Multiple Myeloma
RESEARCH REVIEW™

Making Education Easy

Issue 5 – 2022

In this issue:

Abbreviations used in this issue
CR/PR/VGPR = complete/(very good) partial response
HR = hazard ratio
MM = multiple myeloma
MRD = minimal residual disease
ORR = overall response rate
OS = overall survival
PFS = progression-free survival
PI = proteasome inhibitor
SCT = stem-cell transplantation
VTE = venous thromboembolism

Welcome to issue 5 of Multiple Myeloma Research Review.

This issue begins with interesting research asking whether the commonly held belief that patients with MM entered into clinical trials fare better than those who are not holds true in reality. We then hear from our colleagues in France on their experiences with MM diagnosed prior to age 40 years. There is also research suggesting that direct oral anticoagulants (e.g. rivaroxaban) may provide better protection against VTE (venous thromboembolism) in patients receiving induction therapy, particularly KRd (carfilzomib, lenalidomide, dexamethasone), for newly diagnosed MM. The issue concludes with research providing reassuring information regarding autologous SCT in older, fit patients with myeloma.

We hope you enjoy the research selected, and we look forward to comments and feedback.

Kind regards,

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Do patients with multiple myeloma enrolled in clinical trials live longer?

Authors: Aung TN et al.

Summary: Differences in survival outcomes according to clinical trial enrolment and race/ethnicity were reported for a retrospective cohort of 1285 patients with MM. Compared with nontrial patients, trial participants were of younger mean age (60 vs. 63 years [p<0.001]), were more likely to receive ≥6 therapy lines (39% vs. 17% [p<0.001]) and had more comorbidities, but did not differ significantly for survival (adjusted HR 1.34 [95% CIs 0.90, 1.99]; propensity-matched HR 1.36 [0.83, 2.23]), with similar results on subgroup analysis by lines of therapy. There were also no significant survival differences according to race/ethnicity except that Black/Hispanic nontrial patients had higher mortality than White trial participants (HR 1.76 [95% CI 1.01, 3.08]).

Comment (HC): This retrospective review analysed patients who received myeloma care across multiple institutions within the Mount Sinai Health System in New York. At first glance, their data show that patients who had ever been enrolled in a myeloma clinical trial did not experience any survival benefit over those who never participated in one. This seems to contradict the common belief that clinical trials benefit both future patients and those enrolled. However, before being disheartened by these results, it is worth evaluating the data more closely. First of all, although there was no statistically significant difference in OS, this may be because the study was underpowered. Using the data from their study (17% trial and 83% nontrial patients), it would require a total sample size of over 1700 to detect a 30% difference in survival. Meanwhile, the study did not analyse the types of trials (i.e. early phase versus phase 3) and at which point the patient went to the trial (i.e. early versus late line of treatment). Although the authors did try to compensate for potential confounders with various statistical approaches, including propensity score matching, these strategies may not overcome selection biases due to unknown confounders. Lastly, as there were no details on the types of treatment these patients received, one cannot exclude the possibility of some nontrial patients having access to investigational agents off study, thereby diluting the survival benefit of clinical trials.

Reference: Am J Clin Oncol 2021;44:603–12
Abstract

Independent commentary by Dr Henry Chan

Dr Henry Chan is a consultant haematologist at North Shore Hospital in Auckland. Following completion of specialist training in clinical and laboratory haematology, he completed a clinical fellowship in multiple myeloma and lymphoma at Princess Margaret Cancer Centre in Toronto. He is currently actively involved in clinical research, registrar teaching and patient education.

Epidemiological landscape of young patients with multiple myeloma diagnosed before 40 years of age

Authors: Caulier A et al.

