The Effect of Novel Therapies in High-Molecular-Risk Multiple Myeloma

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Abstract: Multiple myeloma is a heterogeneous disease with a prognosis that varies with patient factors, disease burden, tumor biology, and treatments. Certain molecular abnormalities confer a worse prognosis and thus are considered high-risk. These include t(4;14), del(17p), t(14;16), t(14;20), hypodiploidy, and gain(1q)/del(1p). In our previous review in 2013, we discussed the effect of available therapies on prognosis in these high-risk patients. Since then, seven phase 3 clinical trials in relapsed myeloma with 1 to 3 lines of therapy have been conducted, resulting in the approval of panobinostat, ixazomib, daratumumab, and elotuzumab, as well as additional data on carfilzomib. In our current review of these studies, all the novel therapies resulted in an improvement in progression-free survival for high-risk patients, but none of the trials provided clear statistical evidence that they overcame high-risk status. Moreover, there are several limitations in the currently available data. For example, the patient's Revised International Staging System score is generally not reported, and even when it is reported, it is usually at the time of initial diagnosis rather than at the time of study entry. Furthermore, the methodology used to determine risk suffers from technologic issues. Finally, the clonal and allele burden and concurrent molecular abnormalities can affect risk status and prognosis. To determine the optimal therapy for high-risk patients, future clinical trials should provide standardized risk assessments for all patients in addition to hazard ratios for Kaplan-Meier survival curves of high-risk patients vs those of standard-risk patients to determine if high-risk status has truly been overcome by a novel agent.

Introduction

Multiple myeloma (MM) is a heterogeneous disease with a variable prognosis; the median overall survival (OS) of low-risk patients approaches 10 years. Approximately 10% of patients overall are relapse-free after 10 years, which is a functional definition of cure.[1] However, high-risk patients still have a median OS of only 3 years. In our previous review, we characterized the risk factors that can affect the overall trajectory of MM.[2,3] These include patient factors,

such as age/frailty and renal failure, as well as disease burden and biology, most simply represented by the Revised International Staging System (R-ISS) score. Given the continued inferior OS of elderly patients, those with renal failure, and those at high molecular risk, improvement in the outcomes of these groups will most rapidly increase median OS in MM.

Some progress has been made in understanding tumor biology and its response to newer therapies. We previously discussed the data for thalidomide (Thalomid, Celgene), lenalidomide (Revlimid, Celgene), pomalidomide (Pomalyst, Celgene), bortezomib (Velcade, Millennium/Takeda Oncology), and carfilzomib (Kyprolis, Onyx) in patients with high molecular risk. This was followed by an International Myeloma Working Group (IMWG) consensus paper that discussed these therapies and only briefly touched on more recently approved drugs.[4] These reviews concluded that thalidomide tends to worsen survival, and that lenalidomide, pomalidomide, bortezomib, and double autologous stem cell transplants partly abrogate but do not fully overcome the worse prognosis associated with high molecular risk. Since then, seven phase 3 trials have been conducted that are fundamental to our understanding of molecular risk and prognosis.

In this update, we define high molecular risk and how this classification is important when novel therapies are evaluated. We then summarize the data related to high molecular risk from phase 3 clinical trials of carfilzomib, panobinostat (Farydak, Novartis), ixazomib (Ninlaro, Millennium/Takeda Oncology), daratumumab (Darzalex, Janssen), and elotuzumab (Empliciti, Bristol-Myers Squibb), with the goal of tailoring therapy for higher-risk patients.

Characterization of High Molecular Risk

The IMWG consensus defines t(4;14), del(17p), t(14;16), t(14;20), hypodiploidy, and gain(1q)/del(1p) as high-molecular-risk.[4] The definition is based on multiple studies that demonstrated a worsened prognosis in patients with these abnormalities.[5-8] However, important additional factors must be considered in assessing high molecular risk, including technologic issues, clonal/allele burden, and concurrent abnormalities.

Most published studies of high molecular risk use fluorescence in situ hybridization (FISH) and are performed either on CD138-selected cells or concurrently with cytoplasmic immunoglobulin FISH. Given the importance of the percentage of abnormal plasma cells, it is unclear whether FISH data based on an entire unselected bone marrow aspirate can be generalized. Moreover, recent studies have shown that next-generation sequencing (NGS) is more sensitive than standard FISH and may result in more accurate risk stratification.[9,10] Similarly, some patients identified as high-risk by FISH testing have subsequently been found to be low-risk by gene expression profiling (GEP).[11,12] For example, in one study, FISH with ISS remained a solid prognostic model but was not as precise as GEP combined with ISS.[12] In fact, 75% of patients in the lowest-risk group by GEP with ISS—who had a very favorable survival (median OS not reached at 96 months)—were positive for either t(4;14), del(17p), or gain(1q). This is an evolving field that is frequently being refined, so FISH analyses, which are used in most current clinical trials, may not end up being the most accurate prognostic evaluations. Throughout this article, we use the term *molecular risk* rather than *cytogenetic risk* to emphasize the importance of the molecular diagnostic technique used.

