5 Minute JournalClub

POST-ASH Issue 1, 2016

IFM/DFCI 2009 Trial: Role of ASCT, Implications of MRD Status and Comparison of MRI to PET-CT

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Hematology (ASH) annual meeting, to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. These events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unmatched and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they're aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because they are not only confronted almost overnight with thousands of new presentations and data sets to consider but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on novel agents and therapeutic options for the treatment of newly diagnosed and relapsed/refractory multiple myeloma (MM) from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists, hematology-oncology fellows and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Appraise recent clinical research findings on the effectiveness of investigational immunotherapeutic approaches, including checkpoint inhibitors and CAR T-cell therapy, for patients with relapsed/refractory MM.
- Evaluate the activity and safety of the recently FDA-approved monoclonal antibodies elotuzumab and daratumumab for the treatment of relapsed/refractory MM.
- Investigate the benefits and risks associated with proteasome inhibitors and/or immunomodulatory agents for relapsed/refractory MM.
- Compare the efficacy of the 3-drug regimen of bortezomib, lenalidomide and dexamethasone (RVd) to that of the 2-drug regimen Rd for the front-line treatment of MM.
- Consider the role of autologous stem cell transplant in the treatment of newly diagnosed MM in young patients.
- Assess the safety of pomalidomide and low-dose dexamethasone for patients with relapsed/refractory MM and renal impairment.

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Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

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To go directly to slides and commentary for this issue, **click here**.


Noopur Raje, MD

On October 2 our CME group traveled to New York for the first stop of our annual 4-city "Year in Review" (YiR) tour. To kick off this daylong multitumor meeting and remind those in attendance about just how much is happening in the field, we presented a slide recapping the new agents and indications approved by the FDA in the previous 3 years, with no idea that by the time we headed to Los Angeles just 7 weeks later for the final event in the series, 7 new approvals would be added to the graphic, providing a stunning example of the current unprecedented explosion in oncology research.

While many corners of oncology have seen upheaval as a result of these monumental developments, nowhere has the flurry of regulatory activity been as profound as in multiple myeloma (MM), where over the course of 15 days in November, 3 new agents — ixazomib, daratumumab and elotuzumab — suddenly became available.

This treasure trove of new myeloma riches is only part of the story, because shortly thereafter in December at ASH several landmark Phase III trials were presented that solidified a new model for up-front treatment of the disease. To try to sort out how all this new information has affected the current myeloma treatment landscape, after the holidays I sat down with Dr Noopur Raje, Harvard/MGH's myeloma director, to chat about what happened at ASH and how she is integrating these revolutionary trial findings and new agents into her practice. Throughout this in-depth interview (**click to hear it**) I wondered to myself whether someday we might look back to the fall of 2015 as the beginning of the end of this devastating disease.

Below find our summary of the major themes that emerged during this riveting conversation and a related slide set reviewing the salient findings from 23 key ASH MM papers (**click here**).

1. A new model for up-front management

Over the last few years data from a number of seminal studies have helped support the concept of ***continuous*** antimyeloma treatment using a variety of maintenance

strategies. At ASH 2015 we saw initial data from several much-anticipated trials that provide further evidence of the importance of ***depth*** of response.

SWOG-S0777: RVd versus Rd for patients with previously untreated MM without an intent for immediate autologous stem cell transplantation (ASCT) (525 patients, abstract 25)

This first randomized Phase III trial comparing these 2 classic regimens demonstrated a progression-free survival (PFS) and overall survival benefit with the triplet (medians: 43 versus 30 months and 75 versus 64 months, both statistically significant with *p*-values of 0.0018 and 0.0250, respectively). In keeping with the long-term treatment paradigm, all patients received lenalidomide (len)/dexamethasone maintenance until progression.

IFM 2013-04 trial: Bortezomib, thalidomide and dexamethasone (VTD) versus bortezomib, cyclophosphamide and dexamethasone (CyBorD) prior to ASCT for newly diagnosed MM (340 patients, abstract 393)

These findings have not received as much attention as the SWOG trial results, but they may be no less meaningful, because VTD was shown to be significantly superior to CyBorD in terms of the rates of very good partial response or better and partial response or better after only 4 cycles of therapy. Although thalidomide is largely viewed as an inferior immunomodulatory agent (IMiD) compared to len, this is another example of why using a triplet up front is becoming standard of care in patients with newly diagnosed MM.