Summary: This research from France reported that 214 patients diagnosed with MM (189 symptomatic) at age ≤40 years during the modern treatment era had similar disease characteristics to older patients, with 35% having anaemia, 17% having renal impairment and 13% having hypercalcaemia. In this younger cohort, 52.4%, 27.5% and 20.1% were ISS stage 1–3, respectively, 18% had high-risk cytogenetics, 90% were treated with intensive chemotherapy followed by autologous SCT, and 25% underwent allogeneic SCT (predominantly at relapse). After a median 76 months of follow-up, the respective estimated median OS and PFS durations were 14.5 years and 41 months. Significant predictors of poor outcome were bone lesions (adjusted HR 3.95 [p=0.01]), a high ISS score (2.14 [p=0.03]) and high-risk cytogenetics (4.54 [p<0.0001]), and among predefined time-dependent covariables, onset of progression significantly curtailed OS (13.2 [p<0.0001]). Compared with age- and sex-matched individuals, 5-year relative survival was 83.5%, and the estimated standardised mortality ratio was 69.9.

Comment (NC): These retrospective data from France give a rare glimpse into very young patients diagnosed with MM in the era of novel agents. Around 50% of the patients were diagnosed between 2011 and 2015. The disease presentation was similar to the overall myeloma population, except for higher proportions of patients with ISS-1 disease. The median OS of 175 months is encouraging. The traditional high-risk disease factors as outlined in the abstract are associated with a poorer outcome. Despite incredible advances in myeloma therapy, this group of young myeloma patients still has a 70-fold increase in mortality compared with their age/sex-matched peers. This probably explains why there is a higher than expected proportion of patients who received allogeneic SCT to attempt cure. With the introduction of more novel agents, including immunotherapy, outcomes in this group of patients will hopefully continue to improve. As this occurs, balancing outcome with treatment toxicity will be imperative.

Reference: Blood 2021;138:2686–95
Abstract

MCT1 is a predictive marker for lenalidomide maintenance therapy in multiple myeloma

Authors: Stroh J et al.

Summary: Gene expression profiling and RNA sequencing were performed on cell samples acquired from patients treated with maintenance lenalidomide (n=455), thalidomide (n=98) or bortezomib (n=101) for MM. It was found that lenalidomide recipients with high versus low *MCT1* expression had shorter PFS (31.9 vs. 48.2 months [p=0.03]) and OS (75.9 vs. not reached [p=0.001]), whereas there was no significant difference for PFS or OS according to *MCT1* expression level among bortezomib recipients. In an independent validation cohort of thalidomide recipients, individuals with high versus low *MCT1* expression had shorter OS (83.6 vs. not reached [p=0.03]). Functional validation showed that lenalidomide's efficacy was reduced by MCT1 overexpression in human MM cell lines, whereas there were no apparent changes with bortezomib in an *in vitro* or in an MM xenograft model.

Comment (NC): This group has previously shown that high expression of MCT1 and CD147 is associated with immunomodulatory drug resistance in MM patient samples and xenograft models. In the current study, 1486 patient samples were obtained and gene expression profiling done to determine MCT1 and CD147 expression. As outlined in the abstract, MCT1 (but not CD147) expression was associated with worse PFS/OS in patients treated with lenalidomide maintenance but not bortezomib maintenance. This was further tested and proven in MM cell-line and xenograft models. This finding will need further validation in clinical settings, but may bring us further forward in precision therapy in myeloma treatment.

Reference: Blood Adv 2022;6:515–20
Abstract

Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE)

Authors: Gay F et al.

Summary: Patients aged ≤65 years with newly diagnosed MM were randomised to receive four 28-day induction cycles of KRd or KCd (carfilzomib, lenalidomide/cyclophosphamide, dexamethasone), melphalan-autologous SCT, then four 28-day KRd or KCd consolidation cycles (n=158 for KRd and 159 for KCd) or twelve 28-day cycles of KRd (n=157) in the open-label phase 2 UNITO-MM-01/FORTE trial. After a median 50.9 months of follow-up, the VGPR or better rate was greater for KRd versus KCd recipients (70% vs. 53% [p=0.0002]). Participants were then randomised to maintenance carfilzomib plus lenalidomide (n=178) or lenalidomide alone (n=178), and after a median 37.3 months from this randomisation, the carfilzomib plus lenalidomide arm had a higher 3-year PFS rate than the lenalidomide only arm (75% vs. 65% [p=0.023]). Extensive safety data are also described in the abstract.