It should be noted that it is unknown what percentage of plasma cells must have del(17p) to confer a worse prognosis. Several studies have found that a low clonal percentage of del(17p) is not necessarily high-risk, and typically del(17p) is high-risk only if present in more than 30% to 60% of cells.[13-16] Additionally, traditional indicators of risk, such as age, lactate dehydrogenase level, and ISS score, still play a major role in prognosis even in the presence of a high clonal percentage of del(17p).[17] Clinical trials to date have not reported on R-ISS, which attempts to combine some of these risk factors into a unified staging system. Clinical trials also have been highly variable in their del(17p) cutoffs, ranging from any detected cell to 60%. This variability, as well as differences in baseline risk factors, must be considered when high-risk and standard-risk subgroups are compared across trials. Emerging data also suggest that the allele burden within a cell may be important, with biallelic 17p deletions conferring a worse prognosis than monoallelic deletions.[18,19] In most recently published randomized phase 3 clinical trials, molecular data are missing in 25% to 75% of patients, and there is inconsistency in centralized testing for clonal/allele burden of del(17p) as well as the cutoffs (from any detected cell to 60%) used to characterize high-risk disease.

In addition, it is known that the presence of other molecular abnormalities can modulate the risk of del(17p).[7,8] Specifically, patients with at least 2 of 3 adverse markers (del[17p], gain[1q], and any *IGH* translocation involving chromosome 14) have inferior OS (23 months) compared with patients who have 1 abnormality (38-44 months, depending on the molecular event), and patients with all 3 abnormalities have the worst OS of all (9 months). This finding is not insignificant, given that 72% of patients with *IGH* translocation also had gain(1q) and 12% of these patients also had del(17p).[8] Gain(19q13) plus more than 8 numeric abnormalities were found to be significantly protective in patients with

