

IMW 2019, Boston, Sept 12-15, 2019
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This is my third time attending an International Myeloma Workshop (IMW) meeting which is held every 2 years. This 4-day meeting consists of 3200 attendees from 41 countries, mostly hematologists (70%) with smaller numbers of pharma reps (15%), researchers, and nurses who were there to present and learn from 620 submitted abstracts, each one focusing totally on myeloma! Like ASH, there are also exhibitors and posters but the focus is very much on the oral presentations. This 17th IMW meeting contrasts with the first one held in 1987 with 34 attendees (including Drs Robert Kyle and Brian Durie).

Great Debates

Although this was one of the final sessions, I believe it to be quite illustrative of questions we have today about myeloma. For each debate, one myeloma expert takes “Yes” side and another argues for “No”, with each doctor presenting their arguments and then offering rebuttals. Before each debate, the audience is polled and polled again after the debate. I’ll report the questions below and the final debate results, with some discussion.

- 1) Should we treat Smoldering Myeloma outside of a clinical trial? Yes-38% No-62%
However, had this question been phrased as “High Risk” SMM, I believe the voting would have been reversed.
- 2) Should RVd or KRd be considered as standard front-line therapy? RVd-69% KRd-31%
The thinking was the KRd induction should be reserved for High Risk MM pts, whereas VRd should be given to the older population.
- 3) Should MRD negativity be used in clinical practice to guide tx? Yes-38% No-62%
This is an important question being asked in clinical trials now (e.g. S1803) but we really don’t have data yet to tell us that we can stop treatment, even after years of MRD-. Using MRD- as a clinical trial endpoint was also discussed in the context of earlier FDA new drug approval.
- 4) Is definitive duration or indefinite Revlimid the right choice for maintenance?
Definitive – 51% Indefinite-49%
The primary arguments for limiting duration were an increase of SPM’s (secondary primary malignancies) after 2 years and that refractory Revlimid is difficult to treat.
- 5) Should monoclonal antibodies be included for induction in every MM pt?
Yes-59% No-41%
Up front Dara either as DRd or DRVd has shown benefit except in High Risk MM.
- 6) Will ASCT remain a standard of care in 5 years? Yes-52% No-48%
It was noted that while it’s an SOC (standard of care) today, with the Forte trial (KRd x 12 cycles) and quad induction therapies, more MRD- might be seen after induction. And Dr. Richardson added that long-term MDS and AML are possible SCT outcomes. Dr.

Bensinger theorized that a CAR-T followed by a RIC (Reduced Intensity Condition “Mini”) Allo might be a reasonable treatment plan.

Some Key Unanswered Questions from Dr. Dimopoulos

- 1) Do we treat HR SMM?
- 2) Does age affect SMM treatment?
- 3) Re MRD (Minimal/Measurable Residual Disease)
 - Treat till MRD-?
 - Continue treatment forever in MRD-?
 - Change treatment for MRD+?
 - Do we treat MRD- that becomes MRD+ yet pt has a Stringent CR response?
- 4) What’s a better definition of High Risk MM?
- 5) What’s the best induction for HRMM...VRd or KRd with/without Dara?
- 6) Fixed length induction or induction length based on response?
- 7) Consolidation for whom?
- 8) Best consolidation?
- 9) Best options for frail and elderly?
- 10) There’s an unmet need for R/R MM who relapse within 1 year of an SCT
- 11) What’s the best option for penta-refractory?
- 12) Re CAR-T therapy
 - Optimal dose?
 - Optimal conditioning?
 - Best patient population?
 - For Cytokine Release Syndrome, when to start treatment (Tocilizumab)?
 - Therapy after CAR-T?

