Multiple Myeloma RESEARCH REVIEW™

Making Education Easy

Issue 6 – 2022

In this issue:

Abbreviations used in this issue

BCMA = B-cell maturation antigen
CAR = chimeric antigen receptor
CR = complete response
HR = hazard ratio
ICANS = immune effector cell-associated neurotoxicity syndrome
MM = multiple myeloma
MRD = minimal residual disease
OS = overall survival
PFS = progression-free survival
QOL = quality of life
SCT = stem-cell transplantation
VGPR = very good partial response

Welcome to issue 6 of Multiple Myeloma Research Review.

The first two studies selected for this issue are analyses focussing on MRD using phase 3 trial data of daratumumab-based regimens for the treatment of MM. These are followed by research papers focussing on infections in our patients with MM, one of which describes a simple score for predicting early severe infections, and the other reporting on infectious complications in patients treated with BCMA-targeted CAR T-cell therapy. There is also a cross-sectional study evaluating QOL, psychological distress and perceptions of prognosis according to line of therapy for patients with MM. We conclude with a paper reporting long-term real-world outcomes for patients with newly-diagnosed MM managed with RVD (lenalidomide, bortezomib, dexamethasone) induction followed by melphalan-conditioned autologous SCT and lenalidomide maintenance as standard of care.

We hope you enjoy this update in myeloma research. We appreciate all comments and feedback.

Kind regards,

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Sustained minimal residual disease negativity in newly diagnosed multiple myeloma and the impact of daratumumab in MAIA and ALCYONE

Authors: San-Miguel J et al.

Summary: This *post hoc* analysis from phase 3 trials of daratumumab in patients with newly diagnosed MM (MAIA [n=737] and ALCYONE [n=706]) sought to determine the prognostic value of sustained MRD negativity. Primary analyses from both trials demonstrated that adding daratumumab to standard front-line therapeutic regimens conferred significant reductions in the risk of disease progression or death and elicited higher rates of MRD negativity at stringency thresholds of 10^{-5} and 10^{-6} in transplant-ineligible participants. After median follow-up durations of >3 years, significantly higher rates of sustained MRD negativity were found in the daratumumab-containing arms compared with the standard regimen arms in both intent-to-treat (≥6- and ≥12-month sustained MRD-negativity rates in MAIA; 14.9% vs. 4.3% and 10.9% vs. 2.4% [p<0.001]) and CR or better populations. Achievement of MRD-negativity was associated with an ~80% reduced risk of disease progression or death (HRs 0.15 and 0.21 in MAIA and ALCYONE, respectively), regardless of treatment regimen, although higher rates of MRD negativity, sustained MRD negativity and prolonged PFS were achieved with daratumumab-containing regimens. A positive correlation was detected between duration of MRD-negative status maintenance and prolonged PFS.

Comment (NC): It is now well established that MRD negativity is associated with improved PFS regardless of the response achieved as per IMWG criteria for both transplant-eligible and -ineligible patients. It is logical to assume that sustained MRD negativity is also likely to translate to improved clinical outcomes, and this is shown in this study. A similar result has been reported in the transplant-eligible population in the FORTE trial previously. The unanswered question remains around the optimal time to examine sustained MRD negativity. In this trial, the authors have analysed MRD data at 6 and 12 months. It is worth noting the short follow-up to date (36 months in MAIA and 40 months in ALCYONE), and whether the current conclusion that the achievement of sustained MRD negativity correlates with outcome regardless of therapy received will hold up with longer-term follow-up. Another important point is that a large proportion of transplant-ineligible patients only receive one line of therapy for their myeloma, and the clinical benefit incrementally declines with each line of additional therapy. Therefore, using our best therapeutic option upfront is imperative. While the addition of daratumumab significantly increased the proportion of patients with CR with MRD negativity (25% vs. 7–9%), ultimately only around 10–15% of patients sustained this deep response at 12 months. The standard arms of both trials are also combinations that are less used nowadays. Future trials looking at regimens combining novel therapies may need to consider the use of a response-adapted approach to hopefully individualise therapy to achieve a deeper and more sustained response in a larger proportion of patients.