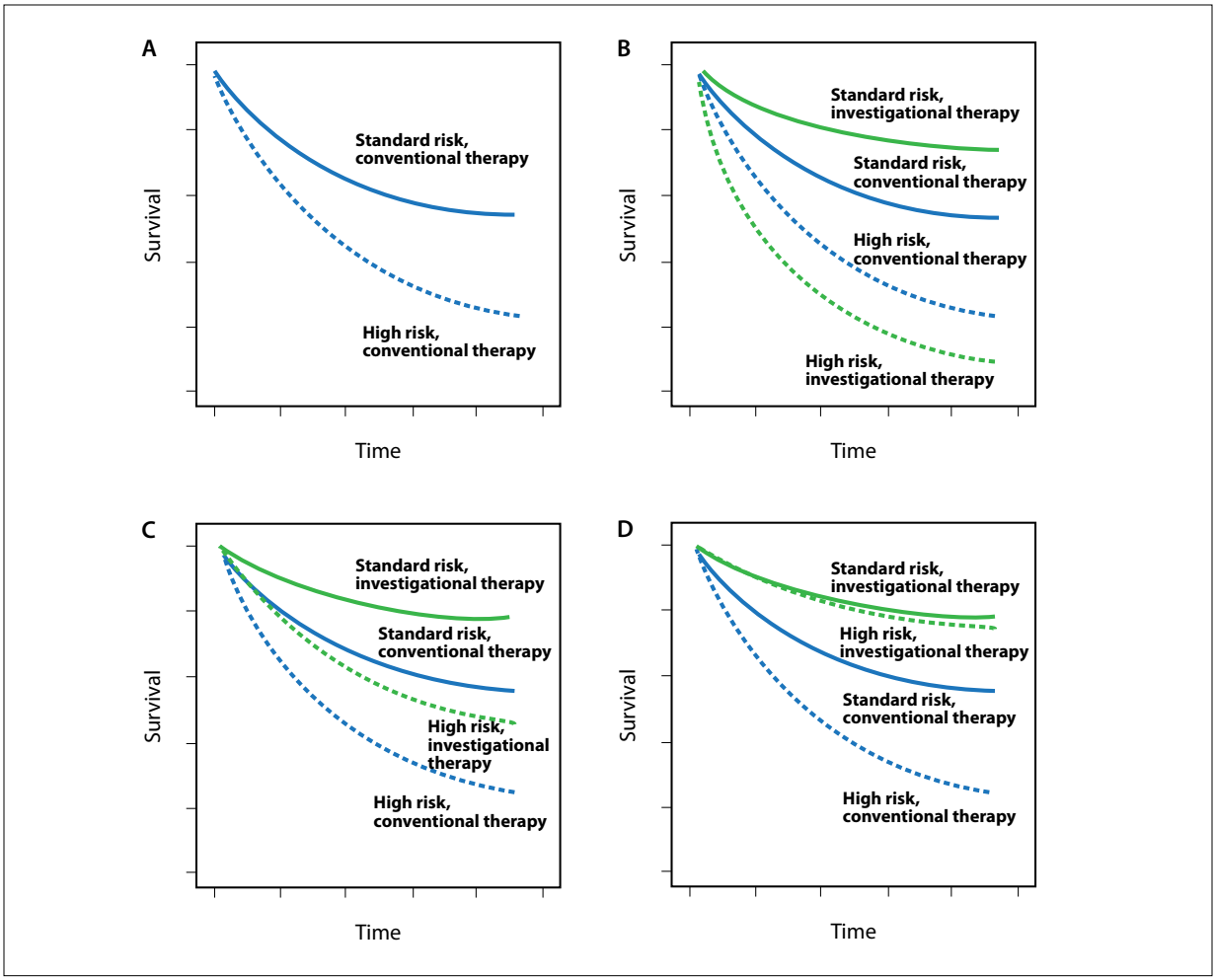

Figure. Sample Kaplan-Meier survival curves. (A) Inferior survival based on current high-risk molecular abnormalities. (B) Worsened survival in high-risk patients receiving novel therapy. (C) Improved survival in high-risk patients receiving novel therapy, but still inferior to that of standard-risk patients receiving novel therapy. (D) High-risk status is overcome with novel therapy, and these patients now have survival equivalent to that of standard-risk patients.

del(17p).[7,17] The effect of other molecular markers is also true for t(4;14). In a study of high-risk patients in which single nucleotide polymorphism array was used, del(1p32) and del(13q14) were associated with worse OS in conjunction with t(4;14).[7] Also, several studies have found that although all t(4;14) MM exhibits overexpression of the *MMSET* gene, which encodes a histone methyltransferase involved in genetic instability/tumor progression, only the truncated forms of the MMSET protein confer a worse prognosis.[20,21] These types of nuances can confound certain analyses because patients in clinical trials will sometimes have multiple adverse molecular risk factors and appear in more than 1 subgroup, so that the true effect of a single molecular event may not be represented.

Because of the abundance of variables affecting prognosis, it is challenging to make meaningful comparisons of outcomes across clinical trials. Although the randomization process will minimize the effect of confounding variables within the experimental and control arms of a given study, none of these studies is powered to detect differences based on molecular risk stratification, let alone specific molecular abnormalities. In this review, we provide a critical appraisal of the available data with these significant caveats in mind.

Reducing vs Overcoming High Risk

Although the outcomes of these studies cannot be compared with one another, the phase 3 study design does provide an invaluable framework for evaluating the outcomes of high-molecular-risk patients. As discussed in our prior review, novel therapies may have 3 different effects on such patients, as shown by the movement of

the hypothetical Kaplan-Meier progression-free survival (PFS) or OS curves for high-risk patients treated with a novel therapy (Figure). Patients at high molecular risk have worse outcomes with conventional therapy than those at standard risk (Figure, part A). In rare cases—for example, thalidomide in the setting of del(17p)—a novel therapy in high-risk patients may worsen outcomes relative to standard therapy in high-risk patients (Figure, part B). In other cases, a novel therapy may improve outcomes in high-risk patients but still fall short of standard-risk patients receiving the novel therapy (Figure, part C). Finally, and ideally, outcomes in high-risk patients will be similar to those in standard-risk patients, and their high-risk status will be overcome (Figure, part D).

