

New Agents and Strategies in the Management of Multiple Myeloma

A Review of Key Clinical Questions Regarding the
Integration of Novel Therapies into Oncology Practice

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U P D A T E



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OVERVIEW OF ACTIVITY

The pace of oncology drug development has accelerated in recent years to previously unmatched levels. Fueled by an increased understanding of the biologic underpinnings of tumor development and progression, clinical research platforms largely focused on evaluating the potential benefits of novel targeted therapeutics possessing unique mechanisms of action and safety profiles have led to improved outcomes in many large and rigorous clinical trials across many different tumor types. The successes yielded by this rational approach to the design and evaluation of new therapies have in turn provided medical oncologists and patients with many additional beneficial FDA-endorsed treatment options.

Although it is indisputable that new and effective treatments are good for all, it is interesting to note that minimal publicly accessible information exists regarding how, if at all, new therapies are being incorporated into practice and what factors may affect this dynamic. Even more, it is poorly documented whether the influx of new agents and the accompanying informational burden are affecting community-based medical oncologists and their need for additional resources. As such, additional strategies and resources are needed to help clinicians overcome the difficulties they are now facing as they attempt to stay up to date and informed. To bridge the gap between research and patient care, this CME activity uses the input of cancer experts to frame a relevant discussion of recent research advances and newly approved agents in multiple myeloma that can be applied to routine clinical practice. This information will help medical oncologists formulate up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Recognize the recent FDA approvals of carfilzomib and pomalidomide, and identify clinical situations for which these agents may be appropriate therapeutic options.
- Effectively counsel patients regarding the expected efficacy and tolerability of newly approved therapeutics for the management of multiple myeloma.
- Develop practical strategies to prevent and/or ameliorate the toxicities associated with recently approved antimyeloma therapies.
- Understand practical considerations in the use of these newly approved agents in order to ensure appropriate administration and patient safety.
- Recall the design of ongoing research efforts attempting to further define the role of recently approved therapies, and counsel appropriate patients with multiple myeloma regarding potential clinical trial participation.

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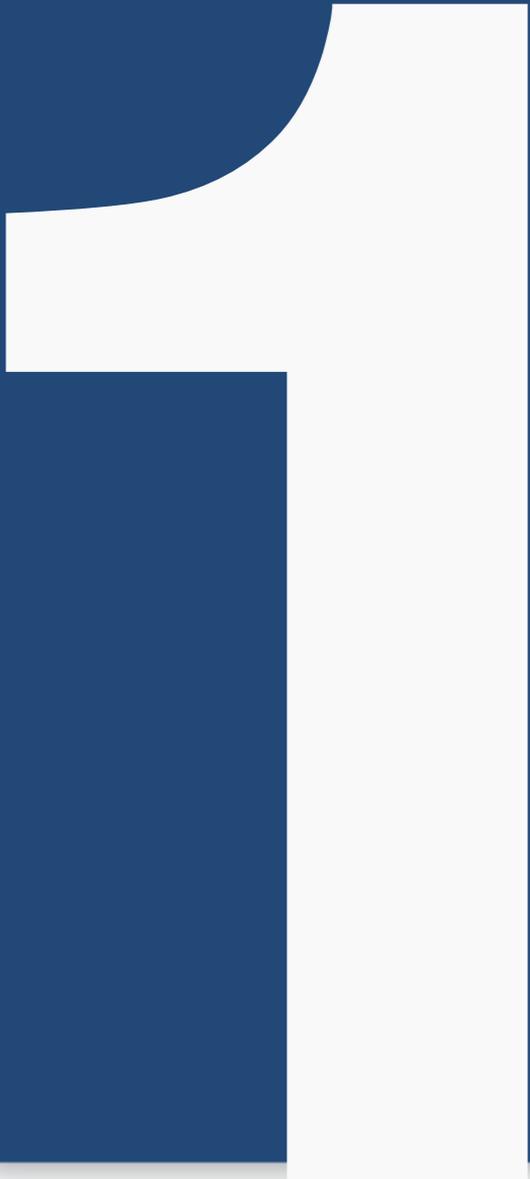
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Last review date: June 2014

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Pomalidomide





Editor's Introduction

On February 8, 2013, the Food and Drug Administration (FDA) granted accelerated approval to pomalidomide for the treatment of multiple myeloma (MM) in patients who have received at least 2 prior therapies, including lenalidomide and bortezomib, and have demonstrated disease progression on or within 60 days of completion of the last therapy. This third-generation, oral immunomodulatory agent represents an important new treatment option for individuals with this challenging disease. To provide insight into how pomalidomide can be appropriately utilized and integrated into clinical care, Drs Morie Gertz and Andrzej Jakubowiak discuss a number of practical issues regarding this agent's safety, efficacy and administration.

Mechanism of action

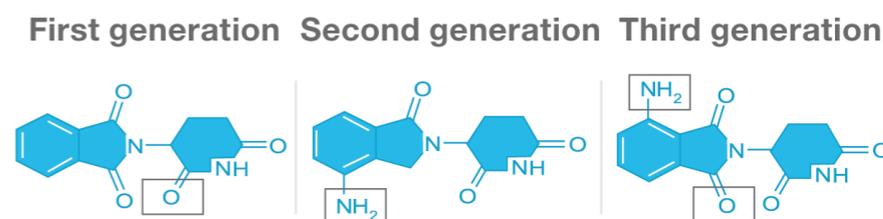
DR LOVE: Morie, would you compare the chemical structure of pomalidomide to that of lenalidomide and thalidomide?

DR GERTZ: Pomalidomide is a third-generation immunomodulatory drug (IMiD), with thalidomide being the first and lenalidomide being the second generation of these agents. The molecular structures of the 3 agents are remarkably similar. If you looked at the chemical structure and blinked, you wouldn't even be able to tell the difference. However, in terms of potency, efficacy and toxicity they are vastly different agents (Latif 2012; Figure 1).

For example, thalidomide doses range from 100 to 200 mg/day. For lenalidomide the doses are about a tenth of that — 15 to 25 mg/day. And when you consider pomalidomide, the doses range from 1 to 4 mg/day, so

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MOLECULAR STRUCTURE AND PHARMACOKINETICS OF THE IMiDS



Thalidomide Lenalidomide Pomalidomide

	Thalidomide	Lenalidomide	Pomalidomide
Administration	Oral	Oral	Oral
Dose	50-200 mg	15-25 mg	1-4 mg
Metabolism/ excretion	Hepatic/ nonrenal	Renal (67% unchanged)	Renal (67% unchanged)
Half-life	4-9 hours	3.1-4.5 hours	6.2-7.9 hours
Dose adjustments	None	Adjust for moderate to severe renal impairment	None

Adapted from Latif T et al. *Exp Hematol Oncol* 2012;1(1):27; Rajkumar SV et al. *J Clin Oncol* 2006;24(3):431-6; Dimopoulos MA et al. *Leukemia* 2009;23(11):2147-52; Richardson PG et al. *Blood* 2014;123(12):1826-32.

it's 5-fold more potent than lenalidomide.

DR LOVE: What's your vision of the molecular mechanism of action of IMiDs in MM?

DR GERTZ: They all appear to act by the same mechanism, by inhibiting a specific ubiquitin-binding protein called cereblon, which has been described by Leif Bergsagel and Keith Stewart, and it appears that the levels of the protein predict responsiveness to IMiDs. For those who aren't familiar, initially cereblon was found to be a protein that binds thalidomide, which like lenalidomide acts by targeting transcription factors.

The gist here is that if the myeloma cells do not express cereblon then no binding, no ubiquitination and ultimately no effect on myeloma cell lines occur. This concept was then taken into the clinical realm, where researchers evaluated bio-banked samples from patients who had undergone treatment with lenalidomide and pomalidomide. Patients with low cereblon expression did not respond. So I believe the potential exists to examine cereblon expression in patients' plasma cells and determine whether administering an IMiD is appropriate.

Expression of cereblon does not guarantee activity, but failure to express cereblon almost certainly means nonresponsiveness to IMiDs.

DR LOVE: What are your thoughts on the presentation by Schuster and colleagues at ASH 2012 on cereblon expression after pomalidomide and dexamethasone in patients with MM?

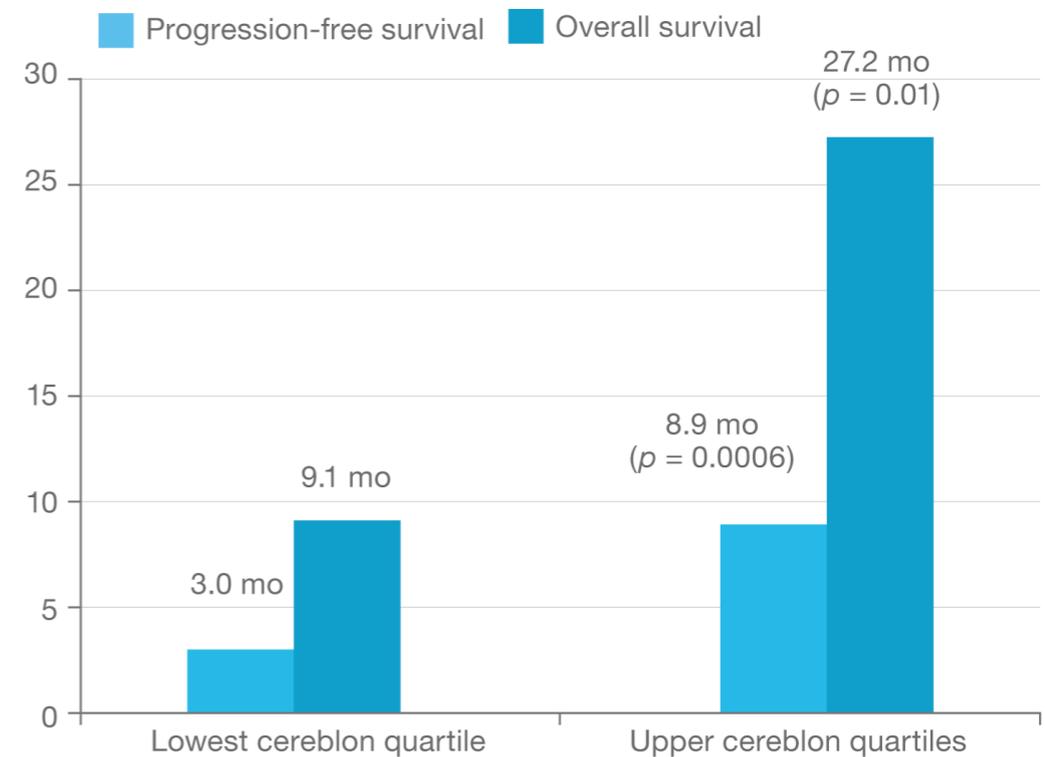
DR GERTZ: This abstract from Keith Stewart's group stated that cereblon expression predicts response and progression-free and overall survival (Schuster 2012; Figure 2). Basically that is the clinical affirmation that with all IMiDs — not just thalidomide and lenalidomide but also pomalidomide — if you don't express cereblon, then the likelihood of response is low.