Comment (HC): There are two randomisations in the FORTE study. The first separated patients into either KRd-autologous SCT-KRd, KRd alone, and KCd-autologous SCT-KCd as initial treatment. After initial treatment, the second randomisation put patients into either lenalidomide alone or carfilzomib plus lenalidomide maintenance. Unsurprisingly, patients in the KRd-autologous SCT-KRd arm had a deeper response, a greater number of participants with 1-year sustained MRD negativity and better PFS than the other two arms. These results are consistent with those reported by IFM2009 and EMN02. Interestingly, unlikely IFM2009, where PFS was similar amongst those who were MRD-negative between the transplant and nontransplant arms, the FORTE study shows that the benefit of autologous SCT was maintained even amongst those who achieved MRD negativity prior to maintenance.

Although there is no doubt that the result achieved by the KRd-autologous SCT-KRd combination is impressive (ORR 97%, stringent CR 46% and MRD negativity 62%), it is also worth noting the comparison between KRd alone and KCd-autologous SCT-KCd. The KRd alone arm had a higher 1-year sustained MRD negativity rate (35% vs. 25%, statistical comparison not reported) and similar PFS to date (median 55.3 vs. 53 months) compared with KCd-autologous SCT-KCd. This raises an interesting resource utilisation question: would using a triple PI-immunomodulatory drug combination but forgoing autologous SCT be a more cost-effective option than using a less effective triple combination together with autologous SCT in the frontline setting? This will certainly depend on the cost of the medication and autologous SCT, which differ from country to country, but this may soon be a relevant question for many countries as the systems struggle to cope with the rising costs of these novel triple and quadruplet combinations. Lastly, although the result from the second randomisation has shown an improved PFS with carfilzomib plus lenalidomide over lenalidomide alone maintenance, the fact that carfilzomib requires intravenous administration is likely to be an ongoing barrier for widespread adoption of such practice due to cost and logistic issues.

Reference: Lancet Oncol 2021;22:1705–20
Abstract

Carfilzomib, lenalidomide, and dexamethasone followed by lenalidomide maintenance for prevention of symptomatic multiple myeloma in patients with high-risk smoldering myeloma

Authors: Kazandjian D et al.

Summary: Fifty-four patients with high-risk smouldering myeloma treated with eight 4-week cycles of KRd then twenty-four 28-day cycles of lenalidomide maintenance in this phase 2 trial had their responses assessed at every KRd cycle and every three cycles subsequently, with bone marrow biopsies and imaging performed by the eighth cycle and then annually. Median potential follow-up was 31.9 months. The MRD-negative CR rate (primary outcome) was 70.4%, with a median sustained duration of 5.5 years, and the 8-year likelihood of freedom from MM progression was 91.2%. The incidence of grade 3 nonhaematological adverse events was 38.9%, including thromboembolism, rash and pulmonary infection; there were no grade 4 events or deaths recorded.