Ultimately, the hope is that these therapies will produce deep and meaningful clinical responses in all patients, especially in high-risk patients, that will translate into a PFS benefit and, of course, an OS benefit. The importance of focusing on survival-based endpoints in high-molecular-risk patients cannot be overstated, as evidenced by the fact that high molecular risk remains an independent risk factor even in patients attaining negativity for minimal residual disease (MRD).[22,23] Kaplan-Meier survival curves can be evaluated in several ways, all of which may be reported in clinical trials. Median PFS is the most intuitive and most frequently emphasized measure, and it can provide a general understanding of the treatment effect. However, it provides little information about the effects throughout the rest of the study, either before or after the median time point. Similarly, time point analyses provide concrete information about survival at a certain time after treatment, but they do little to assess the overall trajectory and differential effects throughout the study period. Hazard ratios, meanwhile, are not associated with concrete measures, but they give a better sense of the effect of treatment throughout the entire study period and serve to elucidate the magnitude of difference between 2 Kaplan-Meier curves. The survival endpoints provided in each clinical trial are included in this review.

Therapy

Therapies are discussed individually in this section. Baseline characteristics for all included studies are shown in Table 1. Survival outcomes by study and molecular abnormality are displayed in Table 2.

Carfilzomib

Carfilzomib is a proteasome inhibitor that received US Food and Drug Administration (FDA) approval for relapsed or refractory multiple myeloma (RRMM) in 2012 on the basis of a phase 2 trial called PX-171-003-A1 (Phase 2 Study of Carfilzomib in Relapsed and Refractory Multiple Myeloma).[24] Since then, 2 additional phase 3 trials have been conducted. ASPIRE (Phase 3 Study Comparing Carfilzomib, Lenalidomide, and Dexamethasone vs Lenalidomide and Dexamethasone in Subjects With Relapsed Multiple Myeloma) randomly assigned patients with relapsed MM to carfilzomib or placebo plus lenalidomide and dexamethasone, whereas ENDEAVOR (Phase 3 Study With Carfilzomib and Dexamethasone Versus Bortezomib and Dexamethasone for Relapsed Multiple Myeloma Patients) randomly assigned patients to either carfilzomib or bortezomib, plus dexamethasone.[25,26]

Detailed subgroup analyses were published for both phase 3 trials. In ASPIRE, high molecular risk was defined as CD138-selected FISH with any t(4;14) or t(14;16), or with del(17p) in at least 60% of plasma cells.[27] Among 100 high-risk patients who received carfilzomib in addition to lenalidomide and dexamethasone, PFS was improved compared with PFS in patients who received only lenalidomide and dexamethasone: 23.1 months vs 13.9 months. This did not differ if patients had only t(4;14) or only del(17p). PFS remained inferior to that in standard-risk patients, who had a median PFS of 29.6 months. Similarly, response rates were improved with the addition of carfilzomib, but the high-risk status was not overcome. Data on OS had not yet matured at the time of this analysis.

In the subgroup analysis of ENDEAVOR, 97 of 210 high-risk patients with t(4;14) or t(14;16) in more than 10% of plasma cells or with del(17p) in more than 20% of plasma cells defined by FISH received carfilzomib in addition to dexamethasone instead of bortezomib and dexamethasone.[28] These patients had significantly improved PFS—8.8 vs 6.0 months. PFS was not estimable in the standard-risk group receiving carfilzomib and was 10.2 months in the bortezomib group, indicating that high-risk status was likely not overcome. Patients with t(4;14) who received carfilzomib fared slightly better, with a statistically significant increase in PFS of 10.1 months vs 6.8 months for those who received bortezomib. There also was a trend toward improvement in PFS with carfilzomib among patients with del(17p)—7.6 months vs 4.9 months with bortezomib. The overall response rate and the proportion with complete response were higher with carfilzomib across the whole high-risk group. Again, OS data had not yet matured.

Overall, the data show that carfilzomib does improve outcomes in high-risk patients compared with standard therapies, with likely more effect in the t(4;14) group, although interpretation of the del(17p) data is confounded by the use of different cutoff points for percentage of plasma cells. In both phase 3 trials, carfilzomib could not overcome high-risk status.