IFM/DFCI 2009 trial: Immediate or delayed ASCT after RVD induction (700 patients, abstract 391)

The Intergroupe Francophone du Myelome initially launched this ambitious trial in tandem with the Dana-Farber Cancer Institute to discern the necessity of ASCT "in the era of new drugs." This report assessed 700 French and Belgian patients age 65 or younger with previously untreated MM, and although both arms resulted in a high very good partial response rate at the end of the stipulated 12 months of maintenance therapy (88% versus 78%), at a median follow-up of 39 months patients who had undergone immediate transplant and 1 year of maintenance len experienced longer PFS (median 43 months versus 34 months with a hazard rate of 0.69 and a *p*-value of <0.001). Importantly, minimal residual disease (MRD) assessment by next-generation sequencing was feasible for 92% of patients, and MRD negativity was shown to be highly predictive of PFS. In addition, PET/CT scan normalization after 3 cycles of RVD and before maintenance therapy was shown to be associated with a significant improvement in PFS and was a predictor for improved overall survival.

Dr Raje believes that a proportion of these patients may be cured but that longer follow-up is required to demonstrate this. The now separate and still ongoing DETERMINATION trial (Dana-Farber's portion of the study) has a similar design but

continues maintenance len until disease progression, which may result in deeper and more prolonged remissions.

These landmark studies fit very well into what Dr Raje describes as an evolving individualized model focused on achieving MRD negativity. In discussing this concept she noted that even in the nontransplant arm of the IFM study patients who were MRD-negative had long-term outcomes similarly favorable to those for MRD-negative patients who underwent ASCT, and thus in her mind, how one arrives at MRD negativity is not as critical as simply getting there. She is hopeful that in the future patients who require transplant will be identified prospectively along with the specific agents or regimens most likely to achieve this outcome.

In this regard it is important to consider the perspective of investigators like Memorial's Dr Ola Landgren, who believe that indirect trial comparisons suggest that regimens containing carfilzomib are more likely to achieve MRD negativity than those that include bortezomib. For now this issue may be more theoretical than practical because carfilzomib is not approved or commonly used up front, but hopefully the ongoing ECOG/ACRIN-E1A11 trial comparing RVd to KRd (carfilzomib/Rd) will soon answer this critical question.

Interestingly, a downside of carfilzomib that hampers its convenience is its twice-weekly administration. However, that may be changing as data presented at ASH demonstrate good tolerability and efficacy with **weekly administration** of this agent.

During the interview with Dr Raje I challenged the myeloma community's passionate belief that significant PFS and MRD benefits will translate to an overall survival advantage, but she was unhesitating in defending this position, citing the extraordinary improvements that are now being observed from the introduction and widespread use of proteasome inhibitors and IMiDs.

Finally, in reflecting on the madness of the last months of 2015, I recall that when the ASH abstracts were posted during our 4-city YiR tour, several faculty members from the highly respected Mayo Clinic myeloma team who participated in our conferences noted that just reading the preliminary data led them to switch their usual approach for patients at standard risk away from a 2-drug regimen (mainly Rd) to triplet therapy (RVd).

2. More on the newly approved agents

Not surprisingly, a number of ASH data sets focused on trying to understand how the 4 recently approved agents (including panobinostat) may best fit into practice. While it will likely take years to fully sort this out, the availability of these therapies has created a plethora of practical clinical and research questions, which were addressed by Dr Raje.

Ixazomib

At ASH 2014 the results of the landmark ASPIRE trial showed an impressive PFS advantage when carfilzomib was added to Rd in relapsed/refractory disease, and at ASH 2015 the results of the Phase III Tourmaline-MM1 trial demonstrated that a similar approach with the oral proteasome inhibitor ixazomib also provided a significant PFS benefit in patients with both high-risk and standard-risk cytogenetics. On the basis of these data this drug was approved in combination with Rd for patients whose MM has progressed after at least 1 prior treatment, and that is mainly how Dr Raje currently uses it. However, her eyes and the eyes of all investigators are fixed squarely on a soon-to-be-reported trial in the up-front setting and other maturing studies evaluating long-term maintenance treatment, for which the convenience of this oral therapy could deliver real quality-of-life benefits that result in greater disease control.

Daratumumab

Dr Rafael Fonseca, one of the aforementioned Mayo investigators, recently joked that 38 Special is now the official myeloma rock band, which seems like a bit of a leap for a drug that is currently indicated as monotherapy after 3 prior lines of therapy. However, every investigator I have spoken with, including Dr Raje, believes that the monotherapy, later-line positioning of this agent will be short-lived and that this important CD38-directed monoclonal antibody will become a standard part of earlier combination regimens. At ASH we saw more impressive data that solidify what we know — a 30% response rate as a single agent and 69% 1-year overall survival in very late-line treatment — and provide an indication of what may soon come, namely 70% to 80% overall response rates in combination with len/dexamethasone or pomalidomide/dexamethasone with no additional toxicities.

One issue that may prove to be a bit of a stumbling block for this agent is the need for prolonged infusion time, particularly early on, to mitigate the risk of acute reactions. Dr Raje believes this problem can be effectively managed but also recognizes that it may create a practical dilemma at locations not adequately staffed to handle the necessary chair times.

