# Multiple Myeloma Research Review™

Making Education Easy

Issue 29 – 2019


## In this issue:



**Abbreviations used in this issue**

**HR** = hazard ratio
**MLPA** = multiplex ligation-dependent probe amplification
**MM** = multiple myeloma
**MRD** = minimal residual disease
**OS** = overall survival
**PFS** = progression-free survival
**PI** = proteasome inhibitor
**SCT** = stem-cell transplantation
**VTE** = venous thromboembolism



# Welcome to issue 29 of Multiple Myeloma Research Review.

This issue begins with research reporting real-life outcomes after autologous SCT for newly diagnosed MM focussing on its role in elderly patients. Another paper selected for this issue compares real-world times to next treatment for common second-line PI-based regimens in patients with relapsed MM. This issue also includes data from two phase 3 trials: the Myeloma XI trial of lenalidomide maintenance versus observation in newly diagnosed patients; and an updated *post hoc* analysis of CASTOR trial data (daratumumab added to bortezomib and dexamethasone), reporting longer follow-up and outcomes based on treatment history. We conclude with research confirming that MRD status has value as a prognostic biomarker in MM.

We hope you enjoy this issue and, as always, we invite you to send us your comments and feedback.

Kind regards,


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## Real-life data on safety and efficacy of autologous stem cell transplantation in elderly patients with multiple myeloma

**Authors:** Marini C et al.


**Summary:** Patients with newly diagnosed MM who had undergone autologous SCT (n=132) were compared with 23 nontransplanted patients with similar clinical characteristics for this retrospective study; 29 of the transplanted group were aged >65 years. The conditioning regimen was melphalan 200 mg/m$^2$, or 140 mg/m$^2$ for half of the elderly patients. No significant age-stratified differences were seen for transplant-related myelotoxicity or nonhaematopoietic toxicity; however, the elderly patients who received melphalan 200 mg/m$^2$ conditioning required significantly more transfusional support and intravenous antibiotics, and experienced higher grades of mucositis, than those who received conditioning with melphalan 140 mg/m$^2$. The overall transplant-related mortality rate was 3.8%, with no influence of age on survival. Responses to induction were similar in both groups. Elderly patients who underwent autologous SCT had significantly longer OS and event-free survival compared with nontransplanted patients (59 vs. 30 months [p=0.037] and 45 vs. 27 months [p=0.014], respectively).


**Comment (KR):** This paper provides some useful data in the ongoing issue of transplantation in the elderly. The OS was significantly better in the older autologous SCT cohort, suggesting that autologous SCT should be carried out if possible. The question of whether it is preferable to use full-dose or a reduced dose of melphalan is not really answered. It will come down to the clinician's risk analysis.

***Reference: Ann Hematol 2019;98:369–79***
Abstract

## Results of an early access treatment protocol of daratumumab in United States patients with relapsed or refractory multiple myeloma

**Authors:** Chari A et al.


**Summary:** This US open-label study assessed an early access daratumumab protocol in pretreated patients with progressive MM. Programme entry criteria included ≥3 prior lines of therapy (including a PI and an immunomodulatory agent) or refractory status to both a PI and an immunomodulatory agent. The study included 348 patients who received daratumumab treatment 16 mg/kg weekly for 8 weeks, every other week for 16 weeks then monthly until either disease progression, unacceptable toxicity or 60 days post-US drug approval. Around half the patients transitioned to commercially available daratumumab at study completion and 37% discontinued due to disease progression. Half the patients experienced grade ≥3 adverse events, the most common of which were thrombocytopenia (15%) and anaemia (14%). Infusion-related reactions occurred in 56% of patients during the first infusion and dropped to 2% for all subsequent infusions. Infusion reaction rates were lower in patients who received montelukast premedication compared with those who did not (38% vs. 59%).


**Comment (KR):** This paper gives some useful background prior to the rollout of compassionate daratumumab in refractory MM patients just commencing in NZ. The number of adverse events was on the high side and infusion reactions were common. It will be a welcome addition to the drug armamentarium in myeloma patients, and hopefully we can organise the collection of similar data in a prospective fashion.