Table 1. Baseline Characteristics of Patients in Studies of Multiple Myeloma

Drug/Study	Comparison	N	Age >75 y, Percentage	ISS 3, Percentage[a]	Lines of Therapy, Median No.	Refractory to PI/IMiD, Percentage	Definition of High Risk	High Risk as Percentage of Available Molecular Risk	Patients With Missing Molecular Data, Percentage
Carfilzomib									
ASPIRE[25]	KRd vs Rd	792	>65 y: 49.6%	43.7%	2	IMiD: 21.8%	t(4;14) or t(14;16) or 60% del(17p)	23.9%	47.3%
ENDEAVOR[26]	Kd vs Vd	929	15.4%	Not reported	2	Lenalidomide: 25.2%	t(4;14) or t(14;16) or 20% del(17p)	24.1%	6.4%
Panobinostat									
PANORAMA-1[29]	PVd vs Vd	768	8.2%	21.2%	1	Not reported	t(4;14) or t(14;16) or del(17p): unknown cutoff	18.1%	73.4%
Ixazomib									
TOURMALINE-MM1[31]	IRd vs Rd	722	>65 y: 52.0%	12%	1	IMiD: 23% PI: 2%	t(4;14) or t(14;16) or 5% del(17p)	24.8%	24%
Daratumumab									
CASTOR[34]	DVd vs Vd	498	11.4%	22.1%	2	Not reported	t(4;14) or t(14;16) or 50% del(17p)	26.9%	29.1%
POLLUX[35]	DRd vs Rd	569	11.2%	19.9%	1	PI only: 18.1% IMiD only: 3.7% PI + IMiD: 3.7%	t(4;14) or t(14;16) or 50% del(17p)	20.9%	45.4%
Elotuzumab									
ELOQUENT-2[38]	ERd vs Rd	646	Not reported	20.7%	2	Bortezomib: 21.8% Thalidomide: 9.9%	t(4,14) or del (17p): any cell	Not reported	1.7%

D, daratumumab; d, dexamethasone; E, elotuzumab; I, ixazomib; IMiD, immunomodulatory drug; ISS, International Staging System; K, carfilzomib; P, panobinostat; PI, proteasome inhibitor; R, lenalidomide; V, bortezomib; y, years.

[a] In ASPIRE, ISS score was at time of diagnosis. Other studies do not report whether ISS score was at time of diagnosis or at study entry.

Panobinostat

Panobinostat is the first histone deacetylase inhibitor approved for MM; approval was based on the results of the phase 3 PANORAMA-1 (Panobinostat or Placebo With Bortezomib and Dexamethasone in Patients With Relapsed Multiple Myeloma) trial. This trial compared bortezomib/dexamethasone plus either panobinostat or placebo in patients with RRMM.[29] A total of 37 high-risk patients had t(4;14), t(14;16), or del(17p) defined by FISH. Owing to the small number of patients, limited data were reported. The hazard ratio for PFS was 0.47 (0.18-1.25) in favor of panobinostat in the high-risk patients, whereas the hazard ratio for PFS in standard-risk patients was 0.88 (0.6-1.29), which was not statistically significant. Median PFS was not reported in months. In an update of PANORAMA-1, there was a trend toward

Table 2. Survival Data From Studies of Multiple Myeloma

Drug/Study	Molecular Testing Methodology	Molecular Abnormality[a]	Total No. of Patients[b]	PFS, Novel Therapy, mo[c]	PFS, Control Therapy, mo[c]	Hazard Ratio[c]
Carfilzomib						
ASPIRE[25] (n=792)	Centralized FISH (CD138-selected)	t(4;14)	55	23.1	16.7	NR
		del(17p): 60%	26	24.5	11.1	NR
		t(4;14), t(14;16), or del(17p): 60%	100	23.1 (12.5-24.2)	13.9 (9.5-16.7)	0.70 (0.43-1.16)
		Standard risk	317	29.6 (24.1-NE)	19.5 (14.8-26.0)	0.66 (0.48-0.90)
ENDEAVOR[26] (n=929)	Centralized FISH (unspecified)	t(4;14)	111	10.1 (6.9-NE)	6.8 (5.6-9.4)	0.63 (0.38-1.02; *P*=.13)
		del(17p): 20%	92	7.6 (5.6-11.2)	4.9 (3.9-7.5)	0.73 (0.42-1.27; *P*=.03)
		t(4;14) or t(14;16) or del(17p): 20%	210	8.8	6.0	0.65 (0.45-0.92; *P*=.0075)
		Standard risk	575	NE	10.2	0.44 (0.33-0.58; *P*<.0001)
Panobinostat				**OS[d]**	**OS[d]**	**OS[d]**
PANORAMA-1[29] (n=768)	FISH (unspecified)	t(4;14), t(14;16), or del(17p): NA	37	33.3 (15.6-NE)	22.8 (7.0-43.3)	0.40 (0.16-0.98; NS)
		Standard risk	167	35.0 (25.4-49.1)	37.8 (26.2-57.9)	1.11 (0.74-1.67; NS)
Ixazomib						
TOURMALINE-MM1[31] (n=722)	Centralized FISH (CD138-selected)	t(4;14)	61	18.5	12.0	0.65 (0.25-1.66)
		del(17p): 5%	69	21.4	9.7	0.60 (0.29-1.24)
		del(17p): 20%	59	21.4	6.7	0.61 (NR)
		del(17p): 60%	33	15.7	5.1	0.49 (NR)
		t(4;14) or t(14;16) or del(17p): 5%	137	21.4	9.7	0.54 (0.32-0.92; *P*=.02)
		Standard risk	415	20.6	15.6	0.64 (NR)
Daratumumab						
CASTOR[34] (n=498)	Centralized NGS	t(4;14), t(14;16), or del(17p): 50%	95	11.2	7.2	0.45 (0.25-0.80; *P*=.0053)
		Standard risk	258	19.6	7.0	0.26 (0.18-0.37; *P*<.0001)
POLLUX[35] (n=569)	Centralized NGS	t(4;14), t(14;16), or del(17p): 50%	65	22.6	10.2	0.53 (0.25-1.13; *P*=.0921)
		Standard risk	246	Not reached	18.5	0.30 (0.20-0.47; *P*<.0001)

