
Although present in only 26 of a total of 168 patients, cytogenetics—including t(4;14), t(14;16), and del(17p)—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...
position 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 will also 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.

References