Elotuzumab

The third part of the November approval landslide, this SLAMF7-directed immunostimulatory antibody was the subject of several important ASH data sets, including follow-up from the Phase III ELOQUENT-2 trial further demonstrating prolonged PFS (19.4 months versus 14.9 months, $p = 0.0014$) from the very rational combination with Rd. Dr Raje believes "elo/Rd" is a logical choice for patients with lower tumor burden who are len naïve or likely to be len sensitive, and she is interested not only in trials utilizing this agent earlier in the disease but specifically in the intriguing

idea of adding elotuzumab to len maintenance. She noted that another 152-patient Phase II randomized trial reported at ASH combined the agent with bortezomib with less impressive results, perhaps due to the lack of the immunologic synergy that occurs with IMiDs.

Panobinostat

This histone deacetylase inhibitor was approved about a year ago in combination with bortezomib and dexamethasone for patients who had received at least 2 prior regimens, but its uptake seems to have been somewhat slow for a variety of reasons, including concerns about toxicity, particularly gastrointestinal problems. At ASH we saw data from 52 patients with the fascinating combination of RVD and this agent, with an excellent overall response rate of 94% and good tolerability. While future research will determine whether a role exists for this regimen, currently Dr Raje and others consider panobinostat/bortezomib an important option in the common scenario of disease progression occurring on len maintenance.

3. Immunotherapy finally arrives at the myeloma door

One of the most interesting comments Dr Raje made during our interview was her response when asked to identify the biggest myeloma story coming out of ASH this year, and while we have grown accustomed to immunotherapy being cited as the brightest light in almost every corner of oncology, apart from the widespread use of IMiDs there hasn't been much discussion of this approach in myeloma.

That changed in a heartbeat in Orlando with 3 riveting presentations — 2 on the anti-PD-1 antibody pembrolizumab and another on chimeric antigen receptor (CAR) T-cell therapy.

While checkpoint inhibitors haven't been particularly active in limited initial studies of monotherapy, at ASH we saw data on the use of **pembrolizumab combined with IMiDs** (Rd in one study and pomalidomide/dexamethasone in another) for patients who had received these agents previously and whose disease in many cases was resistant. Dr Raje pointed out that the handful of impressive responses observed suggests that checkpoint inhibitors might be able to overcome resistance to IMiDs.

Equally relevant, **another eye-opening presentation** at ASH (abstract LBA-1) demonstrated that CAR T-cell therapy may have legs in myeloma. The therapeutic target is B-cell maturation antigen (BCMA), a TNF-like protein expressed in normal and cancerous plasma cells. In this study of 12 patients with heavily pretreated disease, a single infusion of BCMA-targeted CAR T cells produced a number of impressive responses, with 4 patients achieving partial response or better and the remaining 8 patients stable disease. Although toxicities — including cytokine response syndrome —

were observed, this report is the first solid evidence that CAR-T treatment is effective in myeloma, and these findings were met with great enthusiasm by Dr Raje and every other person who saw the data.

Next on this short series Dr Jeff Sharman shares his perspective on another corner of hemato-oncology that is galloping forward with the goal of long-term disease control or cure — chronic lymphocytic leukemia.

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IFM/DFCI 2009 Trial: Role of ASCT, Implications of MRD Status and Comparison of MRI to PET-CT

Presentations discussed in this issue

Attal M et al. **Autologous transplantation for multiple myeloma in the era of new drugs: A phase III study of the Intergroupe Francophone du Myelome (IFM/DFCI 2009 trial).** *Proc ASH* 2015;**Abstract 391**.

Avet-Loiseau H et al. **Evaluation of minimal residual disease (MRD) by next generation sequencing (NGS) is highly predictive of progression free survival in the IFM/DFCI 2009 trial.** *Proc ASH* 2015;**Abstract 191**.

Moreau P et al. **Prospective evaluation of MRI and PET-CT at diagnosis and before maintenance therapy in symptomatic patients with multiple myeloma included in the IFM/DFCI 2009 trial.** *Proc ASH* 2015;**Abstract 395**.

Slides from presentations at ASH 2015 and transcribed comments from a recent interview with Noopur Raje, MD (2/10/16)

IFM/DFCI 2009 Trial: Autologous Stem Cell Transplantation (ASCT) for Multiple Myeloma (MM) in the Era of New Drugs

- Phase III study of lenalidomide/bortezomib/dexamethasone (RVD), with and without ASCT, followed by 1 year of maintenance lenalidomide
- N = 700 patients with previously untreated MM, age ≤65 years
- **Primary study endpoint:** Progression-free survival (PFS)

Survival	RVD (n = 350)	RVD + ASCT (n = 350)	Hazard ratio, *p*-value
Median PFS	34 mo	43 mo	0.69,<0.001
PFS rate (4 y)	35%	47%	

Attal M et al. *Proc ASH* 2015;Abstract 391.