(Table continued on next page)

Table 2. *(Continued)* Survival Data From Studies of Multiple Myeloma

Drug/Study	Molecular Testing Methodology	Molecular Abnormality[afn/a]	Total No. of Patients[b]	PFS, Novel Therapy, mo[c]	PFS, Control Therapy, mo[c]	Hazard Ratio[c]
Elotuzumab						
ELOQUENT-2[38] (n=646)	Centralized FISH (unspecified)	t(4;14)	61	15.8 (8.4-18.5)	5.6 (3.1-10.3)	0.52 (0.29-0.93; *P*=.027)
		t(4;14) negative	575	20.3 (17.3-23.3)	15.7 (13.0-18.5)	0.74 (0.60-0.91; *P*=.004)
		del(17p): any cell	206	21.2 (16.6-27.5)	14.9 (10.6-18.5)	0.70 (0.49–0.99; *P*=.042)
		del(17p) negative	431	18.5 (15.8-22.8)	14.8 (11.7-18.4)	0.73 (0.58–0.92; *P*=.007)

FISH, fluorescence in situ hybridization; mo, months; NA, not available; NE, not estimable; NGS, next-generation sequencing; No., number; NR, not reported; NS, not significant; OS, overall survival.

[a] Cutoffs stated next to del(17p).

[b] Numbers not cumulative.

[c] 95% confidence intervals when reported.

[d] PFS not reported in months in original study. Data taken from update on OS.[30]

improved OS in high-risk patients who received panobinostat vs placebo—33.3 months vs 22.8—but the difference was not statistically significant, likely owing to the small sample size.[30] This OS was similar to OS in standard-risk patients receiving panobinostat, which was 35.0 months. Interestingly, OS was improved for high-risk but not standard-risk patients, who had a slightly lower OS with panobinostat than with placebo.

Overall, data on panobinostat are limited owing to the small numbers of high-risk patients enrolled. Furthermore, there is no report of the cutoffs used for del(17p). Panobinostat appears to improve OS and may even overcome high-risk status based on these very preliminary findings. However, more randomized controlled trials will be needed before any firm conclusions can be drawn.

Ixazomib

Ixazomib is an oral proteasome inhibitor approved by the FDA in 2015 for the treatment of MM along with lenalidomide and dexamethasone in patients with at least 1 prior therapy. The approval was based on results from the phase 3 TOURMALINE-MM1 trial (A Phase 3 Study Comparing Oral Ixazomib Plus Lenalidomide and Dexamethasone Versus Placebo Plus Lenalidomide and Dexamethasone in Adult Patients With Relapsed and/or Refractory Multiple Myeloma). In this trial, patients with RRMM were randomly assigned to either ixazomib or placebo, plus lenalidomide/dexamethasone.[31] The study enrolled a total of 137 patients with high molecular risk, defined by 5% of cells positive for del(17p), 3% for t(4;14), or 3% for t(14;16) with CD138-selected FISH. In these patients, PFS favored ixazomib over placebo, 21.4 months vs 9.7 months. PFS was the same as in the overall high-risk group in patients who had del(17p), whereas it was slightly lower in the patients who had only t(4;14) (18.5 vs 12 months). Impressively, the PFS for high-risk patients receiving ixazomib appeared to reach that of standard-risk patients receiving ixazomib (21.4 vs 20.6 months).

One criticism of this trial is the use of a 5% cutoff for del(17p). This concern was addressed in a subsequent abstract presented at the American Society of Clinical Oncology (ASCO) annual meeting in 2016.[32] PFS for patients receiving ixazomib was similar when a cutoff of 20% involved cells was used, but it came down to 15.7 months when the more conservative 60% threshold was used. Rates of complete response, very good partial response, and overall response were similar in the high-risk and standard-risk groups, but these were with a cutoff of 5% for del (17p). About half of the high-risk patients had del(17p), which confounds this comparison based on molecular risk. OS data were not yet mature, but at a median follow-up of 23 months, there appeared to be a lower rate of death in high-risk patients receiving ixazomib than in those receiving placebo (15/75 vs 24/62).

