MultipleMyelomaHub

General MM

IMW 2019 | Great debates in myeloma

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On Sunday 15th September 2019, during the XVII International Myeloma Workshop (IMW) in Boston, US, a session entitled "Great debates in myeloma" was held. The debates were chaired by Professor (Prof.) Maria-Victoria Mateos and Doctor (Dr) Vincent Rajkumar who took to the stage dressed as referees. Each speaker was permitted five data-based slides, five minutes to speak, and a two-minute rebuttal to their opponent's argument. The audience was asked to vote before, and after, each debate to see if they had been persuaded by the debaters. Additionally, the Multiple Myeloma (MM) Hub held interactive online polls on Twitter, allowing delegates at the congress, and those unable to attend, to join in the conversation. This article provides a summary of a selection of these debates focusing on induction, maintenance and autologous stem cell transplant (ASCT).[1]

Should bortezomib (V), lenalidomide (R) and dexamethasone (d, VRd) / carfilzomib (K), R and d (KRd) be considered the standard frontline induction regimen?

In this debate, Prof. Paul Richardson argued in favor of the VRd regimen as frontline induction, whilst Prof. Keith Stewart argued KRd should be the preferred choice (**Table 1**).

Table 1. Summary of debate: VRd *versus* KRd as frontline induction[1]

Paul Richardson – VRd	**Keith Stewart – KRd**
Efficacy is not only a function of activity, but also of tolerability, both short- and long-term. The toxicity profile of any treatment regimen should be predictable and manageable. • VRd induces consistent, high-quality responses, including in patients with adverse cytogenetics • It is a well-tolerated combination, with most cases of peripheral neuropathy (PN) being manageable • The subcutaneous (SC) administration of V further improves tolerability	Carfilzomib, a second-generation proteasome inhibitor (PI), was shown to have benefits over bortezomib in preclinical studies: • More selective - reduced off-target effects • Irreversible - increased target inhibition (high level and long duration of proteasome inhibition) • Carfilzomib overcame bortezomib resistance *in vivo*

VRd improved progression-free survival (PFS) and overall survival (OS), compared to Rd alone, in the phase III SWOG S0777 trial in patients for whom transplant was not immediately planned:[2] • Median PFS (VRd *vs* Rd): 43 *vs* 30 months (hazard ratio [HR]: 0.712, 96% CI, 0.56–0.906, p= 0.0018) • Median OS (VRd *vs* Rd): 75 *vs* 64 months (HR: 0.709, 95% CI, 0.524–0.959, p= 0.025) • Clear benefit of VRd over Rd	The phase III ENDEAVOR trial, in patients with relapsed/refractory (RR) MM (RRMM), Kd was superior to Vd:[3] • Median PFS (Kd *vs* Vd): 18.7 *vs* 9.4 months (HR: 0.53, 95% CI, 0.44–0.65, p< 0.0001) This benefit was also seen in patients who had prior exposure to bortezomib: • Median PFS (Kd *vs* Vd): 15.6 *vs* 8.1 months (HR: 0.56, 95% CI, 0.44–0.73)
In the transplant ineligible population, VRd-lite (R: 15mg orally days one–21, V: 1.3mg/m^2 SC, weekly on days one, eight, 15 and 22, d: 20mg) is well-tolerated and active, with a last-reported median PFS currently of 35.1 months.[4]	There is no difference in response with K-containing regimens, compared to VRd, but there is little survival data available.
A 'one size fits all' approach is not feasible in the treatment of MM and risk stratification and tailored approaches should be used.	CLARION trial (VMP *vs* KMP): no difference between the use of V or K, in an elderly population who were not destined for transplant. However, determining the appropriate drug depends on patient comorbidities and the adverse event (AE) profiles of the drugs.[5]
Whilst KRd is a powerful combination, it is associated with an increased rate of vascular toxicity.	Since V and K have different side effects, toxicity as well as cost are important considerations.
Guiding principles of initial therapy in patients with newly diagnosed MM (NDMM): • Triplets are the preferred option • It is important to be strategic • Consider V + thalidomide + d (VTd), cyclophosphamide, V, d (CVd) or RVd, with KRd for high-risk patients • Consider adding a monoclonal antibody (mAb) to these triplets, such as daratumumab (dara)	No trial has compared KRd to VRd in high-risk or transplant-eligible patients, so KRd should be the triplet of choice since carfilzomib: • Is a more potent PI • Has the greatest risk tolerance in high-risk younger patients • Causes less PN • Nearly all cardio-renal events are reversible

Consider real-world value and cost implications of both therapies.	As part of the questioning, Prof. Mateos asked what the second-line choice of therapy would be if KRd was used upfront. Prof. Stewart stated that if K was used upfront, the next therapy would be B-cell maturation antigen (BCMA)-targeted such as chimeric antigen receptor (CAR) T-cell therapy.
In the CLARION trial (K + melphalan [M] + prednisone [P, KMP] *vs* VMP), whilst carfilzomib provided higher responses, there was a distinction in tolerability. Grade ≥ three acute renal failure, cardiac failure and hypertension were all more frequent in the carfilzomib arm (KMP *vs* VMP):[5] • Acute renal failure: 7.4% *vs* 2.1% • Cardiac failure: 8.2% *vs* 2.8% • Hypertension: 10.1% *vs* 3.6%	
Both debaters agreed that KRd is not the optimal choice of regimen for elderly patients with comorbidities, though standard-risk patients with high-risk disease may favor KRd. Both debaters agreed it must be a strategic decision, considering potential options at relapse.	