Major Discussion Topics

Treatments for Smoldering Myeloma and Newly Diagnosed Patients

Dr. Kyle remarked “90% of MGUS patients will die of other causes” so treatment for SMM patients is being investigated. The classic definition of SMM is an M-protein > 3g/dL and no myeloma defining events. Dr. San Miguel noted “There are 51 clinical trials assessing early treatment in SMM.” Researchers are focusing on high-risk MM where the definitions of high-risk vary. Dr Rajkumar said “High risk SMM is whatever factors result in a 50% progression to MM within 2 years.” Some doctors look at M-protein and call it high-risk if it’s increasing by more than 10% within 6 mos. Others use the 20-2-20 definition of 20% plasma cell, 2% m-protein, and 20 FLC ratio. Genomic profiling may further improve the definition. Treatments being offered to HR SMM patients include “preventive” regimens such as Rev (+ dex) and “curative” regimens with trials.

IMW provided updates on newly diagnosed TE (transplant eligible) MM that included KCRd (Myeloma XI trial) and DaraVRd (Griffen) as well as added convenience with weekly Kyprolis and subQ Dara. And for non TE pts, RVd is better than Rd which is better than Vd (except for high-risk).

Treatments for Previously Treated Myeloma

While there are many treatment options, choosing therapy should be guided by 1) what is known about a patient's myeloma (e.g. prior therapy & efficacy, cytogenetics) and 2) what is known about the patient (e.g. age, other medical problems, side effects from past therapies, personal preferences).

IMW provided updates on the use of Empliciti (ERd) (Eloquent trial), weekly Kyprolis (Arrow), Pom with Kyprolis (pooled studies) or Velcade (Optimism), and Xpovio (approved with dex (Storm) but is in trial with other drugs). And new drug updates were shown for Venetoclax + Vd (Bellini) (targeted for t(11;14)), Melflufen + dex (Horizon) for extramedullary disease, and a Ph 1 trial of AMG176, an MCL-1 inhibitor.

Immunotherapeutic Approaches

Dr. Ken Anderson emphasized that using our own immune system to fight myeloma could be the best solution. These types of therapies fall into the categories of Monoclonal Antibodies, IMiDs & Checkpoints, CAR-T, and Vaccines. Isatuximab is a CD38 mAb (similar to Dara) where in combination with Pom-dex showed benefit for RR MM pts, including high-risk (ICARIA-MM trial) and Isa+KRd showed positive early results for 10 ND HRMM pts. While positive results for the BiTE AMG420 were updated, Amgen has decided to refocus their efforts on their extended half-life BiTE AMG701. And the ADC GSK'916 (DREAMM-) continues to show promise.

Iberdomide (CC220 "CelMoD") is the newest IMiD from Celgene and can apparently overcome resistance to other IMiDs and is being testing in trials with Dara and Vel.

CAR-T therapy keeps moving forward, primarily targeting BCMA but also other targets (GPC5D, NY-ESO-1) and is expanding to Allo CAR-T as well as CAR NK-cell therapy.

Guiding Treatment Decisions...Prognostic, Genetics, MRD, and Maintenance

Cytogenic/FISH tests are used to look at chromosomal changes but newer tests (GEP, NGS) can assess changes in the DNA and may well be the future, especially if results can be tied to treatment decisions. At IMW, the MMRF CoMMpass study is showing early results of a new high-risk subtype and predictors of early relapse.

MRD continues to be discussed and shown to be excellent for prognostic purposes but not used on any regular basis to guide therapy outside of clinical trials. However, I thought an interesting point was made that the role of maintenance is to sustain MRD-. And maintenance trials at IMW showed that either Rev or Vel or even Kyprolis can be given as effective maintenance.

Summary

Beyond what I've written, even more was discussed, such as targeting mutations and pathways like RAS (KRAS, NRAS), BRAF, MEK, BCL2 (found in t(11;14) and treated with Venetoclax), and MCL-1. Some drugs already exist for these and are incorporated in the MMRF's MyDRUG precision medicine trial.

PS. I try to be accurate with my note taking but material is presented quickly. If you have any questions, please feel free to email me jackaiello@comcast.net.