Overall, ixazomib appears promising for patients

with high molecular risk. It certainly improves PFS for these patients relative to placebo. The question of whether it overcomes high-risk status remains open, largely owing to the uncertainty regarding cutoffs for del(17p). In the subgroups with t(4;14) only or more than 60% of cells with del (17p), PFS was indeed slightly lower than in the high-risk group as a whole, indicating that some analyses may have been confounded by the large number of patients with a lower burden of del(17p).

Daratumumab

Daratumumab is a monoclonal antibody directed against CD38, which is overexpressed in MM cells.[33] It was initially approved by the FDA in 2015 as monotherapy for patients with at least 3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent, or with disease doubly refractory to a proteasome inhibitor and an immunomodulatory agent. Approval was based on the CASTOR (Addition of Daratumumab to Combination of Bortezomib and Dexamethasone in Participants With Relapsed or Refractory Multiple Myeloma) and POLLUX (A Study Comparing Daratumumab, Lenalidomide, and Dexamethasone With Lenalidomide and Dexamethasone in Relapsed or Refractory Multiple Myeloma) studies.[34,35]

CASTOR was a phase 3 trial comparing bortezomib, dexamethasone, and either daratumumab or placebo in patients with RRMM. Data on molecular risk were not presented in the original trial because a separate analysis was planned. An abstract for this subgroup with high risk, which was defined as del(17p) with 50% cutoff, t(4;14), or t(14;16) based on NGS, was presented at the 2017 ASCO meeting.[36] The analysis demonstrated that PFS was greater in the high-risk patients receiving daratumumab than in those receiving placebo, 11.2 vs 7.2 months, but it still fell far short of the 19.6 months reached in the daratumumab standard-risk group. The overall response rate in the high-risk group was higher with daratumumab than with placebo (82% vs 62%), as was the complete response rate (30% vs 9%).

Similarly, the phase 3 POLLUX trial comparing lenalidomide, dexamethasone, and daratumumab or placebo did not report outcomes by molecular risk. Subgroup data from patients with high molecular risk, defined as del(17p) with 50% cutoff, t(4;14), or t(14;16), were presented at the American Society of Hematology (ASH) meeting in 2016. These demonstrated that PFS and the rates of complete response, very good partial response, and overall response were all significantly better with daratumumab than with placebo.[37] However, even though median PFS was not reached in this group, the Kaplan-Meier curves show that high-risk status was not overcome. In an update from the 2017 ASCO meeting, the values for median PFS were 22.6 vs 10.2 months in the high-risk groups, but median PFS was still not reached in the standard-risk daratumumab group.[36] Once again, a marked increase in overall response (85 % vs 67%) and complete response (33% vs 6%) was observed for daratumumab compared with placebo.

CASTOR and POLLUX are the only phase 3 trials to date to report on MRD, which was assessed by NGS. In CASTOR, 6 of 44 (14%) high-risk patients receiving daratumumab were MRD-negative, compared with 0% in the placebo arm. None of these 6 patients had disease progression by 15 months of follow-up. Similarly, the MRD-negative rate in this group in POLLUX was 6 of 26 (23%), compared with 0% in the placebo arm. None of these 6 patients had disease progression at 24 months of follow-up. Although MRD negativity has been associated with increases in both PFS and OS in a recent meta-analysis by Munshi and colleagues,[23] high-risk status remains independently prognostic such that MRD negativity in high-risk patients does not have the same magnitude of benefit as it does in standard-risk patients.[22,23] If longer follow-up and larger numbers of patients from other phase 3 studies confirm the findings from CASTOR and POLLUX, perhaps MRD negativity will be an important endpoint in high-risk patients treated with daratumumab.

Elotuzumab

Elotuzumab is a monoclonal antibody targeting signaling lymphocytic activation molecule F7 (SLAMF7). It was FDA-approved for MM in 2015 based on the ELOQUENT-2 trial (Phase III Study of Lenalidomide and Dexamethasone With or Without Elotuzumab to Treat Relapsed or Refractory Multiple Myeloma).[38] In this study, elotuzumab was evaluated against placebo in addition to lenalidomide and dexamethasone. High-risk disease was defined as FISH with any t(4;14) or t(14;16), or any cell with del(17p). In a subsequent subgroup analysis, PFS in patients with del(17p) receiving elotuzumab was better than PFS in patients receiving placebo and about the same as in patients without this abnormality.[39] Patients with t(4;14) did better with elotuzumab but not as well as patients negative for t(4;14). In terms of OS, high-risk patients did better with elotuzumab than with placebo (29.8 vs 24.8 months), but results still fell far short of those in the standard-risk group (43.7 months).