Comment (HC): In the last decades, several studies have evaluated the role of pre-emptive treatment in patients with high-risk smouldering myeloma before their disease has progressed. Two of the original studies using lenalidomide (Mateos M-V et al., N Engl J Med 2013;369:438–47, Lonial S et al., J Clin Oncol 2020;38:1126–37) included some patients who would be classified to have myeloma-defining events in today's practice based on the latest SLiM CRAB criteria. This raises the question of whether the magnitude of benefit seen in those trials (improved PFS to symptomatic myeloma and OS) would still apply to today's smouldering myeloma patients. As this study was started before the introduction of the SLiM CRAB criteria, it also included ten patients (18.5%) who met those myeloma-defining criteria. The result from this study appears to be better than what has been demonstrated in the previously mentioned studies using lenalidomide (albeit the limitations of cross-study comparison). These patients treated with KRd followed by lenalidomide maintenance for 2 years had a very low risk of biochemical (23% in 8 years) and clinical progression (8.8% in 8 years). More impressively, 77.8% achieved MRD negativity, and the probability of sustained MRD negativity in these patients was 54.5% at 5 years. This sustained MRD-negative result raises the hope that such combination treatment could potentially change the biology of the disease for some patients when treated early.However, one of the main barriers for all these interventional studies for smouldering myeloma patients is how best to identify patients who would benefit from treatment. Many clinicians would have examples of patients fulfilling these biochemical definitions of high-risk smouldering myeloma yet remain stable for years. Meanwhile, there are also those who initially had a lower paraprotein or light chain level that quickly progressed. Unfortunately, biochemical markers can be imprecise in predicting disease progression on an individual level, especially when only taken from one single timepoint. Using genetic profiling, such as the presence of APOBEC genomic signature, could potentially be a better method for identifying patients at high risk of progression and thereby benefit from pre-emptive treatment.

Reference: JAMA Oncol 2021;7:1678–85
Abstract

Oral ixazomib-dexamethasone vs oral pomalidomide-dexamethasone for lenalidomide-refractory, proteasome inhibitor-exposed multiple myeloma

Authors: Dimopoulos MA et al.

Summary: Carfilzomib and/or bortezomib-exposed/intolerant, lenalidomide-refractory patients with MM who had received ≥2 lines of therapy were randomised to received ixazomib plus dexamethasone (n=73) or pomalidomide plus dexamethasone (n=49) until progression or toxicity in this phase 2 trial. After respective median follow-up periods of 15.3 and 17.3 months for the ixazomib/dexamethasone and pomalidomide/dexamethasone arms, there was no significant difference between them for median PFS duration (7.1 vs. 4.8 months [p=0.477]), including for the subgroups with two and ≥3 prior lines of therapy; there was also no significant between-group difference for quality of life. Treatment-emergent adverse events for the respective ixazomib/dexamethasone and pomalidomide/dexamethasone arms were 69% and 81% for those that were grade ≥3, 51% and 53% for those classified as serious, 39% and 36% for those leading to drug discontinuation, and 44% and 32% for those leading to dose reductions; 13% of participants from each arm died during the study.

Comment (NC): This trial examined an oral doublet combination in patients who were refractory to lenalidomide. This is a challenging situation, especially in frail patients. It showed that the ixazomib and pomalidomide doublet combinations only had modest activity with no significant difference in PFS. Both were well tolerated with similar rates of serious adverse events and quality of life. The serious adverse event profile differed between ixazomib and pomalidomide, which may be used to guide the treatment choice for patients in conjunction with their treatment history. It has been consistently shown in trials that triplets are superior to doublet combinations. This may be challenging to administer for older patients, but the addition of cyclophosphamide is a potential option. For younger patients, triplet combinations with the addition of bortezomib or daratumumab to pomalidomide/dexamethasone are likely to achieve a significantly better outcome. Hopefully we will see some of these agents funded in NZ in the near future.

Reference: Blood Cancer J 2022;12:9
Abstract

Longer term outcomes with single-agent belantamab mafodotin in patients with relapsed or refractory multiple myeloma

Authors: Lonial S et al.

Summary: Outcomes after 13 months of follow-up were reported for participants who received belantamab mafodotin 2.5 mg/kg for relapsed-refractory MM as part of the open-label phase 2 DREAMM-2 trial; 10% of participants were still receiving belantamab mafodotin 2.5 mg/kg as at Jan 31, 2020. Among 97 participants, the ORR was 32%, with 18 responders achieving a VGPR or better. The respective estimated median response, OS and PFS durations were 11.0 months, 13.7 months and 2.8 months, with results for participants with high-risk cytogenetics or renal impairment consistent with the overall study population. Patients with extramedullary disease had worse outcomes. Among participants who achieved a clinical response and prolonged dose delays, responses were maintained or deepened during their first prolonged dose delay in 88%. No new safety signals were noted.