The results of the Twitter poll conducted by the MM Hub on Twitter showed 83% of voters agreed with Prof. Richardson that RVd should be the standard frontline induction regimen in MM.

Should mAbs be included for induction in every patient with MM?

The next debate was held between Assoc. Prof. Efstathios Kastritis who argued mAbs should be used in all induction regimens, and Assoc. Prof. Peter Voorhees who argued against their use in all induction regimens (**Table 2**).

Table 2. Summary of debate on the use of mAbs in induction regimens[1]

Efstathios Kastritis – YES mAbs should be in all induction regimens	**Peter Voorhees - NO mAbs should not be in all induction regimens**

Significant data to support the addition of mAbs to traditional regimens. Several phase III studies have shown the addition of a mAb to a traditional backbone reduces the risk of progression or death by 44–57%.[6-8] Adding a mAb also reduces treatment failure rates. HRs for the following regimens favored the dara-containing combination: • ALYCONE: dara-VMP *vs* VMP, HR: 0.43[6] • MAIA: dara-Rd *vs* Rd, HR: 0.56[7] • CASSIOPEIA: dara-VTd *vs* VTd, HR: 0.47[8]	PFS is a surrogate endpoint for OS, which is the goal of myeloma therapy. Therefore, improvements in PFS, such as those seen with dara-combinations, do not necessarily translate into improvements in OS: • SWOG S0777 trial in transplant ineligible MM (VRd *vs* Rd). There was an improvement in overall response rate (ORR), depth of response, median PFS and median OS with VRd. It was noted that this trial was representative of the real-world scenario[2] • MAIA trial (dara-Rd *vs* Rd): improvement in ORR, depth of response, and PFS, however, currently, no significant OS advantage[7] Will dara-containing regimens will show an OS benefit that is statistically significant? Based on the current evidence, VRd should be standard-of-care (SOC) due to the proven OS benefit.
Another important consideration is toxicity:[6-8] • Grade five events in the ALYCONE, MAIA and CASSIOPEIA trials were comparable between study arms, as were discontinuations due to toxicity and grade ≥ three infections • Less patients discontinued in the dara-containing arms as well, particularly in the MAIA and ALYCONE trials The addition of mAbs to traditional induction regimens does not increase toxicity significantly	The efficacy of combinations involving mAbs is affected by the choice of backbone treatment and whether treatment is continuous or definitive duration.
Should we keep mAbs for relapse? No; 20–25% of patients will not reach second-line therapy and miss the opportunity to receive a mAb. We cannot postpone the use of this therapy.	Regimens involving mAbs have a higher cost implication.
mAbs are most effective with a functioning immune system, in earlier lines of therapy. With subsequent lines of treatment, myeloma patients lose immune system functionality and several immune cell populations are reduced/eliminated. mAbs lose their effectiveness as there is a lack of effector cells present.	Dara-containing regimens used in the MAIA, ALYCONE and CASSIOPEIA trials showed less of a benefit in high-risk patients compared to standard-risk patients.[6-8]

• Around 50% less patients require salvage therapy after treatment with a mAb-containing regimen • We should use our most effective therapies upfront to achieve best response • Delaying the use of mAbs may compromise their efficacy • Waiting until later lines of treatment reduces the number of patients eligible to receive mAb-based therapy • The safety profile is favorable in combinations with two or three other drugs	

Following this debate, the MM Hub Twitter poll showed 62% of voters believed monoclonal antibodies should be used in all induction regimens.

Will ASCT remain a SOC in MM in five years?

The following debate was between Prof. Pieter Sonneveld and Prof. Ola Landgren who debated whether ASCT will be SOC in five-years. Prof. Sonneveld argued it will be, whilst Prof. Landgren provided evidence that it would not be (**Table 3**)[1].

Table 3. Summary of debate of whether ASCT will be SOC in five-years[1]

Pieter Sonneveld – YES ASCT will be SOC in five-years	**Ola Landgren – NO ASCT will not be SOC in five-years**
Goals of transplant in patients with NDMM who are <70 years old: • Induction: control disease and reduce number of tumor cells • Autograft: three-log reduction in tumor • Consolidation: upgrade the response • Maintenance: prevent progression	Life and medicine are not designed to stay the same over many years, with therapies improving and advancing all the time.