DR LOVE: Do you see this technology coming into the clinic?

DR GERTZ: I would envision so, especially when you consider the fact that these agents are not inexpensive. At the same time, clinicians don't want to invest 3 or 4 months trying to figure out if an agent is going to work. I'm sure most clinicians have heard the oncology buzzword *individualized* cancer care, and measurement of cereblon is truly a method to determine whether it would be appropriate or inappropriate to consider administering an IMiD. So I believe this will have a role because the negative predictive value is high. If cereblon is not expressed, then an

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HIGHER CEREBLON EXPRESSION PREDICTS A 3-FOLD INCREASE IN SURVIVAL AFTER POMALIDOMIDE AND DEXAMETHASONE (N = 148)



Schuster SR et al. *Proc ASH 2012*; Abstract 194.

IMiD is not going to work. If it is expressed, then an IMiD is worth a try, but it's not a guarantee of efficacy.

DR LOVE: Overall, do you believe IMiDs are working via an immune-based mechanism?

DR GERTZ: I suspect the term immunomodulatory was used in the first place because of anti-angiogenic activity. It's clear that these agents also have apoptotic activity and direct cytotoxic activity. So the original use of thalidomide was somewhat empiric based on anti-angiogenics but not with a clear-cut understanding of the mechanism of action. Now the subsequent-generation drugs have been tested through their ability to kill plasma cells both in vitro and in animal tumor models in myeloma.

DR LOVE: Does the antitumor effect act by directly affecting the myeloma cells or somehow through the microenvironment?

DR GERTZ: I believe it could be both. I don't think it's possible to separate the mechanism of action at this point, however. The possibility that it has a microenvironment effect is real because a large number of reports indicate that thalidomide is not particularly effective in extramedullary myeloma, which is a form of myeloma that has escaped the regulatory controls of the microenvironment, which keep homing the circulating B cells back into the bone marrow.

Key clinical trial results with pomalidomide

DR LOVE: Would you discuss what was observed during the early-phase clinical trials of pomalidomide in MM (Lacy 2013; Figure 3)?

DR GERTZ: Two main groups have led these research efforts. The group at the Dana-Farber Cancer Institute performed successive pomalidomide trials, the first of which were in patients with relapsed MM (Jagannath 2012; Richardson 2014). They've also run trials for patients with IMiD-resistant disease and those with both IMiD- and proteasome inhibitor-resistant disease, using primarily a 4-mg dose administration.

Researchers at the Mayo Clinic have also performed similar successive studies. Of course, the response rates fall from 50% to 25% or 30% as you study the agent in more refractory disease, but it's shocking to evaluate 2 studies performed at 2 different institutions with such remarkably similar results. So even though the patient populations may be different, the efficacy of pomalidomide in studies from Paul Richardson's work at Dana-Farber and Martha Lacy's work at the Mayo Clinic provides confidence that 25% to 30% of patients with heavily pretreated disease and those with disease refractory to both bortezomib and lenalidomide can still respond to this agent (Figure 3).

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EARLY CLINICAL TRIALS OF POMALIDOMIDE (POM): EFFICACY IN PATIENTS WITH DISEASE REFRACTORY TO LENALIDOMIDE, BORTEZOMIB OR BOTH

Bortezomib refractory	Regimen	No. of prior therapies (range)	ORR
Lacy 2009	Pom + d	1-3	60%
Lenalidomide refractory	Regimen	No. of prior therapies (range)	ORR (range)
Lacy 2010	Pom + d	1-3	23%-38%
Lacy 2009	Pom + d	1-3	63%
Dual refractory	Regimen	No. of prior therapies (range)	ORR (range)
Leleu 2013	Pom + d	2-14	30%-47%
Richardson 2013	Pom ± d	2-17	21%
Jagannath 2012	Pom + d	≥2	25%
Lacy 2011	Pom + d	2-11	43%-49%
Lacy 2009	Pom + d	1-3	60%

d = low-dose dexamethasone; ORR = overall response rate

Lacy MQ, McCurdy AR. *Blood* 2013;122(14):2305-9; Richardson PG et al. *Blood* 2013;121(11):1961-7.

DR LOVE: Can you discuss the Phase II MM-002 trial that led to the approval of pomalidomide (Figure 4)?

DR GERTZ: This randomized Phase II trial compared pomalidomide with weekly dexamethasone to pomalidomide alone. The key here is this was a cohort of patients with heavily pretreated disease who had received 2 or more prior therapies, but more important, these patients had to have experienced disease progression within 2 months of their last therapy. So these were not patients who stopped treatment 2 years ago, experienced relapse and then received pomalidomide. These were patients whose disease was refractory within 2 months, so clearly they were experiencing relapse on therapy, which is known to be an adverse factor in patients with myeloma.

Outcomes were independently reported whether prior treatment with lenalidomide, bortezomib or both had failed or whether or not patients had extramedullary disease, which is another known adverse factor. We're talking about a group with highly refractory disease, and still pomalidomide demonstrated significant activity. It was clear that using pomalidomide with low-dose dexamethasone produced better outcomes than just using pomalidomide alone. Toxicity was pretty much equal between the 2 groups because pomalidomide is not a neurotoxic drug.

The clinical benefit of a month or 2 of improved progression-free survival doesn't sound like a lot, but inevitably pomalidomide will be moved up from multiply relapsed disease to patients with 1 relapse. Presumably in the future we'll be using pomalidomide for patients with newly diagnosed MM. So the issue here isn't that month or 2 of progression-free survival benefit but that a signal of activity is clear in patients for whom everything else has failed.

DR LOVE: What was the thinking in having the key issue be the corticosteroid addition?

DR GERTZ: A couple of studies have evaluated "on-demand corticosteroids" because nonhematologic toxicities associated with dexamethasone, such as mood swings, fluid retention and insomnia, are hard for our patients. In fact, few patients can tolerate the standard 40-mg weekly dexamethasone dose. So attempts to find a steroid-free regimen were designed to reduce toxicity. But the reality here is that pomalidomide is better with dexamethasone even if it is also more toxic.

In true practice, what ends up happening for most patients is they'll start with 40 mg once a week. By 4 months, more than half will require a reduction to 20 mg once a week because for most patients an indefinite exposure to 40 mg weekly is unsustainable. Many patients will then need to have the dose reduced to less than 20 mg, down to 12 mg or

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MM-002 AND MM-003: SURVIVAL OUTCOMES AND BEST RESPONSE RATES

	MM-002 ¹		MM-003 ²	
	Pom + d (n = 113)	Pom (n = 108)	Pom + d (n = 302)	D (n = 153)
Median PFS	4.2 mo	2.7 mo	4.0 mo	1.9 mo
	HR 0.68, <i>p</i> = 0.003		HR 0.48, <i>p</i> < 0.0001	
Median OS	16.5 mo	13.6 mo	12.7 mo	8.1 mo
	HR 0.94, <i>p</i> = 0.709		HR 0.74, <i>p</i> = 0.0285	
Overall response rate	33%	18%	31%	10%

Pom = pomalidomide; d = low-dose dexamethasone; D = high-dose dexamethasone; PFS = progression-free survival; HR = hazard ratio; OS = overall survival

¹ Richardson PG et al. *Blood* 2014;123(12):1826-32. ² San Miguel J et al. *Lancet Oncol* 2013;14(11):1055-66. San Miguel J et al. *Proc ASH* 2013;Abstract 686.

8 mg, and some have it discontinued. The toxicity of dexamethasone far exceeds the toxicity of pomalidomide.

DR LOVE: What were some of the most common adverse events reported on the MM-002 study (Richardson 2014; Figure 5), and what side effects have you noted in clinical practice?

DR GERTZ: Myelosuppression is fairly typical for an IMiD in a population of patients with heavily pretreated disease. Most nonhematologic toxicities were in the 10% range, which I believe is manageable. Patients can experience pneumonia, but, of course, infections in patients who have heavily pretreated disease and are receiving high-dose corticosteroids even weekly may not be directly related. Overall, I'd say this is a manageable regimen.