Reference: Blood 2022;139:492–501
Abstract

Prognostic value of minimal residual disease negativity in myeloma

Authors: Cavo M et al.

Summary: This combined analysis of the phase 3 POLLUX, CASTOR, ALCYONE and MAIA trials aimed to assess if MRD negativity allows prognostication in MM; the trials assessed the addition of daratumumab to standard-of-care regimens in 1067 participants with relapsed/refractory disease and 1443 with newly diagnosed transplant-ineligible MM. Overall, MRD-negative status was achieved by 16.7% of participants and a CR or better by 34%. There were higher rates of MRD-negativity, deep response of at least a CR and deep remission (MRD-negative status plus CR or better) with the daratumumab-based versus standard care regimens (26.8% vs. 6.5%, 45.9% vs. 22.2% and 57.5% vs. 29.5%, respectively [p<0.0001]); significantly higher rates of deep remission persisted across the trials when assessed individually (15–28.6% vs. 0–8.9%). The achievement of deep remission, comprised of at least a CR without evidence of residual disease, conferred an 80% reduction in the risk of disease progression or death (48-month PFS rates, 70.4% vs. 23.9%; HR 0.20 [95% CI 0.16, 0.24]) and this benefit was consistent regardless of treatment regimen, disease setting or cytogenetic risk; however, the magnitude of benefit was most pronounced with daratumumab-based regimens compared with standard regimens (0.55 [0.36, 0.84]).

Comment (HC): This is a somewhat unusual study, as it pooled patient data from both frontline and relapsed settings together. However, the message is consistent – MRD negativity is associated with improved survival regardless of treatment setting – which is in line with publications in this area over the last decade. However, unlike some other studies where survival outcomes were similar amongst MRD-negative patients regardless of treatment received, this analysis shows that patients with daratumumab did better even within the MRD-negative group. The separation in the PFS curve appears to have started around the 24-month mark. The study did not explore the exact reasons for this improvement in survival among those who received daratumumab. Still, possible explanations may include a deeper response beyond the sensitivity of the current MRD assessment and the potential legacy benefit of daratumumab. The latter appears to be further supported by superior PFS2 (PFS at the subsequent line of treatment) in the daratumumab cohort.

Reference: Blood 2022;139:835–44
Abstract

A simple score to predict early severe infections in patients with newly diagnosed multiple myeloma

Authors: Encinas C et al., & GEM/PETHEMA (Grupo Español de Mieloma/Programa para el Estudio de la Terapéutica en Hemopatías Malignas) cooperative study group

Summary: This was a *post hoc* analysis of infections reported in 1347 participants, including 847 candidates for SCT, from four clinical trials from the Spanish Myeloma Group. Severe infections within the first 6 months were reported at an incidence of 13.8%, with most affected participants experiencing their first episode within 4 months. The respective 4- and 6-month mortality rates due to infections were 1% and 1.2%. Factors associated with increased severe infection risk within 4 months included serum albumin level ≤30 g/L, Eastern Cooperative Oncology Group performance status >1, male sex and non-IgA type MM. These variables were used to develop a simple risk score to stratify patients into three severe infection risk groups, for which the probabilities of severe infection were 8.2% for the low-risk group (score 0–2), 19.2% for the intermediate-risk group (score 3) and 28.3% for the high-risk group (score 4).