In the IFM 2009 trial, PFS was improved with high dose melphalan (HDM) + ASCT + VRd compared to VRd alone, and several other studies have confirmed the role of ASCT compared to standard therapy.	We must identify the true needs of the patients, which change over time. We may begin to use measurable residual disease (MRD)-negativity as an endpoint of therapy, which will change how we use treatments. New effective treatments such as new four-drug combinations with mAbs or CAR T-cell therapy, which induce high MRD-negativity rates, show great promise and are likely to be widely available shortly. Personalized medicine in myeloma using MRD-status to guide treatment is also becoming a possibility.
Long-term outcomes with transplant are also improved. In a meta-analysis of European studies, at nearly ten-years follow-up, OS was >70% in patients receiving double transplant and 60% in those receiving single transplant.[9]	HDM conditioning is cytotoxic, inducing DNA damage and increases a patient's long-term risk of developing acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). The mutations induced by HDM do not go away. Therefore, we should not use ASCT so that we can avoid long-term complications.
Prof. Sonneveld also added that he expects the soon-to-be-updated European Society of Medical Oncology (ESMO) guidelines to advise triplet/four drug induction (with PI, immunomodulatory drug [IMiD] and mAb), then HDM + ASCT, and consolidation and maintenance with novel agents, stating that "more is better."	As part of the rebuttal, Prof. Landgren stated that if a patient is MRD-negative, ASCT is not necessary in his opinion, and so ASCT should only be utilized when MRD cannot be assessed.
If we have a proven, effective treatment, we should use it. We can/will incorporate novel agents, but we should not replace proven strategies.	

The MM Hub Twitter poll identified that 77% of voters believe ASCT will remain SOC in five-years' time.

Is definitive duration or indefinite lenalidomide (len) the right choice for maintenance?

In the next debate, Dr Cyrille Touzeau excellently stepped in for Prof. Philippe Moreau, to argue that len should be given as maintenance for a definitive duration post-ASCT, whilst Prof. Philip McCarthy argued for indefinite len maintenance (**Table 4**).[1]

Table 4. Summary of debate on the duration of len maintenance[1]

Cyrille Touzeau – definitive	**Philip McCarthy – indefinite**
To determine the optimal duration, we must consider: • Efficacy • The risk of inducing resistant disease • Toxicity profile and patient quality of life (QoL) • Cost-effectiveness of treatment	The SOC for maintenance post-transplant is len until disease progression (PD) which is approved by both the European Medicines Agency (EMA) and United States (US) Food & Drug Administration (FDA)
Maintenance with len has been proven to prolong PFS in four randomized controlled trials (including IFM 2005-02 and Myeloma XI), and extend OS in a meta-analysis[10]	No data from phase III studies have shown a benefit of fixed duration len maintenance compared to maintenance until PD - this has not yet been studied.
There is no plateau on PFS curves: all patients receiving len maintenance will progress, if given indefinitely. This is an issue because len-refractory patients are difficult to treat, with few effective therapies. We need to seek maintenance therapies that do not induce len-refractory disease.	Maintenance continues to provide an effect • Patients in the Myeloma XI, EMN 02 and BMTCTN0702 trials converted to MRD-negativity during len maintenance treatment
Patients who remain sensitive to len have better outcomes at first relapse. POLLUX trial: dara-Rd was effective in patients who are not len-refractory at first relapse.[11]	In post-hoc and meta-analyses, fixed duration maintenance is inferior to maintenance until PD. In an exploratory analysis from the Myeloma XI study of 132 patients who stopped treatment for reasons other than PD, patients receiving >12 months of treatment had improved median PFS compared to those receiving <12 months:[12] • Median PFS (<12 *vs* >12 months): 31 *vs* 49 months (HR: 0.35, 95% CI, 0.18–0.68)
Maintenance with len is not well-tolerated by all patients, in the long-term. In a study by Attal M. *et al.*, len maintenance was shown to cause grade 3–4 neutropenia in 51% of patients and grade 3–4 infections in 13%.[13]	Economic considerations of long-term maintenance must be weighed against cost of earlier progression and salvage therapies

Len maintenance, after two years, causes an increase in the cumulative incidence of secondary primary malignancies (SPMs) compared to placebo or observation.[12]	Whilst cross-trial comparisons are not recommended, Prof. McCarthy showed a comparison of nine trials of various consolidation/maintenance regimens in transplant eligible patients with NDMM • PFS was longer in patients treated with len until PD compared to those treated for a definitive duration, patients who stopped len early, and control arms
• Significant cost implication in providing len maintenance long-term • Significant burden for the country's healthcare system or patient	In future, MRD status may guide treatment decisions on the duration of len maintenance, however many questions remain regarding the use of this in day-to-day practice
Indefinite len maintenance is inducing len-refractory disease which is a challenge to treat, QoL on long-term len is sub-optimal, and there is a high cost impact	

The results of the Twitter poll for this debate indicated 60% of voters felt lenalidomide maintenance should be given indefinitely.

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