In my experience with lenalidomide and pomalidomide, my sense has

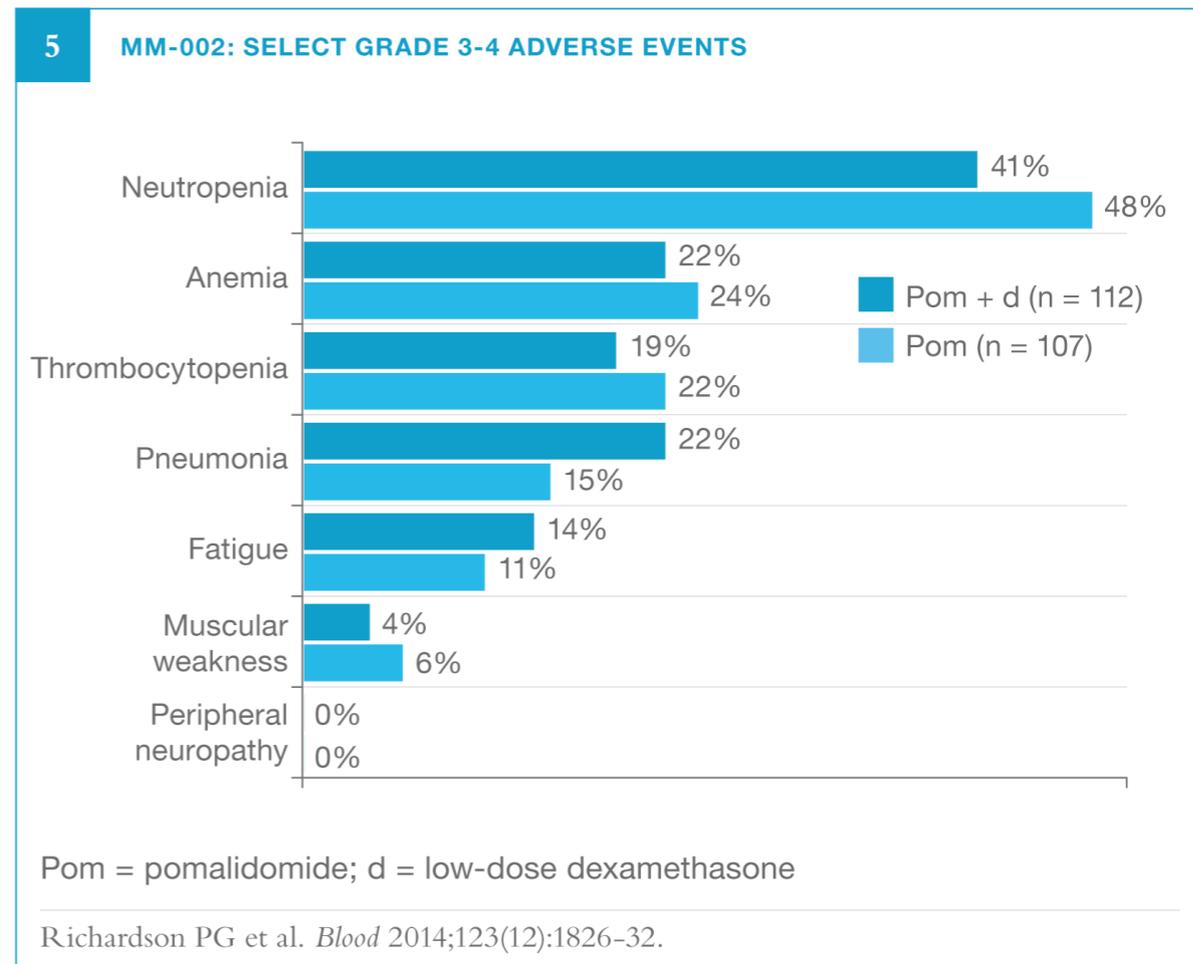
been that cutaneous toxicities such as skin rashes seem to be somewhat more limited with pomalidomide than was previously reported with lenalidomide in a similar population. Another toxicity I've noticed is cramping. The cramping is not a dose-limiting toxicity, but it's bothersome for a lot of patients taking lenalidomide. Those cramps appear less frequently with pomalidomide.

DR LOVE: Did we learn anything from the MM-003 trial, which evaluated pomalidomide in combination with low-dose dexamethasone versus high-dose dexamethasone, that wasn't observed in the pivotal study?

DR GERTZ: MM-003 would be considered a regulatory trial in which you would be able to demonstrate improved outcomes with pomalidomide and low-dose dexamethasone when compared to the previous standard, dexamethasone. That was the pathway for approval both in terms of thalidomide and lenalidomide.

When you evaluate the efficacy results from the MM-003 study, significant benefits were observed in terms of overall and progression-free survival with the combination (San Miguel 2013; Figure 4). This regimen had activity in patients with high-risk cytogenetics, the worst of which is del(17p) (Dimopoulos 2013a). In addition, patients with lower-stage disease and normal LDH had longer time to progression and overall survival (Leleu 2014). So the biologic predictors still help.

Another abstract by this group also demonstrated that pomalidomide and low-dose dexamethasone could be used in patients with impaired renal function (Seigel 2012), and another reported an improvement in health-related quality of life (Dimopoulos 2013b). Not all measures were improved with the combination, but fatigue and emotional functioning were better. I believe these are critical studies that will lead to widespread, global approval of pomalidomide.



Role for patients with renal impairment

DR LOVE: Would you elaborate a little more about the safety of using pomalidomide in patients with renal impairment?

DR GERTZ: At presentation about 50% of patients with MM exhibit renal insufficiency. About half of those cases result from proven myeloma cast nephropathy. It's known that IMiDs undergo renal excretion, so concerns exist about excessive toxicity if you administer these agents in patients who have reduced creatinine clearance. The investigators evaluated a cohort of about 110 patients, of whom a little more than a third had some degree of renal insufficiency, and examined the magnitude of both hematologic and nonhematologic adverse events. The truth of the matter

is, without dose modification the frequency of adverse events was the same independent of baseline renal functioning.

Now the numbers aren't big — 14 patients with a creatinine clearance of 45 to 60 mL/min and 26 with a creatinine clearance of less than 45 mL/min — but it looks like it ought to be reasonably safe to administer pomalidomide in this group of patients without modifying the dose.

DR JAKUBOWIAK: I would say pomalidomide can be administered fairly safely to patients with renal insufficiency. We need more data, but that's what has emerged so far from all the studies.

DR LOVE: Would you say there's a difference in that regard compared to lenalidomide?

DR GERTZ: We have dosing guidelines for lenalidomide. With lenalidomide it is recommended that the dose be reduced from 25 mg to 15 mg, then to 10 mg and down to 5 mg per day in patients undergoing dialysis based on pharmacokinetic rather than toxicologic studies.

The MM-003 study results suggested that you don't even have to do a dose modification to safely administer pomalidomide. But what isn't clear is whether patients with renal insufficiency long term will be able to sustain it. Keep in mind that the duration of therapy for these patients, because of the short relapse-free survival, was relatively short. We don't know whether that's going to be a tolerable dose 6 to 12 months in. So I would reserve final comment.

Current clinical application

DR LOVE: In which specific clinical situations are you currently using pomalidomide?

DR GERTZ: Because of the insurance considerations, you have to be careful

that you're prescribing within the approved indication, which is that patients have to have received 2 prior therapies that included both lenalidomide and bortezomib and they must have experienced disease progression within 60 days of stopping either the lenalidomide or bortezomib. So this is a dual-refractory population of patients, either with rising M protein on treatment or a response that is lost within 2 months of the cessation of therapy.

Reimbursement issues aside, I'm so impressed with the low toxicity associated with the agent. I believe it's easier to use than lenalidomide and I believe someday it will achieve approval as initial therapy and will replace lenalidomide completely. So if cost weren't a consideration, I would be moving pomalidomide up the line in terms of its use in treating myeloma.

DR LOVE: Let's take a step back and talk about what you initially discuss with patients about to begin therapy with pomalidomide/low-dose dexamethasone. What are some of the aspects you educate them about?

DR GERTZ: First I explain that like the other IMiDs, pomalidomide is administered orally on a 21-day out of 28-day basis. I discuss that pomalidomide should be taken on a fasting stomach and that patients should not eat any food within 2 hours of the dose to be absolutely certain that nothing affects absorption. As with all IMiDs, I talk to them about the risk of deep venous thrombosis. Also, even though the risks are low, I talk to them about skin rash because otherwise I'll get a phone call 4 days later and we may have to start and stop drug and initiate topical steroids. I tell them we're going to need to monitor their counts because the regimen could suppress their white count and platelet count, particularly over time. I warn them about musculoskeletal cramping because that can be problematic for patients. Those are the big things that I talk about.

Additionally, because we know of a risk of second cancers in patients who receive lenalidomide, it's likely this will also turn out to be the case with

pomalidomide. But I have not yet been talking about second cancers to my patients because they are receiving this combination in the refractory setting. The immediate threat is trying to salvage them from multiply relapsed disease — it's not second cancers 4 years from now — so I don't focus on that.

Side effects and toxicities

DR LOVE: Andrzej, what's your take on the key side effects you consider when starting patients on pomalidomide?

DR JAKUBOWIAK: The main issue with pomalidomide is myelosuppression, and that's something we must be mindful of and carefully monitor patients (Figure 5, page 10). Some patients have experienced profound fatigue and dyspnea with pomalidomide but not to the extent we have observed with lenalidomide. Those are emerging side effects. We have also observed a level of neuropathy with pomalidomide. It's probably lower than that observed with lenalidomide or thalidomide. I have observed dizziness in patients receiving pomalidomide, though to a lesser extent than has been reported with lenalidomide. In general, I consider the pomalidomide and dexamethasone combination to be well tolerated.

DR LOVE: Morie, what is your approach to follow-up for patients receiving pomalidomide?

DR GERTZ: We're following 2 issues — toxicity and efficacy. So every 28-day cycle, I monitor protein markers to ensure that we're seeing at least stabilization of the disease that's been progressive up to this point. I also perform a relatively brief evaluation for potential toxicities, which can include thrombocytopenia-associated neutropenia. I'd also ask questions pertinent to venous thromboembolism, unilateral calf swelling, unexplained sudden onset dyspnea, those sorts of issues.

The big draw for me with pomalidomide is the fact that I haven't observed many of the problems we saw with thalidomide, such as neurotoxicity and skin and gut reactions. In my practice I've observed a lower incidence of the cramping that occurs in the lower extremities and the calves that you sometimes see with lenalidomide, which, although not dose limiting, can be bothersome. Pomalidomide is a remarkably well tolerated yet highly effective systemic therapy. I find it to be a true contribution for the myeloma patient community.