***Reference: Cancer 2018;124:4342–9***
Abstract

## Venous thromboembolism in relapsed or refractory multiple myeloma patients treated with lenalidomide plus dexamethasone

**Authors:** Shin J et al., Korean Multiple Myeloma 151 Investigators

**Summary:** The cumulative incidence and prognostic value of VTE was evaluated in the following two consecutive cohorts of patients with relapsed/refractory MM who had been treated with lenalidomide plus dexamethasone: the KMM151 cohort (n=542; medical record data) and the HIRA cohort (n=1559; health insurance claims data). The respective VTE rates for the KMM151 and HIRA cohorts were 4.4% and 5.1%, with the cumulative incidence reaching a plateau ~2 years after lenalidomide plus dexamethasone was started; the respective 2-year incidences were 4.9% and 8%. The risk of VTE was significantly increased by a higher starting lenalidomide dose, a prior history of VTE and older age. Early-onset VTE significantly reduced the odds of survival.

**Comment (KR):** This study gives us a clearer picture of the actual incidence of VTE in lenalidomide-treated patients. The incidence of up to 8% does mean that a VTE history should be always taken prior to commencing lenalidomide and appropriate prophylaxis be given according to the VTE risk.

***Reference: Int J Hematol 2019;109:79–90***
Abstract

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## A real-world comparative analysis of carfilzomib and other systemic multiple myeloma chemotherapies in a US community oncology setting

**Authors:** Rifkin RM et al.

**Summary:** This research compared time to next treatment during second-line therapy for 718 adults with MM who had received common PI-based triplet regimens during treatment. Second-line regimens of interest included KRd (carfilzomib, lenalidomide and a steroid; n=112), VRd (bortezomib, lenalidomide and a steroid; n=27) and VCyd (bortezomib, cyclophosphamide and a steroid; n=17). Compared with VRd recipients, KRd recipients had a significantly longer median time to start of next (third-line) treatment (25.3 vs. 10.2 months; adjusted HR 0.19 [95% CI 0.11, 0.37]); the median time to start of third-line treatment was even shorter for VCyd recipients at 6.5 months.

**Comment (KR):** This was a large study that confirms the prior ASPIRE study findings that the use of KRd therapy at relapse confers a significant time to next treatment interval in patients who have two prior therapies. This is not a regimen that we can use in NZ, but is more evidence relating to the important place that carfilzomib holds in the relapse setting.

***Reference: Ther Adv Hematol; Published online Jan 11, 2019***
Abstract

**Independent commentary by Dr Ken Romeril,** FRACP, FRCPA Haematologist specialising in malignant haematology, Wellington Hospital. He has a particular interest in translational myeloma research and genetics. **For full bio CLICK HERE**

**Independent commentary by Dr David Simpson,** MBChB, FRACP, FRCPA, Consultant Haematologist North Shore Hospital. His interests are in malignant haematology. **For full bio CLICK HERE**

## Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma XI)

**Authors:** Jackson GH et al., for the UK NCRI Haemato-oncology Clinical Studies Group

**Summary:** Participants with newly diagnosed MM enrolled in the phase 3 Myeloma XI trial were randomised to receive open-label oral lenalidomide on days 1–21 of a 28-day cycle (n=1137) or observation (n=834). Median follow-up was 31 months. Compared with observation, lenalidomide maintenance recipients had longer median PFS (39 vs. 20 months; HR 0.46 [95% CI 0.41, 0.53]) with the benefit seen across prespecified subgroups. The 3-year OS rate was not significantly greater with lenalidomide maintenance versus observation (78.6% vs. 75.8% [p=0.15]), but was significantly greater in transplant-eligible participants (87.5% vs. 80.2% [p=0.014]) and not in transplant-ineligible participants (66.8% vs. 69.8% [p=0.88]). For transplant-eligible and transplant-ineligible patients, the respective 3-year OS rates of 86.4% and 81.3% for standard cytogenetic risk participants, 74.9% and 63.7% for high-risk participants and 62.9% and 43.5% for ultra-high-risk participants should be interpreted with caution due to lack of power to detect differences. The most common grade 3–4 adverse events for lenalidomide recipients were haematological (neutropenia in 33%, thrombocytopenia in 7% and anaemia in 4%), and the serious adverse event rate was 45%, compared with 17% in the observation group, consisting mainly of infections in both groups. None of the deaths in the lenalidomide arm were considered to be related to treatment.