Comment (HC): There was genuine excitement when the data for belantamab mafodotin were first presented a few years ago as the first-in-class antibody-drug conjugate targeting BCMA (B-cell maturation antigen) on malignant plasma cells. However, it appears that the enthusiasm for this agent has subsided somewhat in recent times, due to the advent of newer agents, such as bispecific antibodies (ORR ~70%) and anti-BCMA CAR (chimeric antigen receptor) T-cells (ORR ~90%), and the issues with keratopathy. In the DREAMM-2 study, triple-class-refractory patients were given either 2.5 mg/m^2 or 3.4 mg/m^2 of belantamab. This paper focuses on those who had 2.5 mg/m^2, as that was the eventually approved dose in the US and EU after demonstrating similar efficacy and a lower rate of keratopathy than 3.4 mg/m^2. In this extended follow-up, the efficacy data were similar to what have been presented previously – an ORR of 32% and a median duration of response of 11 months. Keratopathy remains an issue for 72% of the patients, even at the 2.5 mg/m^2 dose. More concerningly, 23% of those who experienced keratopathy had not yet recovered fully by the time of data analysis, and for those who did recover, the recovery could take a median of 86.5 days. Fortunately, for those who had achieved at least a PR, a significant delay in treatment (>3 cycles) secondary to keratopathy did not result in disease progression in most patients, with only 2/16 of these cases progressing during dose interruption. As it appears that the risk of keratopathy is partly dose-related, more work is needed to find the optimal dose and schedule for belantamab. Hopefully, with the potential synergistic effect of belantamab with other agents, such as bortezomib (DREAMM-7) and pomalidomide (DREAMM-8), there may be room to reduce the dose of belantamab when given in combination, thereby reducing the risk of keratopathy whilst maintaining clinically meaningful efficacy.

Reference: Cancer 2021;127:4198–212
Abstract

Impact of COVID-19 in patients with multiple myeloma based on a global data network

Authors: Martinez-Lopez J et al.

Summary: This was a report from Spain on the impact of COVID-19 in patients with MM on both local and global scales. Propensity score matched analyses revealed that new MM diagnoses were lower in 2020 than they were in 2019 (relative risk 0.86 [95% CI 0.76, 0.96]) and survival of newly diagnosed MM cases decreased (HR 0.61 [0.38, 0.81]). The risk of SARS-COV-2 infection was increased in patients with MM (relative risk 2.09 [95% CI 1.58, 2.76]), with such patients having a 9% higher excess mortality in 2020 than those without MM.

Comment (NC): This is a global study utilising electronic medical records to help understand the overall impact of COVID-19 on myeloma patients in the early phase of the pandemic. The study has shown an increased risk of infection and excess mortality in myeloma patients compared with matched nonmyeloma cohorts. It also showed a reduction in number of myeloma diagnoses and worse survival in 2020 compared with 2019. While the authors did not further explore the possible reasons for these findings, the poorer outcome is likely contributed by overload of health system by the pandemic, modification of therapy to minimise infection risks and potentially reduced clinic/hospital visits due to patients' concerns around infection risk. The survival of the matched cohort improved in the later half of 2020, but not for myeloma patients. NZ has been less impacted by COVID-19 compared with other countries, but the strain on our health system is still palpable. It will be worth monitoring our local data, especially with the arrival of the omicron variant.

Reference: Blood Cancer J 2021;11:198
Abstract

Comparison of venous thromboembolism incidence in newly diagnosed multiple myeloma patients receiving bortezomib, lenalidomide, dexamethasone (RVD) or carfilzomib, lenalidomide, dexamethasone (KRD) with aspirin or rivaroxaban thromboprophylaxis

Authors: Piedra K et al.