DR LOVE: Andrzej, would you elaborate on the issue of venous thrombosis in these patients? What kind of prophylaxis do you use, and is your approach similar to what you do with lenalidomide?

DR JAKUBOWIAK: It's similar to what I do with lenalidomide. We have a practice that in patients with established increased risk we use enoxaparin, at least in the initial treatment phase, if not for the entire period of treatment. At the minimum, we use aspirin.

DR GERTZ: Our approach to venous thrombosis is risk associated. So, in the average patient who has no predisposition to venous thromboembolism, our group uses aspirin — either 81 mg or 325 mg — because we do not have data to help determine which is more appropriate.

Patients with an indwelling catheter or postoperative patients, such as those with a lytic lesion in the femur that's been pinned by an orthopedist, are a little different because they're now considered predisposed. Such patients are at a higher risk and require something more intense. We tend to administer warfarin, but warfarin use is complex in these patients. The reason for that is that most patients with myeloma, when they start treatment, need antibiotic prophylaxis in the form of a fluoroquinolone or sulfamethoxazole/trimethoprim, which complicates the use of warfarin.

Moreover, almost all of the regimens we use in myeloma involve dexamethasone once a week, even though a once-a-week pulse of

dexamethasone can affect the prothrombin time. Thus, trying to regulate the international normalized ratio (INR) during the course of IMiD-based therapy can be challenging. So I use warfarin when I have to, but I try to get away with aspirin.

DR LOVE: Have tumor flare reactions been reported with pomalidomide, similar to what's been reported with lenalidomide in lymphoid malignancies?

DR GERTZ: I haven't observed any tumor flare reactions with pomalidomide, either in terms of a systemic cytokine reaction or in terms of a sharp rise in the M protein.

DR LOVE: How is birth control addressed with patients who are receiving pomalidomide?

DR GERTZ: As with the other IMiDs, strict restrictive prescribing is required to ensure no possibility of the agent being administered to a male or female with reproductive potential.

Because of the catastrophe of the 1950s, the regulations are strict regarding the prescribing programs for these agents. Patients must take a monthly survey by telephone validating that they're not sexually active, they have no reproductive potential or, if they have reproductive potential, they are adhering to a strict program regarding birth control methods.

The requirements are such that individuals who are of reproductive age must use 2 forms of birth control. That includes men because it is unknown whether pomalidomide is excreted into the semen. Even men who've had vasectomies could have active agent in their semen.

DR LOVE: Do you alter the dose of pomalidomide for elderly patients?

DR GERTZ: I do not adjust the dose for elderly patients. Pomalidomide

6 INCIDENCE OF SECOND PRIMARY MALIGNANCIES (SPM) IN PATIENTS RECEIVING LENALIDOMIDE			
Study	Patient population	Treatment	SPM
MM-015 (n = 455)	Elderly, transplant ineligible	MP	3%
		MPR	7%
		MPR-R	7%
IFM 2005-02 (n = 608)	Newly diagnosed, post SCT	Placebo	4%
		Lenalidomide	8%
CALGB-100104 (n = 460)	Newly diagnosed, post SCT	Placebo	2.6%
		Lenalidomide	7.8%

M = melphalan; P = prednisone; R = lenalidomide; SCT = stem cell transplant

Latif T et al. *Exp Hematol Oncol* 2012;1(1):27.

causes myelosuppression, but I know how to deal with it easily. And because these patients are by and large those with dual-refractory disease, I don't want to start low, see no response and think maybe I didn't administer enough. So I'll come in right out of the starting gate with a full dose for elderly patients, and I'll manage the myelosuppression.

DR LOVE: Do we have any information now in terms of second cancers with pomalidomide?

DR GERTZ: Not yet. Obviously, a 3% to 4% increase in myelodysplasia and acute leukemia has been reported in patients who received lenalidomide and who have previously received melphalan (Attal 2012; McCarthy 2012; Latif 2012; Figure 6), but those data aren't available yet for pomalidomide.

DR LOVE: What number do you have for lenalidomide alone, without a prior alkylating agent or melphalan?

DR GERTZ: We don't have much experience because either the patients received autotransplant prior or they received melphalan/prednisone/

lenalidomide. The data are mostly limited to the ECOG studies that evaluated lenalidomide/dexamethasone, and we have not observed an increased risk of second cancers in that population. If you review the Mayo Clinic data on more than 1,000 patients, we've only had 1 patient who developed MDS on lenalidomide, which was not associated with prior melphalan exposure.

Future research areas

DR LOVE: What are some of the large ongoing trials evaluating pomalidomide in MM?

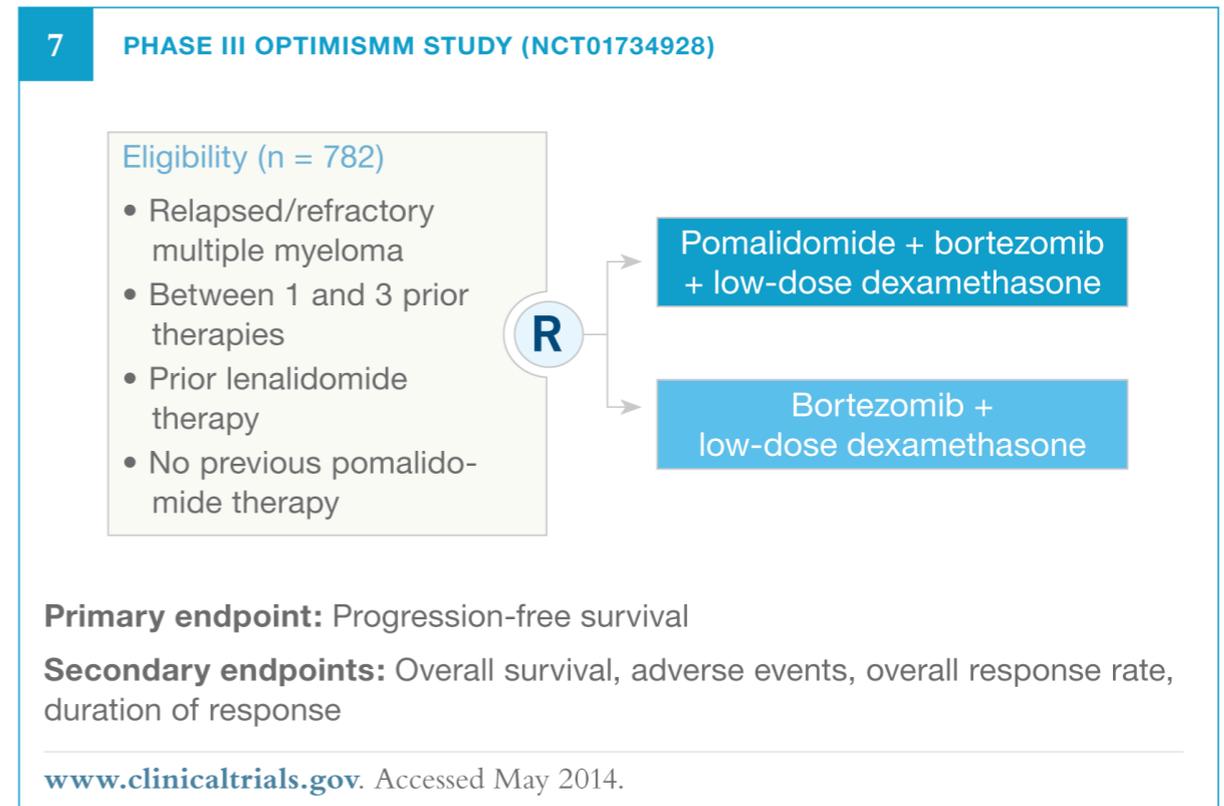
DR GERTZ: The large Phase III trial called OPTIMISMM is combining pomalidomide with bortezomib and low-dose dexamethasone (Figure 7). Clearly that's a logical approach to evaluate because one of the current US standards for patients with relapsed MM is lenalidomide/bortezomib/dexamethasone (RVD).

Because pomalidomide exhibits activity in patients with lenalidomide-refractory disease, it makes perfect sense to study the combination of pomalidomide/bortezomib and dexamethasone. The estimated enrollment is 782 patients, so this is a large trial.

Bortezomib is administered in its original standard dosage. Obviously issues exist with regard to the standard dosing of bortezomib, which may turn out to have significant neurotoxicity associated with it, but of course that's the approved labeling.

DR LOVE: If that trial is positive, do you think we'll then be evaluating the pomalidomide/bortezomib/low-dose dexamethasone combination in the up-front setting?

DR GERTZ: RVD is probably the number 1 induction regimen used in the community for newly diagnosed myeloma, and that is exactly how it



migrated to that setting. So I can see the rationale for potentially using pomalidomide/bortezomib/dexamethasone up front.

DR LOVE: Are you interested in any other current trial concepts involving pomalidomide?

DR JAKUBOWIAK: We have an ongoing study through the Multiple Myeloma Research Consortium evaluating an interesting combination — pomalidomide/carfilzomib/dexamethasone — for patients with relapsed/refractory MM (NCT01665794).

I believe that pomalidomide has more activity individually than lenalidomide. It has been shown to reverse refractory status to lenalidomide and appeared to be more active as an individual agent in less pretreated disease in early development. I believe this is an important combination that we should develop further.

I am disappointed that currently the use of pomalidomide is limited to patients who have been previously exposed to lenalidomide, which limits its development. I believe it should be moved to earlier phases of myeloma, taking advantage of the well-established activity and potentially taking the best of both worlds — a proteasome inhibitor and an IMiD — and combining them in an earlier setting. I would like to see a clinical trial evaluating carfilzomib, pomalidomide and dexamethasone for patients with newly diagnosed myeloma sooner rather than later.