PFS for del(17p) appeared to reach that of standard-risk patients; however, this finding was based on the lowest del(17p) cutoff used of any trial, which makes accurate interpretation difficult. Outcomes for t(4;14) were improved but not overcome. OS in the high-risk group was improved, but the difference between high-risk and standard-risk patients was not overcome.

Discussion

Prognosis in MM remains heterogeneous and dependent on several variables, including patient factors, disease burden, tumor biology, and treatment. Although our understanding of molecular risk is rapidly evolving, it is generally agreed that certain high-risk markers confer a worse prognosis, including t(4;14), del(17p), t(14;16), t(14;20), hypodiploidy, and gain(1q)/del(1p). Determining the optimal therapy for patients with high molecular risk remains a challenge.

Several issues complicate the interpretation of currently available data. Notably, there is significant controversy regarding the threshold for determining high-risk status based on del(17p). Trials using lower cutoffs may be capturing standard-risk patients in a high-risk group, which would inflate apparent efficacy in high-risk patients. Additionally, recent data have shown that prognostication with NGS and GEP may be more precise than with FISH, with some high-risk patients by FISH standards down-staged when these newer techniques are used. The complex interplay among the molecular abnormalities affecting prognosis is not yet fully understood. Risk models incorporating GEP will likely prove to be more useful once validated and more widely available. Even the relatively straightforward R-ISS, which attempts to combine traditional risk factors with molecular risk, was not reported in any of the trials reviewed here, which used the older ISS staging. In fact, only one trial, ASPIRE, reported whether ISS staging was done at initial diagnosis or at study entry. Recent data suggest that R-ISS is predictive in both newly diagnosed MM and RRMM[40]; therefore, trials should present R-ISS at study entry to capture risk profiles most accurately.

Other relevant statistical issues must be considered. Given that high-risk data were missing for 25% to 75% of patients in most of the studies, the high-risk outcomes discussed in this review are limited to complete case (CC) analyses restricted to individuals who have no missing data. A CC approach leads to a loss in power; however, the results are valid if the missing data occur at random and the probability of being a CC is independent of the outcome. However, if the mechanism of missing data is not independent of the outcome (eg, if high-risk data are more likely to be missing from certain resource-poor sites that also lacked access to novel therapies before study entry or as salvage options after progression on study), a CC analysis can be biased. Although valid statistical methods, such as multiple imputations, allow individuals with incomplete data to be included in the analysis, these have not typically been applied in MM.

Ideally, trials should also be powered to investigate outcomes of high-risk patients specifically, but this has proven to be difficult in practice. Given that high-risk outcomes are subgroup analyses, they may not necessarily provide an adequate basis for definitive conclusions. Guidelines for assessing reported subgroup effect estimates should be adhered to and should include a priori hypotheses stated, clinical importance of effect estimate, proper assessment of statistical significance, and consistency across studies.[41]

Further analyses of recent phase 3 trials are eagerly anticipated. Going forward, future clinical trials should ideally assess molecular risk in all patients, with centralized molecular risk assessment and standardized cutoffs to minimize missing and noncomparable data. Integration of molecular risk with MRD assessment may help identify early those high-risk patients requiring intensification of therapy. Furthermore, if the pathophysiologic basis of clonal persistence could be determined, such as by using NGS techniques to identify potentially targetable somatic mutations in the residual clone, personalized therapy could help patients achieve a durable MRD-negative status.

Finally, in the real world, most patients are not undergoing bone marrow aspiration with each relapse. Given clonal evolution, risk stratification is clearly a dynamic process. Thus, many patients are beginning therapies for relapse with unknown risk. Although the proteasome inhibitors have been able to overcome t(4;14) in some clinical trials, the hope that monoclonal antibodies would be more genome-agnostic and therefore able to overcome high-risk disease has not yet been borne out. Data are eagerly awaited from the next wave of promising antimyeloma therapies, including selinexor, checkpoint inhibitors, chimeric antigen receptor T cells, and bispecific antibodies. As more data accumulate from well-designed phase 3 trials, we will be better able to tailor therapies to individuals and fulfill the goal of personalized medicine.

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