**Comment (KR):** Lenalidomide maintenance has now become standard of care in many countries and this paper is the largest data collection. There is an OS improvement in the transplant-eligible group but no significant result detected in the nontransplant group, which seems surprising. The poor-risk cytogenetic group did not fare as well, and this group is likely to benefit more from a bortezomib-based consolidation and possibly a maintenance strategy, particularly for the 17p deleted patients.

**Comment (DS):** Lenalidomide maintenance in post-transplant patients is in widespread use in NZ and internationally. This paper showed it prolonged PFS in all subgroups analysed, both young and old, and good- and poor-risk cytogenetics. Although the improvement in PFS seemed similar in both transplant and nontransplant patients, OS was only significantly improved in transplant-eligible patients (HR 0.69) but not nontransplant patients (HR 1.02). The reasons for the difference are not clear, although there were more non-myeloma deaths in the older patients. Given the benefit in PFS and time to next treatment, it can be argued there are significant benefits in older patients as well. There was an increase in second primary malignancies at 3 years (5.1% vs. 3%) in the lenalidomide arm. The dose of lenalidomide was initially 25mg, but most patients were treated after a protocol amendment on 10mg on days 1–21 of a 28-day cycle. All patients in this study received an immumomodulatory drug as part of induction, and the benefits may be more marked in PI-treated patients. This study supports the use of lenalidomide maintenance to all myeloma patients forever. With more effective induction treatments being developed, the question will be are there subsets of patients who can stop it.

***Reference: Lancet Oncol 2019;20:57–73***
Abstract

## Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma

**Authors:** Spencer A et al.

**Summary:** This *post hoc* analysis of phase 3 CASTOR trial data focussed on treatment histories and outcomes over median follow-up of 19.4 months for participants treated with bortezomib and dexamethasone with or without daratumumab. Compared with bortezomib and dexamethasone alone, the addition of daratumumab was associated with longer median PFS (16.7 vs. 7.1 months; HR 0.31 [95% CI 0.24, 0.39]), especially for participants who had received one prior line of therapy (not reached vs. 7.9 months; 0.19 [0.12, 0.29]). The addition of daratumumab to bortezomib and dexamethasone was also associated with: i) a greater overall response rate (83.8% vs. 63.2% [p<0.0001]); ii) better outcomes in subgroups based on prior treatment exposure (bortezomib, thalidomide or lenalidomide), lenalidomide-refractory status, time since last therapy and cytogenetic risk; and iii) MRD-negative rates that were >2.5-fold higher across subgroups. The safety profile of daratumumab, bortezomib and dexamethasone remained consistent over the extended follow-up.

**Comment (DS):** Daratumumab improves the depth and duration of response when added to any chemotherapy so far tested. This updated analysis of the CASTOR study shows the responses are maintained with the suggestion of a plateau in the PFS curve. The data also show that MRD is important and achieving a negative status by any means is beneficial. The subgroup analysis showed that all subgroups benefit. Daratumumab would make a good addition to any regimen.

***Reference: Haematologica 2018;103:2079–87***
Abstract

## BH3-mimetic toolkit guides the respective use of BCL2 and MCL1 BH3-mimetics in myeloma treatment

**Authors:** Gomez-Bougie P et al.

**Summary:** Dependencies on BCL2, BCLXL or MCL1 in malignant plasma cells from 60 patients were studied using a BH3-mimetic toolkit. Findings included: i) dependency on BCL2 in 83% of the CCND1 subgroup; ii) a significant increase in dependency on MCL1 from 33% at diagnosis to 69% at relapse; iii) codependencies on either BCL2/MCL1 or BCLXL/MCL1 in 35% of samples overall; and iv) the identification of a group of patients not targeted by any of the BH3 mimetics, mainly at diagnosis in patients without common recurrent translocations. The researchers also showed that BAK was necessary for cell death induced by the MCL1 mimetic A1210477, and reported additional data supporting the role of BCLXL in A1210477 resistance.