DR GERTZ: Obviously, everywhere that lenalidomide has been used we are starting to think about pomalidomide. So pomalidomide is under evaluation with proteasome inhibitors and with alkylating agents in the relapsed/refractory setting. At some point the question will arise about pomalidomide for patients with newly diagnosed MM. I believe combinations such as pomalidomide/dexamethasone, pomalidomide/bortezomib/dexamethasone, pomalidomide/carfilzomib/dexamethasone and pomalidomide/cyclophosphamide/dexamethasone are all reasonable options for eventual clinical investigation in the newly diagnosed setting. A trial of the oral proteasome inhibitor ixazomib (MLN 9708) and pomalidomide is also ongoing (NCT02004275).

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Carfilzomib

2



Editor's Introduction

The clinical development of carfilzomib in many ways mimics that of pomalidomide in that it represents the “next generation” in an important class of agents. Approved on July 20, 2012 for the treatment of MM in patients who have received at least 2 prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of the completion of the last therapy, carfilzomib is now being evaluated in a number of clinical situations, including the induction setting. To gain some perspectives on where we are and where we are going with this novel therapeutic agent, we asked Drs Gertz and Jakubowiak to discuss key data leading to its FDA approval as well as a number of practical issues regarding the agent’s safety, efficacy and administration.

Mechanism of action

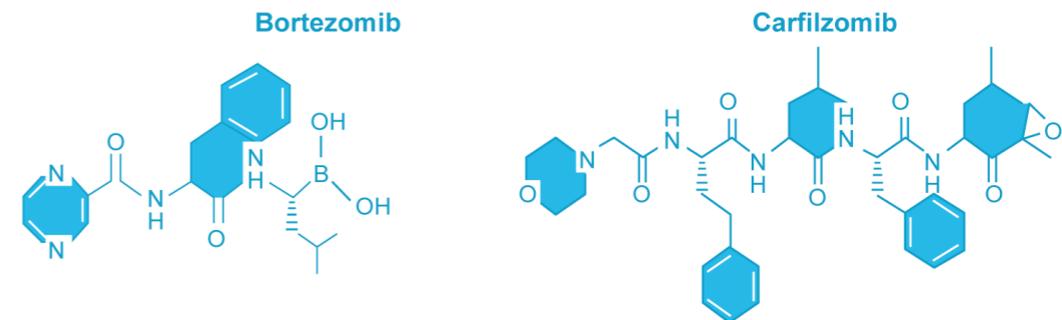
DR LOVE: Andrzej, would you compare the similarities and differences in the mechanisms of action of carfilzomib to that of bortezomib?

DR JAKUBOWIAK: Inhibition of the proteasome leads to increased probability of apoptosis of cancerous myeloma cells. Until recently, we had only 1 proteasome inhibitor approved in myeloma — bortezomib.

An important part of early and subsequent development of bortezomib (Buac 2013) and other proteasome inhibitors, which is important in the context of carfilzomib, was that these agents are not only active on their own. They also improve the efficacy of other agents established as active in myeloma, including traditional agents like cytotoxic drugs and IMiDs like thalidomide and lenalidomide (Wang 2007; Richardson 2009).

8

MOLECULAR STRUCTURE AND PHARMACOKINETICS OF CARFILZOMIB VERSUS BORTEZOMIB



Characteristic	Bortezomib	Carfilzomib
Active moiety	Boronate	Epoxyketone
Subunits inhibited		
Constitutive proteasome	$\beta 5, \beta 1$	$\beta 5$
Immunoproteasome	$\beta 5i$	$\beta 5i$
IC₅₀, nM		
Chymotrypsin	2.4-7.9	6
Trypsin	590-4,200	3,600
Caspase	24-74	2,400
IC ₅₀ against RPMI 8226 MM cell line, nM	5.7	5
Binding kinetics	Slowly reversible	Irreversible
Half-life, minutes	110	<30
Route of administration	IV/SC	IV

IV = intravenous; SC = subcutaneous

Adapted from Arastu-Kapur S et al. *Clin Cancer Res* 2011;17(9):2734-43; Moreau P et al. *Blood* 2012;120(5):947-59.

Those results established further development of agents in both classes with the understanding that new agents may have (1) differential activity because of differences in their chemical structure and (2) potentially

different side-effect profiles. That brings us to carfilzomib as the next generation and the second approved proteasome inhibitor for multiple myeloma. It has a different chemical structure than that of bortezomib (Arastu-Kapur 2011; Figure 8) — that’s the first difference.

Number 2, it is more specifically targeting 1 of 3 subunits of the proteasome — an important difference. Initially, it was unknown whether this aspect of carfilzomib’s structure would be a vulnerability or an advantage, but it turned out to be an advantage. We do not understand why yet, but it seems to have some potential advantages.

Number 3, in contrast to bortezomib, which is a reversible proteasome inhibitor, carfilzomib is an irreversible proteasome inhibitor. Whether this feature is critical to differences noted in the clinic is still under investigation, but it is presumed that these characteristics have led to the following: First, in the preclinical setting and also in the clinic, carfilzomib may be active either in cell lines that are refractory to bortezomib or in patients with disease that has previously been refractory to bortezomib. That is an important feature, regardless of the mechanistic aspects of the agent.

Second, we have noted a difference in the toxicity profiles of these drugs. This could either be a reflection of more specific targeted inhibition of the chymotrypsin subunit, which is the primary target for bortezomib, or may relate to bortezomib’s potential activity with other subunits (Moreau 2012; Figure 8).

This may be important because some people argue that some of the off-target, or maybe multiple-target, effects result in the higher prevalence of peripheral neuropathy associated with bortezomib, which I can safely say is now established as much less prevalent with carfilzomib.

9 PX-171-003-A1 (PIVOTAL CARFILZOMIB STUDY): SURVIVAL OUTCOMES AND BEST RESPONSE RATES

Responses	All patients (n = 257)	Patients with unfavorable cytogenetics (n = 71)
Overall response rate	23.7%	29.6%
Complete response	0.4%	0%
Very good partial response	5.1%	4.2%
Partial response	18.3%	25.4%
Minimal response	13.2%	4.2%
Stable disease	31.5%	39.4%
Progressive disease	26.8%	21.1%
Clinical benefit rate	37.0%	33.8%
Median progression-free survival	3.7 mo	3.6 mo
Median overall survival	15.6 mo	Not reported
Median duration of response	7.8 mo	6.9 mo

Siegel DS et al. *Blood* 2012;120(14):2817-25.

Key clinical trials leading to FDA approval

DR LOVE: Morie, would you discuss the Phase II PX-171-003-A1 trial in relapsed and refractory MM that led to the approval of carfilzomib (Figures 9 and 10)?

DR GERTZ: This trial accrued 266 patients with relapsed/refractory disease. The median number of prior lines of therapy was 5, although it was only required that at least 1 prior regimen had failed. Carfilzomib was administered according to the currently FDA-approved schedule with a reduced dose for the first 2 doses to avoid tumor lysis syndrome. The primary trial endpoint was overall response rate, with response duration and progression-free survival as secondary endpoints.

Given that patients received a median of 5 prior regimens, I thought the reported overall response rate of 24% and median duration of response of

7.8 months were reputable. A number of other important facets emerged from this trial. Carfilzomib was well tolerated and didn't cause issues such as peripheral neuropathy. In fact, the rate of Grade 3/4 peripheral neuropathy was only 1.1%. Only 1 in 8 patients, or about 12.5%, withdrew from therapy.

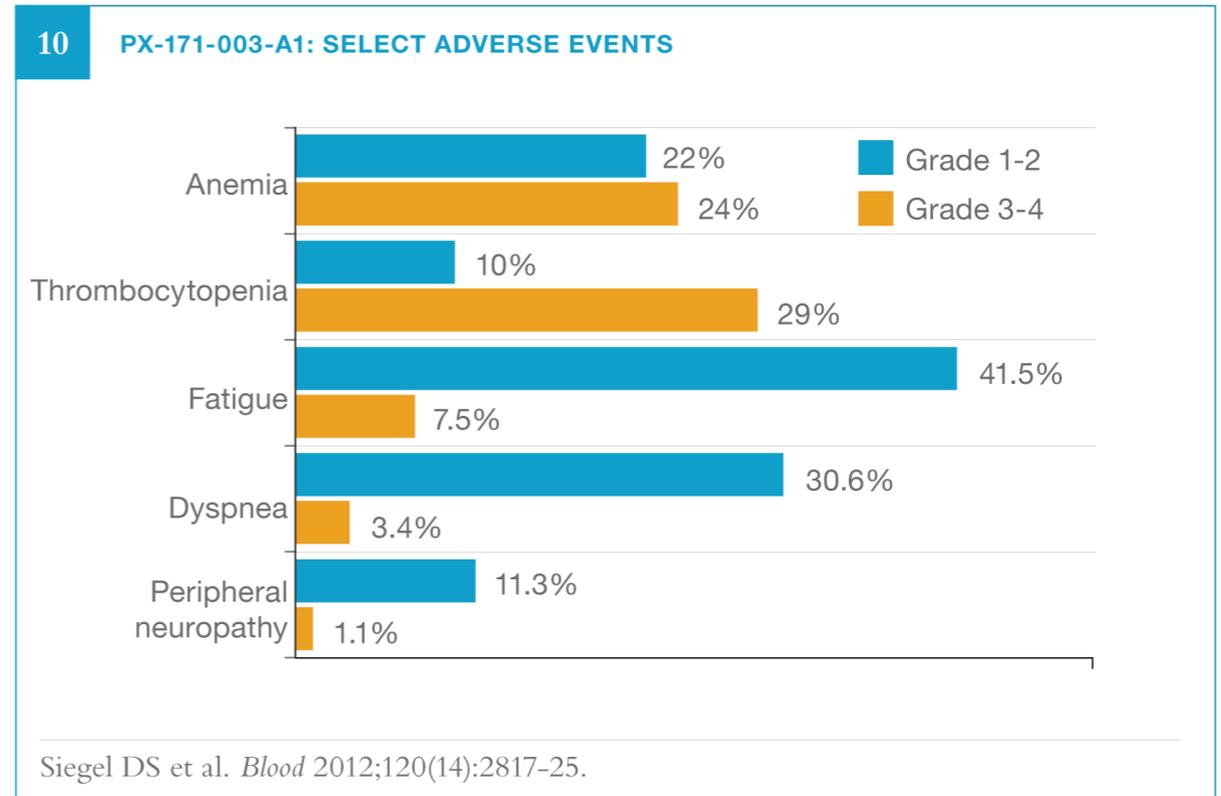
Carfilzomib also appeared to be active in all the various subsets based on age, gender, genetics and renal function, and none of those factors appeared to affect the median response rate of 24%. The median progression-free survival was 3.7 months. That's comparable to what we discussed earlier with the pivotal pomalidomide trial, again showing a 25% salvage rate in patients who've received extensive prior therapy. In this trial all of the patients had received prior bortezomib, 94% had received prior lenalidomide, 75% prior thalidomide, 92% a prior alkylating agent and 74% a prior transplant, so these patients had been through the gamut of therapies and still experienced significant activity with this agent.