IFM/DFCI 2009: Conclusions

- For patients with newly diagnosed MM, the addition of ASCT to RVD is associated with a 31% reduced risk of progression or death ($p < 0.001$):
  - Improved time to disease progression ($p < 0.001$) and rate of minimal residual disease (MRD) negativity (80% vs 65%, $p < 0.001$)
- ASCT should remain a standard procedure for young patients with de novo myeloma.
- Further follow-up is needed to make any conclusions about overall survival (OS) as the number of deaths is still low in both arms.
- An ongoing parallel trial in the United States (NCT01208662) uses a similar design but, importantly, administers lenalidomide maintenance continuously until progression in both study arms.

Attal M et al. *Proc ASH* 2015;Abstract 391.

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Predictive Value of MRD by Next-Generation Sequencing (NGS) in the IFM/DFCI 2009 Trial

- Bone marrow MRD evaluation before and after maintenance therapy in patients with very good partial response (VGPR) or better
- MRD assessment by flow cytometry (FCM) and NGS
- Prediction of PFS by MRD status as determined by NGS
- **Comparison of MRD sensitivity of NGS and FCM**
  - Sensitivity: FCM = 10^{-4}; NGS = 10^{-6}
  - Of 163 patients MRD-negative by FCM, 84 (51%) were positive by NGS

	Three-year PFS for patients achieving complete response	
	MRD-negative by NGS ($<10^{-6}$)	MRD-positive by NGS ($\geq 10^{-6}$)
Before maintenance	87%	63%
After maintenance	92%	64%

Avet-Loiseau H et al. *Proc ASH* 2015;Abstract 191.

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Predictive Value of MRD in IFM/ DFCI 2009: Conclusions

- Evaluation of MRD by NGS is feasible in 92% of patients and is highly sensitive ($<10^{-6}$)
  - This sensitivity is achieved in 100% of patients
- MRD negativity at 10^{-6} sensitivity is strongly predictive of PFS at 3 years.
- 13 of 26 patients with t(4;14) and none of 16 patients with del(17p) achieved MRD negativity.
- MRD evaluation may identify patients with MM who are cured. This warrants further evaluation in clinical trials.

Avet-Loiseau H et al. *Proc ASH* 2015;Abstract 191.

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IMAJEM Study: Evaluation of MRI and PET-CT in Patients with MM in the IFM/DFCI 2009 Trial

- Comparison of whole-body PET-CT to MRI of the spine and pelvis among 134 patients at diagnosis, after 3 cycles of RVD and before maintenance therapy

	Correlation with PFS (*p*-value)	Correlation with OS (*p*-value)
MRI normalization		
After RVD (3 cycles)	0.29	0.61
Before maintenance	0.30	0.30
PET-CT normalization		
After RVD (3 cycles)	0.04	0.12
Before maintenance	<0.001	0.003

Moreau P et al. *Proc ASH* 2015;Abstract 395.

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IMAJEM: Conclusions

- The 2 modalities are equally effective in detecting bone involvement at diagnosis (MRI: 94.7%; PET-CT: 91%).
- Normalization of MRI after 3 cycles of RVD and before maintenance therapy has no prognostic value for PFS or OS.
- PET-CT normalization after 3 cycles of RVD and before maintenance therapy is associated with a significant improvement in PFS.
- Normalization of PET-CT before maintenance was a predictor for improved OS.
- PET-CT should be incorporated in the follow-up of young patients receiving novel agent-based therapy, to predict outcome.

Moreau P et al. *Proc ASH* 2015;Abstract 395.

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Investigator Commentary: FM/DFCI 2009 Trial of RVD with or without ASCT for MM

All 3 presentations were based on the IFM trial comparing ASCT to continued RVD treatment. Dr Attal presented the interim analysis with 700 patients, which showed a PFS benefit with transplant (median 43 mo vs 34 mo), but the rate of VGPR or better at the end of the designated 12-month maintenance therapy was high in both arms (88% and 78%).

MRD testing by NGS was performed for 41% of patients (n = 289) at the initiation and the end of maintenance, and those data were presented by Dr Avet-Loiseau. MRD negativity by NGS was highly predictive of PFS, and testing was feasible for 92% of patients: With MRD negativity achieved, a portion of patients may be cured, but longer follow-up is required to demonstrate this. The DETERMINATION trial is using lenalidomide maintenance until disease progression, which may contribute to deepening remissions and increased MRD negativity.

In an imaging trial with 134 of the 700 patients, 95% and 91% had positive MRIs or PET CT scans, suggesting high sensitivity for detecting bone disease. MRI did not change before maintenance therapy for 83%, but PET CT was normalized for 79% and correlated well with PFS, which suggests its value as a predictive tool in subsets of patients.

Interview with Noopur Raje, MD, February 10, 2016