Summary: These researchers retrospectively compared incidences of VTE in patients with newly diagnosed MM undergoing induction therapy with RVd (bortezomib, lenalidomide, dexamethasone) or KRd with aspirin or rivaroxaban thromboprophylaxis. An analysis of a cohort of 305 patients revealed a significantly higher rate of VTE in patients who received the carfilzomib-based regimen versus the bortezomib-based regimen when aspirin was utilised (16.1% vs. 4.8%). This excess risk was mitigated by using low-dose rivaroxaban thromboprophylaxis instead of aspirin in patients receiving KRd (4.8%) without an increase in bleeding.

Comment (HC): MM and its treatment are known to be thrombogenic. Although there are established thromboprophylactic guidelines, they are lagging behind the changing treatment landscape where novel triplet therapies are becoming the norm. This single-centre retrospective study highlights the increased risk of VTE associated with the KRd combination, which was >3 times greater than RVd (16.1% vs. 4.8%) when only aspirin was used as prophylaxis; this risk was lowered to 4.8% amongst those who had rivaroxaban 10mg daily instead. In addition to highlighting the risk of KRd and the potential benefit of using rivaroxaban as prophylaxis, the study also found no increased bleeding risk associated with rivaroxaban (1% minor bleeding). In conjunction with data extrapolated from other clinical trials in nonmyeloma-related settings, it is reasonable to suggest that aspirin is not particularly effective in preventing venous thrombosis, and direct oral anticoagulants may be a safe and more effective option.

Reference: Br J Haematol 2022;196:105–9
Abstract

Autologous stem cell transplantation is safe and effective for fit, older myeloma patients

Authors: Pawlyn C et al.

Summary: This exploratory analysis of data from the phase 3 Myeloma XI randomised trial of pathways for transplant-eligible and -ineligible patients with myeloma examined the efficacy and toxicity of autologous SCT in older participants. Within the trial's transplant-eligible pathway, older participants were less likely to undergo stem cell harvest after induction than younger patients, and of those who underwent autologous SCT, there was an association between reduced PFS and increasing age. The tolerability of autologous SCT in older patients was good, with no differences in morbidity or mortality between patients aged <65, 65–69 and 70–75 years. An analysis of age-matched participants from the transplant- eligible and -ineligible pathways revealed that undergoing autologous SCT was associated with significantly better PFS and OS (respective HRs 0.41 and 0.51 [both p<0.0001]), even after adjusting for baseline covariates (including frailty-related and induction response).

Comment (NC): The study examined the use of autologous SCT in those over the age of 65 years compared with younger patients and the impact of autologous SCT on outcomes in the older patients. In the transplant-eligible group, 32% of patients were over the age of 65 years. Forty-five percent of patients over 70 years old received reduced-dose melphalan for the transplant. There was no difference in survival outcome for patients of similar age who received full- or reduced-dose melphalan. Conflicting results have been shown in previous retrospective studies on this. Despite a similar depth of response, those aged <65 years had significantly longer PFS compared with older patients. However, autologous SCT-related mortality was similar across age groups. This analysis showed fit patients over the age of 65 years benefited from autologous SCT with improved PFS and OS. However, transplant eligibility was determined by the treating clinicians, and despite the authors' best effort to balance fitness and response between the two groups, the analysis does still carry an inherent element of bias. Unfortunately, we still don't have randomised data on whether autologous SCT is beneficial for older patients compared with chemotherapy alone. However, this study does add further to our current body of evidence that autologous SCT is safe and feasible.

Reference: Haematological 2022;107:231–42
Abstract

Independent commentary by
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Dr Chien is a consultant haematologist at Auckland City Hospital. She completed her haematology training in Auckland and undertook a fellowship in bone marrow transplant and multiple myeloma at Vancouver General Hospital in Canada. Her main area of research interest is in therapy for plasma cell disorders.