DR LOVE: What is known about the issue of cytogenetics and benefit from carfilzomib in this study?

DR GERTZ: The authors evaluated unfavorable and favorable cytogenetics. About 71 patients had unfavorable cytogenetics, so about a third of the cohort, and about 150 were normal. The overall response rate was 22.8% for patients with favorable cytogenetics and 29.6% for patients with unfavorable cytogenetics. Those 2 responses are not that different. The important aspect is that with unfavorable genetics, carfilzomib wasn't inferior.

DR LOVE: What about the issue of renal functioning on this study?

DR GERTZ: I don't believe any modifications were required for renal function. They studied patients with normal renal function, and patients were allowed on study as long as they had a creatinine clearance of 30 mL/



minute. No difference was observed in overall response rate, and no dose modification was specified in the protocol based on renal function.

Cardiac and pulmonary toxicity

DR LOVE: Would you compare and contrast the toxicity profiles of bortezomib and carfilzomib?

DR JAKUBOWIAK: Some potential differences in tolerability and toxicity may occur. Some may favor carfilzomib, such as lack of peripheral neuropathy, but others may favor bortezomib. We have observed some cardiomyopathies and even other rare issues including lung toxicities with carfilzomib.

DR LOVE: Morie, what about the issue of cardiac events and pulmonary symptoms with carfilzomib?

DR GERTZ: On the pivotal trial, dyspnea was reported in nearly a third of the patients. No direct reports of cardiotoxicity occurred, but I believe people are concerned about this potential. I know it's being monitored carefully as the trials go on.

I believe all investigators have observed patients who've reported dyspnea and tachycardia associated with the administration of this agent. It's difficult to define whether it induces clear cardiotoxicity. Investigators have tried to deal with this by recommending slowing of the infusion time, and although it's not in the peer-reviewed literature, apparently patients experience less dyspnea when you slow the infusion time down to about 30 minutes (Papadopoulos 2011).

DR GERTZ: We don't perform any active cardiac monitoring. We did the standard chest x-ray and EKG. I do not perform echocardiography. I do not conduct an ejection fraction assessment before I start the carfilzomib. I ascertain whether there's any cardiac history at all, and then I proceed straight to therapy. When the infusion is administered, we quiz the patient as to whether they have any shortness of breath.

DR LOVE: Andrzej, do you believe that carfilzomib causes cardiomyopathy?

DR JAKUBOWIAK: I have not observed definite evidence of cardiac toxicity, even if I am aware of reports of it from our own CRd trial in newly diagnosed myeloma. We've not noted any cardiac events associated with carfilzomib treatment. We did have a small number — fewer than 10% of patients — complaining of dyspnea or shortness of breath. That's still being evaluated as one of the features associated with carfilzomib and not necessarily as much with bortezomib.

Cardiopulmonary issues have been reported. Some people feel strongly about them. Others, including myself, are not convinced that they are as strong. I believe these to be brief, reversible issues that are related to quick

tumor reduction in the initial phase of therapy.

Again, using our CRd trial as an example, in the initial phase of treatment we observed a couple of cases of this nature, which we attributed to CRd, but retrospectively we believed that they were related in part to overaggressive hydration. We did not note any dyspnea or shortness of breath in patients enrolled in the study later on once we realized that overhydration may have been contributing to that phenomenon.

Now, is this something that is exclusively related to overhydration? I suspect that it is a combination of factors. In the setting of fluid overload, there may be a higher propensity for developing some transient shortness of breath, which is easily reversible and manageable.

DR LOVE: Do you believe there's any evidence of direct pulmonary toxicity associated with carfilzomib?

DR JAKUBOWIAK: Not that I am aware of. Again, in my own experience, all of these issues were reversible. I would not be surprised if these types of issues were found and attributed directly to carfilzomib in less than 1% of cases. I doubt that this is direct long-lasting toxicity.

Other side effects

DR LOVE: Does carfilzomib cause peripheral neuropathy? In other words, if there hadn't been a bortezomib before this, and carfilzomib was coming out as a new agent, would it be labeled as causing peripheral neuropathy?

DR JAKUBOWIAK: In my mind, the short answer is, "No, it would not." Now, do we have reports of peripheral neuropathy with the CRd combination? We had more than 20% of patients with Grade 1/2 neuropathy on the trial, almost all of which was attributed to lenalidomide by the investigators. Lenalidomide modifications have reduced the level of

neuropathy in those cases when needed.

I am aware that in single-arm studies and in some combinations, some evidence of carfilzomib-related neuropathy has been reported. So it's always difficult in combinations to point to one agent or the other if both are potentially considered a cause of the problem. Again, speaking from my own experience, lenalidomide dose modification in all of those cases led to improvement of peripheral neuropathy. My impression is that, if there is any peripheral neuropathy associated with carfilzomib administration, it's of a minimal nature and very limited.

DR GERTZ: I have not observed any neurotoxicity with carfilzomib. Of course, a lot of the patients I'm seeing have received prior bortezomib, so I don't see increased neurotoxicity. It's not that easy to gauge, but I don't believe that patients are getting worse.

DR LOVE: Are there any other side effects you believe are associated with this agent?

DR GERTZ: You can't ignore the myelosuppression. I've never observed tumor lysis syndrome, even though it's been reported, and even though there are reports of hepatic impairment, I haven't observed that either.

DR JAKUBOWIAK: I've administered multiple therapies to patients with multiple cancers, and I've never seen such good tolerance for as long as I have observed with CRd. A great majority of patients experience essentially zero side effects.

DR LOVE: Morie, what are some of the other key points about using carfilzomib that you emphasize when you give talks or interact with your fellows?

DR GERTZ: I believe the lack of neurotoxicity is a big deal, and I am impressed with the rapidity of response. I believe carfilzomib will likely

track along with what we've observed with bortezomib in that it's highly effective and does not require any dose modification in patients with renal failure. Also, bortezomib has been shown to be effective even in patients with adverse genetics. This is where using a proteasome inhibitor becomes important because the biology is bad. I believe the same will hold true for carfilzomib.

DR LOVE: Morie, when you are about to start a patient on carfilzomib, what are some of the things that you go over with them?

DR GERTZ: I talk about the dyspnea because I don't want them to get nervous about the possibility that they'll experience shortness of breath, but I inform them that it's a temporary side effect. I warn patients that instances of tumor lysis syndrome have been reported with carfilzomib, although I have not observed any cases in my practice. In my experience a number of patients experience lower-extremity swelling, and diarrhea is fairly common with carfilzomib, as it is with bortezomib. Also, a significant proportion of patients get a headache when receiving carfilzomib. Those are the main points I emphasize to patients about to begin carfilzomib therapy.

Other key supporting Phase II studies of single-agent carfilzomib in relapsed/refractory MM

DR LOVE: Let's talk about some other key trials involving single-agent carfilzomib. Morie, what are your thoughts on the PX-171-004-AO study of carfilzomib alone for patients with bortezomib-naïve, relapsed and/or refractory MM (Vij 2012)?

DR GERTZ: The activity was high in that trial, and patients who received carfilzomib without prior proteasome inhibitor exposure had a much higher activity level. Prior bortezomib exposure reduces the response rate

to carfilzomib, but in patients with bortezomib-naïve disease carfilzomib clearly has a much higher level of activity.

Another trial by Dr Jakubowiak and colleagues evaluated single-agent carfilzomib in patients with relapsed/refractory MM and high-risk cytogenetics. They observed a difference in terms of overall survival but not progression-free survival in patients with high-risk versus standard genetics (Jakubowiak 2013). So these data reaffirm that carfilzomib has the potential to neutralize the adverse cytogenetics associated with relapsed/refractory myeloma.

DR JAKUBOWIAK: I want to stress a few other important aspects. Single-agent data from the 004 trial and subsequent evaluation of the agent as a single agent in the 007 trial gave us 2 important observations that are part of the current development of carfilzomib (Vij 2012; Papadopoulos 2011).

Number 1, a higher activity has been observed as a single agent in patients with less pretreated disease than in those with more pretreated disease. If you evaluate the 004 trial results, the overall response rate reaches 52%, partial response or better, which is in contrast to about a 24% response rate for patients with refractory disease (Kortuem 2013; Figure 11).

With all the caveats of comparison between different trials, these data give me a sense that carfilzomib is more active than bortezomib is in an equivalent patient population based on the APEX trial (Richardson 2005).

Number 2, we have learned from the 004 trial and from follow-up of the 007 trial that single-agent carfilzomib has dose-dependent activity. You will have a better overall response rate and progression-free survival with the 27 mg/m² dose starting from cycle 2 than with the 20 mg/m² dose for all patients in extended treatment. That was further supported by the results of the 007 study, in which the maximum tolerated dose was eventually established at 56 mg/m² (Papadopoulos 2011).