**Comment (DS):** BH3 mimetics are likely to have an increasing role in myeloma. This paper looked at *ex vivo* testing of myeloma cells and found, as in previous studies, the BCL2 inhibitor venetoclax was most effective in CCND1 myeloma. The MCL1 inhibitors were more effective in non-CCND1 patients and, unlike most other drugs, the myeloma cells gained sensitivity at relapse, although the increase was mostly due to increased numbers of intermediate sensitive cells. This paper hints that *ex vivo* testing may help guide rational BH3 mimetic therapy. MCL1 inhibitors are an exciting prospect in myeloma – watch this space.

***Reference: Blood 2018;132:2656–69***
Abstract

## Subclonal *TP53* copy number is associated with prognosis in multiple myeloma

**Authors:** Shah V et al., on behalf of the National Cancer Research Institute Haematology Clinical Studies Group

**Summary:** The prognostic relevance of clonal heterogeneity of *TP53* copy number was studied using MLPA (multiplex ligation-dependent probe amplification) applied to tumours from 1777 participants with newly diagnosed MM from the Myeloma XI trial. An independent association was detected between subclonal *TP53* deletions and shorter OS (HR 1.8 [95% CI 1.2, 2.8]), and clonal but not subclonal *TP53* deletions were significantly associated with lower platelet counts (p<0.001), increased lactate dehydrogenase levels (p<0.001) and greater frequencies of del(13q) and del(1p). The incidence of biallelic *TP53* loss-of-function by mutation and deletion was low at 2.4%, but was associated with advanced disease.

**Comment (DS):** In myeloma it is usually the subclones that eventually kill the patient. This analysis looked at detecting lower levels of *TP53* deletions using an MLPA technique, which is a dynamic PCR technique that can be used in routine clinical practice. They found that small fractions of mutated cells had the same prognostic significance as fully clonal patients, even though they lacked other features of transformed disease. This type of technique detects *TP53* mutations in 10.8% of patients and will be helpful in risk stratifying patients.

***Reference: Blood 2018;132:2465–9***
Abstract

## Minimal residual disease negativity using deep sequencing is a major prognostic factor in multiple myeloma

**Authors:** Perrot A et al.

**Summary:** The prognostic value of MRD measured during maintenance therapy was evaluated using data acquired from a clinical trial that evaluated the role of transplantation in patients with newly diagnosed myeloma treated with lenalidomide, bortezomib and dexamethasone. MRD negativity ($<10^{-6}$) occurred at least once during maintenance in 25% of the participants. At initiation of maintenance therapy, MRD was a strong prognostic factor for PFS and OS (respective adjusted HRs 0.22 [95% CI 0.15, 0.34] and 0.24 [0.11, 0.54]). Compared with participants with detectable residual disease, those who were MRD-negative were more likely to achieve prolonged PFS, irrespective of whether they underwent transplantation, their cytogenetic risk profile and their ISS disease stage at diagnosis. Similar results were seen after maintenance therapy was completed.

**Comment (DS):** We all know that the best predictor of outcome is response the treatment. As myeloma treatments have improved, new response criteria have needed to be invented to measure those with very deep responses. This paper confirms that very deep responses matter, with improved PFS and OS if next-generation sequencing MRD to less than $10^{-6}$ is achieved. This matters more than conventional response criteria, with about a third of MRD patients only achieving a very good partial response yet still having the same outcome as MRD-negative complete remission. Treatment and cytogenetic risk still affect duration of MRD-negative remissions, but are less important. MRD is now standard in clinical trials and likely to become a standard to judge efficacy of new treatments. Risk-adapted algorithms based on MRD status need trial confirmation.

***Reference: Blood 2018;132:2456–64***
Abstract