11

PHASE II STUDIES OF SINGLE-AGENT CARFILZOMIB (CFZ) IN RELAPSED/REFRACTORY MULTIPLE MYELOMA

Study	Phase	Setting	CFZ dosage	ORR
PX-171-003-A0	II	≥2 previous therapies, including BTZ and an IMiD	20 mg/m ²	17%
PX-171-003-A1	II	BTZ pretreated	20/27 mg/m ² (step up)	24%
PX-171-004-A0	II	BTZ naïve	20/27 mg/m ² (step up)	42%/52%
PX-171-005	II	Patients with renal impairment	15-27 mg/m ²	21%
PX-171-007	Ib/II	≥2 prior regimens	20-70 mg/m ²	60%

ORR = overall response rate; BTZ = bortezomib

Kortuem KM, Stewart AK. *Blood* 2013;121(6):893-7.

So overall, single-agent carfilzomib is active, and it appears to be more active in comparable patient populations than bortezomib. It also appears to be more active at higher doses with no dramatic change in durability between lower and higher doses.

Combination studies in relapsed/refractory and newly diagnosed MM

DR LOVE: Morie, would you comment on the 006 study of CRd in relapsed/refractory MM (Figure 12)?

DR GERTZ: This was a dose-expansion trial of CRd, and as a lot of these expansion trials do, it focused on toxicity. Lenalidomide was administered at a highly variable dose because this started as a Phase I/Phase II trial with lenalidomide at 10 mg per day, but then the maximum tolerated dose was the standard dose, 25 mg per day. Carfilzomib was escalated to its

current FDA-label dose of 20 followed by 27 mg/m² on days 1, 2, 8, 9, 15 and 16.

In the expansion cohort, patients had received a median of 3 prior lines of therapy, and the median number of cycles that had been received was approximately 10. The authors reported an overall response rate of 77%, and if you consider the overall cohort of 84 patients, which now includes the dose-escalation part, the overall response rate was 81% in the relapsed/refractory setting (Wang 2013). These results were impressive.

DR LOVE: What are your thoughts on the use of CRd as front-line therapy?

DR GERTZ: One study that evaluated CRd in this setting was published by Dr Jakubowiak and reported an overall response rate of 100% and a very good partial response rate or better of 81% with minimal neurotoxicity (Jakubowiak 2012; Figure 13, page 25). That was an exciting publication.

DR LOVE: Another study with similar results was presented at ASH (Figures 14, 15). What is known about the combination of carfilzomib/cyclophosphamide and dexamethasone (CCd)?

DR GERTZ: An abstract reported by an Italian group at ASH 2013 evaluated this combination for patients with newly diagnosed disease who were not eligible for transplant (Bringhen 2013). They enrolled 58 patients and by cycle 9 had achieved at least a partial response in almost 100% of patients and a very good partial response or better in about 80% of patients. That's impressively high activity and a high proportion of deep responses.

This trial did have a maintenance phase in which cyclophosphamide was discontinued and patients continued on a modified carfilzomib cycle on days 1, 2, 15 and 16 after they completed the 9-cycle induction. A near complete response rate or better of 68% was seen during this phase.

Study	Phase	Setting	CFZ dosage	ORR
PX-171-006 ¹	Ib	CRd in R/R	15-27 mg/m ²	78%
NCT01464034 ²	I/II	C-Pom-d in R/R	20/27 mg/m ²	70%
NCT01402284 ³	II	CRd → R in N/D	20/36 mg/m ²	98%
NCT01346787 ⁴	II	CCd in N/D	20/36 mg/m ²	96%
NCT01029054 ¹	I/II	CRd in N/D	20/27/36 mg/m ²	98%
NCT01279694 (CARMYSAP) ⁵	I/II	CMP in elderly N/D	20/27/36/45 mg/m ²	89.5%

C or CFZ = carfilzomib; ORR = overall response rate; R = lenalidomide; d = low-dose dexamethasone; R/R = relapsed/refractory; Pom = pomalidomide; N/D = newly diagnosed; M = melphalan

¹ Kortuem KM, Stewart AK. *Blood* 2013;121(6):893-7; ² Shah JJ et al. *Proc ASH* 2013;Abstract 690; ³ Korde N et al. *Proc ASH* 2013;Abstract 538; ⁴ Bringhen S et al. *Proc ASH* 2013;Abstract 685; ⁵ Moreau P et al. *Proc ASH* 2013;Abstract 1933.

Current clinical applications

DR LOVE: In terms of your use of the agent outside a protocol setting, are you generally administering carfilzomib as part of induction therapy or only in the relapsed/refractory setting?

DR GERTZ: I primarily use carfilzomib for patients with dual-refractory disease, so those whose disease has progressed on both an IMiD and bortezomib. If a patient broke through on bortezomib therapy, I'd go with pomalidomide. But if they've broken through on lenalidomide, I'd be inclined to go with carfilzomib.

DR LOVE: In what situations, if any, would you consider administering carfilzomib up front?

DR GERTZ: Currently there is an approval issue with administering carfilzomib for patients with newly diagnosed myeloma. But as we

mentioned already, the study by Dr Jakubowiak has reported data on the use of carfilzomib/lenalidomide/dexamethasone in the newly diagnosed setting, and the combination has a 100% response rate (Jakubowiak 2012; Figure 13). That’s pretty difficult to compete with.

I don’t believe that patients who present with preexisting neuropathy are good candidates to receive bortezomib, and as you know a number of patients do present with MM who also have some degree of peripheral neuropathy. I believe significant concern exists that these patients would be unduly predisposed to develop enhanced neurotoxicity with bortezomib. Because carfilzomib doesn’t cause neurotoxicity, it seems rational in those situations to consider using carfilzomib earlier in the course of the disease, although that would be off-label prescribing at this point. Once the labeling issues are resolved, it will be an appropriate agent for consideration in newly diagnosed MM.

DR LOVE: Andrzej, in what situations are you using carfilzomib?

DR JAKUBOWIAK: I now use this agent in all settings. CRd is our preferred front-line treatment regimen rather than RVD now that CRd has been added to the NCCN guidelines. On occasion I use CRd as a preferred salvage regimen in patients with intolerance or a history of refractory status, but I also may go with cyclophosphamide instead of lenalidomide in that combination.

For patients with relapsed myeloma, I use the CRd combination as well (Wang 2013; Figure 16). As you may know, we now have data demonstrating that the combination of pomalidomide, carfilzomib and dexamethasone is quite active (Shah 2013). I have now used that combination off protocol as my preferred choice for patients with advanced disease with evidence of prior refractory status to bortezomib and lenalidomide.

13 PHASE I/II STUDY OF CRd AS FRONT-LINE THERAPY FOR MULTIPLE MYELOMA

Efficacy		n = 53
Overall response rate		100%
≥Near complete response (CR)		62%
Stringent CR		42%
≥Very good partial response		81%
≥Partial response		98%
2-year progression-free survival		92%
Select Grade 3-4 adverse events		
Hypophosphatemia		25%
Hyperglycemia		23%
Thrombocytopenia		17%
Neutropenia		17%
Peripheral neuropathy (Grade 1-2)		23%

Jakubowiak AJ et al. *Blood* 2012;120(9):1801-9.

DR LOVE: How do you go about deciding between pomalidomide and carfilzomib in patients who have received neither?

DR JAKUBOWIAK: That decision is driven by prior history and characteristics of the disease. In general, we favor a proteasome inhibitor rather than an IMiD for a patient with poor-prognosis characteristics. Another modifier is a history of a response to agents from the same class. If a patient had experienced a favorable response to prior IMiD therapy, then that may sway me toward selecting pomalidomide. Alternatively, given a patient for whom a proteasome inhibitor showed good activity in the past, I would be swayed toward carfilzomib.

In my judgment, both agents would be used sooner or later in the relapsed setting. The sequence has not yet been thoroughly established in practice, and I believe every oncologist will be making their choices based on their

own assessment of what is the best agent or which has the highest likelihood of achieving response in a given patient.

DR LOVE: Do you have any thoughts in terms of relative efficacy of pomalidomide versus carfilzomib? In your mind is it kind of a “coin flip,” or do you think that one might be superior to the other?

DR JAKUBOWIAK: Comparing one label approval to another is a bit like comparing apples to oranges. As a single agent, there’s no doubt that carfilzomib is more active. Pomalidomide has marginal activity as a single agent and is approved in combination with dexamethasone. What I envision eventually happening is that these 2 clearly effective agents are likely to be approved for use in combination.

Route of administration, dosing and fluid management

DR LOVE: How do you approach dosing and infusion time for carfilzomib?

DR GERTZ: We now use the longer infusion time of 30 minutes for all of our patients. With regard to dosing, we use standard dosing, which is 20 mg/m² for the first cycle, because of early reports of tumor lysis syndrome. Then we escalate to the approved dose of 27 mg/m² with subsequent cycles, keeping in mind that the maximum tolerated dose of carfilzomib is not known. It may be that the appropriate dose could be substantially higher.

DR JAKUBOWIAK: I usually start the first 2 days at 20 mg/m², then I move to 27 mg/m². If the patient is tolerating therapy, I escalate to 36 mg/m². But I do also go from 20 to 36 mg/m² on the eighth and ninth day in patients with less tumor burden and less risk of developing any early side effects, so that’s my typical escalation schema. I don’t wait, as per label, until cycle 2 to escalate. I start escalating from day 8.

14 PHASE II STUDY OF CRD INDUCTION THERAPY

8 cycles CRd combination therapy

Cfz 20/36 mg/m², 30-min infusion

Day 1, 2, 8, 9, 15, 16

Ln 25 mg/day

Day 1-21

Dexamethasone 20/10 mg

Day 1, 2, 8, 9, 15, 16, 22, 23

SD or better?

24 cycles extended dosing

Ln 10 mg/day, day 1-21

- Each cycle is 28 days
- Stem cell harvest after ≥4 cycles of CRd for patients <75 years of age
- Cycle 1, day 1, 2: Cfz dose is 20 mg/m²
- Cycles 1-4: Dexamethasone dose is 20 mg; cycles 5-8: Dexamethasone dose is 10 mg

CRd = carfilzomib (Cfz)/lenalidomide (Ln)/dexamethasone; SD = stable disease

Korde N et al. *Proc ASH 2013*; Abstract 538.

15 RESPONSE RATES

Response	2 cycles	8 cycles	Best response*
RR (≥PR)	98%	97%	98%
≥VGPR	51%	91%	88%
nCR/CR/sCR	16%	73%	67%
CR/sCR	7%	42%	51%
VGPR	35%	18%	21%
PR	47%	6%	9%
SD	2%	3%	2%
PFS at 12 months	97%		

ORR = overall response rate; PR = partial response; VGPR = very good PR; nCR = near complete response (CR); sCR = stringent CR; PFS = progression-free survival

* Median 12 cycles of carfilzomib/lenalidomide (Ln)/dexamethasone → Ln maintenance

Korde N et al. *Proc ASH 2013*; Abstract 538.

DR LOVE: What is your dosing strategy in older patients and those with poor performance status?

DR JAKUBOWIAK: For older patients with poor performance status, I generally do not escalate beyond 27 mg/m². I stick to the label, but I do escalate earlier at day 8. I believe that the data for higher doses are still limited. I have administered 36 mg/m² for a newly diagnosed patient, but in elderly patients with relapsed disease I typically do not escalate beyond 27 mg/m². This is probably in part because I rarely administer carfilzomib alone. I typically use it in the context of a combination or on a clinical trial. It appears that when carfilzomib is combined with other agents such as CRd that 36 mg/m² may be the maximum tolerated dose.

In a front-line study of carfilzomib, 45 mg/m² was too toxic and investigators had to reduce the dose back down to 36 mg/m² (Toureau 2013).

DR LOVE: What about patients with hepatic dysfunction and renal dysfunction?

DR JAKUBOWIAK: We've observed some mild transient transaminase elevations on our CRd trial, though these have not necessarily required any dose modifications thus far. So I would be careful with using the agent in patients with hepatic dysfunction without having additional data. However, strong data show carfilzomib does not lead to renal insufficiency, and it can be safely used in patients with advanced renal disease (Badros 2013). I've been administering it in patients with creatinine clearance between 10 and 30 mL/minute and have helped some patients with light chain-related renal failure to reverse their dialysis dependence by using carfilzomib with cyclophosphamide/dexamethasone.

A small proportion of patients on our Phase I/II front-line trial of CRd experienced Grade 1 and 2 renal insufficiency, which we attributed to

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PX-171-006: PHASE II DOSE-EXPANSION STUDY OF CRd IN RELAPSED OR PROGRESSIVE MULTIPLE MYELOMA (MM)

Efficacy	n = 52
Overall response rate (ORR)	76.9%
ORR in patients with bortezomib-refractory MM	69.2%
ORR in patients with lenalidomide-refractory MM	69.6%
Median duration of response (DOR)	22.1 mo
Median DOR in patients with bortezomib-refractory MM	22.1 mo
Median DOR in patients with lenalidomide-refractory MM	10.8 mo
Median progression-free survival	15.4 mo
Select Grade 3-4 adverse events	n = 52
Lymphopenia	48.1%
Neutropenia	32.7%
Thrombocytopenia	19.2%
Anemia	19.2%

Wang M et al. *Blood* 2013;122(18):3122-8.

carfilzomib. These were transient and mild to moderate in severity (Jakubowiak 2012; Figure 13, page 25). We administered CRd to 53 patients on this trial, and most of them received 24 cycles of the regimen at reduced doses.

DR LOVE: The package insert for carfilzomib contains a set of recommendations regarding hydration and fluid management. Do you follow those exact recommendations, or do you use a different approach?

DR JAKUBOWIAK: You may recall that in the early phases of development of carfilzomib, a number of patients developed hypotension and/or GI toxicities, which were mostly eliminated by incorporating hydration. So I follow the recommendations, and for the most part it works. I believe that hydration is needed, but I have been careful for some time not to overdo it by preemptively overhydrating patients. Recently, I have been carefully

trying to keep patients on their fluid balance with an additional dose of furosemide on day 3, which is usually the time when those issues have been noted in my experience.

DR LOVE: Do you generally go ahead and administer furosemide, or do you wait and see if they develop a problem?

DR JAKUBOWIAK: I wait to see if they develop a problem, but I prepare patients for these types of developments. Again, this is a rare phenomenon, probably in the 10% range of all patients who receive treatment, and is more likely to occur in patients who have high tumor burden and experience extremely brisk responses to combination treatment.

I ask patients to call me if they develop any signs of dyspnea. Most of them do not experience any issues, but we have provided treatment for those few who have.

DR LOVE: The package insert also calls for the agent to be administered over 2 to 10 minutes. Was it ever initially administered as a push in early studies, or has it always been administered this way?

DR JAKUBOWIAK: To my knowledge, and since I began using this agent, it has always been administered over 2 to 10 minutes. Our practice is to administer it over 10 minutes. I believe that the duration of infusion could be important and some of these issues may be related to the fact that carfilzomib is sometimes administered as a push when it could be administered as a short infusion.

Higher doses of carfilzomib have been adopted as part of the ongoing ENDEAVOR trial that is evaluating carfilzomib/dexamethasone versus bortezomib/dexamethasone for relapsed MM (Figure 18). Infusions are administered over a 30-minute period because it was noted that higher doses are better tolerated with longer infusion time with preservation of improved efficacy. For now I would recommend that people stick to the

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PHASE III ECOG-E1A11 STUDY

Target accrual (n = 756)

- Newly diagnosed, symptomatic standard-risk multiple myeloma
- No prior history of Grade 2 or higher peripheral neuropathy

R

Carfilzomib + lenalidomide + low-dose dexamethasone → lenalidomide maintenance

Bortezomib + lenalidomide + low-dose dexamethasone → lenalidomide maintenance

Primary endpoint: Overall survival

Select secondary endpoints: Progression-free survival, overall response rate, duration of response

www.clinicaltrials.gov. Accessed May 2014.

package recommendations, and I would prefer 10 minutes to 2 minutes of infusion for doses up to 27 mg/m² as currently approved for carfilzomib.

Future directions

DR LOVE: What ongoing trials are evaluating head-to-head comparisons of bortezomib and carfilzomib?

DR GERTZ: That is an interesting question because all the oncologists in practice are asking whether one agent is superior. Is bortezomib better than carfilzomib, is carfilzomib better than bortezomib or are they identical? A lot of the initial data were driven by the fact that carfilzomib lacked neurotoxicity, but now that bortezomib regimens are being administered weekly and subcutaneously instead of intravenously the toxicity that's being reported with bortezomib has fallen dramatically. So neurotoxicity may not be the sole driver. People want to use the agent that is the most efficacious. So the Phase III ECOG-E1A11 trial in the United

States for patients with newly diagnosed standard-risk MM evaluating carfilzomib/lenalidomide/dexamethasone versus bortezomib/lenalidomide/dexamethasone is pertinent (Figure 17). I believe this trial will answer an incredibly important question about the superiority and up-front selection of a proteasome inhibitor.

DR JAKUBOWIAK: That study has a complex design and also has some maintenance questions incorporated into it.

Another relevant trial called ENDEAVOR is evaluating a more definitive comparison of these 2 agents for patients with relapsed disease. This study is evaluating carfilzomib at 56 mg/m² with dexamethasone to bortezomib/dexamethasone (Figure 18).

DR GERTZ: ENDEAVOR, which is an enormous global trial with a target accrual of 898 patients, will be evaluating not only toxicity but also efficacy and relapse-free survival. The trial should answer critical questions with regard to which proteasome inhibitor we want to be using in practice as we go forward.

DR LOVE: Morie, what are your thoughts on another ongoing Phase III trial, the CLARION study of carfilzomib/melphalan and prednisone versus bortezomib/melphalan and prednisone?

DR GERTZ: If you evaluate the way in which bortezomib was developed in Europe, the Spanish group pioneered bortezomib/melphalan/prednisone as being a standard treatment for transplant-ineligible patients with MM. So clearly it's logical as the next step to ask the same question with the next-generation proteasome inhibitor carfilzomib (Figure 19). That in turn will lead to questions with regard to the neurotoxicity, the cardiac effects in a population that's not eligible for transplant and overall efficacy and response rates relative to what we know about bortezomib/melphalan/prednisone.

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PHASE III ENDEAVOR STUDY

Target accrual (n = 898)

- Relapsed multiple myeloma
- 1-3 prior therapies
- ECOG PS 0-2
- At least partial response to at least 1 line of prior therapy

R

Carfilzomib + low-dose dexamethasone

Bortezomib + low-dose dexamethasone

Primary endpoint: Progression-free survival

www.clinicaltrials.gov. Accessed May 2014.

DR LOVE: Will this trial be relevant in the United States?

DR GERTZ: In my experience, no. Melphalan-based regimens in my referral practice are uncommon — seeing a patient with newly diagnosed disease who receives either melphalan/prednisone/lenalidomide or bortezomib/melphalan/prednisone is extremely uncommon. More likely such patients will receive 1 of 3 regimens in my practice — lenalidomide/dexamethasone, bortezomib/dexamethasone or bortezomib/lenalidomide/dexamethasone.

Even though we have evidence that bortezomib/melphalan/prednisone is active, it isn't being used in the United States. I believe oncologists have opted out. If I had to speculate about that, I'd tell you melphalan/prednisone regimens are myelosuppressive. And it's hard to deliver the drug, certainly at the doses that have been published in the literature.

19 PHASE III CLARION STUDY

Target accrual (n = 882)

- Newly diagnosed symptomatic multiple myeloma
- Transplant ineligible
- Left ventricular ejection fraction $\geq 40\%$
- No significant neuropathy (Grade ≥ 2) within 14 days prior to randomization

R

Carfilzomib + melphalan + prednisone

Bortezomib + melphalan + prednisone

Primary endpoint: Progression-free survival

Select secondary endpoints: Overall survival, complete response rate, overall response rate, quality of life

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