Comment (NC): It has been well reported that newly diagnosed myeloma patients have an increased risk of infections, especially during the first few months of initiating treatment. This is likely due to a combination of disease- and treatment-related factors. Multiple groups (GMMG, EMN/HOVON and FIRST trial) have investigated the risk of severe infection (CTCAE grade ≥3 or respiratory infection of any grade) in transplant-eligible and/or -ineligible patients, and have attempted to form a scoring system to stratify early infection risk. The rate of early severe infection in the first 4–6 months is between 12% and 15%, with mortality rates of 1–2%. This is comparable with the result of the current trial. The authors attempted to apply the FIRST score system to this population, and found it to be nondiscriminatory at stratifying early infection risk in both transplant-eligible and -ineligible populations. The scoring system proposed by this group appears to be more discriminatory. The authors suggest that intermediate- and high-risk patients should be offered prophylactic antibiotics. This is based on the TEAMM (Drayson MT et al. Lancet Oncol 2019;20:1760–72) and GEM10>65 trial results. TEAMM is a randomised controlled trial comparing 3 months of placebo versus levofloxacin prophylaxis for newly diagnosed myeloma patients undergoing treatment. It showed a reduced risk of febrile episodes or death without an increase in resistant organisms or *Clostridioides difficile* infections. GEM10>65 mandated the same antibiotic prophylaxis regimen for all patients, and when compared with GEM05>65 had a reduced percentage of infection. One of the advantages of having a scoring system is to stratify infection risk and allow antibiotic use to high-risk patients only, which will minimise toxicities and costs. The scoring system and the suggested antibiotic prophylaxis approach will require validation in future trials.

Reference: Blood Cancer J 2022;12:68
Abstract

Infectious complications in patients with relapsed refractory multiple myeloma after BCMA CAR T-cell therapy

Authors: Kambhampati S et al.

Summary: Infections occurring ≤1 year after BCMA-targeted CAR T-cell therapy for MM were reported in this single-centre retrospective analysis of 55 patients. Prior to lymphodepletion, 35% and 18% of the patients had severe hypogammaglobulinaemia and lymphopenia, respectively, and 68% had received bridging chemotherapy prior to lymphodepletion. All but one patient developed grade 3–4 neutropenia during their first month of CAR T-cell therapy, and hypogammaglobulinaemia had developed in 76% within 1 year. Over a median 6.0 months of follow-up, there were 47 infection events in 29 patients (53% within 10 days of CAR T-cell infusion), of which 40% were bacterial, 53% were viral and 6% were fungal, 92% were mild or moderate, and 68% were lower/upper respiratory tract infections.

Comment (HC): Although this study represents the largest sample to date in evaluating the infectious complications of patients who received anti-BCMA CAR T-cell therapy, it is still a relatively small study population. Therefore, even though it did not demonstrate any significant association between factors such as the use of bridging chemotherapy, tocilizumab and steroid with infectious complications, it does not necessarily mean that there are no associations. The result could simply be because this study was underpowered. Regardless, it is reassuring that, although infections were common, they were mostly respiratory and viral, which is not dissimilar to those seen amongst patients with advanced relapsed myeloma. Considering that most of the current studies on anti-BCMA CAR T-cell therapies are still in phase 1–2 with small sample sizes and short follow-up, these real-world data provide an essential insight into the long-term safety profile of such treatment.

Reference: Blood Adv 2022;6:2045–54
Abstract

Quality of life, psychological distress, and prognostic perceptions in patients with multiple myeloma

Authors: O'Donnell EK et al.

Summary: Patients undergoing treatment (excluding maintenance) for newly diagnosed MM were recruited into one of the following three cohorts according to whether they were receiving first-line (n=60), second or third-line (n=60) or fourth-line or beyond (n=60). There were no significant differences according to treatment line group for QOL, symptom burden, fatigue or psychological distress. For the entire study population, the respective rates of clinically significant depression, anxiety and post-traumatic stress disorder symptoms were 23.9%, 23.9% and 24.4%. Despite 84.7% of the patients reporting they had been told their cancer was incurable by their oncologist, only 42.0% thought their cancer was incurable and only 30.6% acknowledged being terminally ill.

Comment (NC): While there are several limitations of this study, it still presents some very interesting data. There is a sizable proportion of myeloma patients (25%) who have clinically significant psychological stress due to their diagnosis. Furthermore, despite 85% of patients being told about the incurable nature of their disease, when asked about goal of therapy, 23% reported this to be curative, regardless of line of therapy they were receiving. Those who acknowledged the terminal illness nature of their diagnosis had higher psychological stress, symptom burden and lower QOL. In other haematological malignancies, patients' QOL and symptom burdens improve with time; however, this study clearly shows this is not the case for myeloma patients. The study is limited by the fact that it is a cross-sectional rather than longitudinal study. It also did not include patients who were in the maintenance phase of their therapy, where one may assume the impact of disease/treatment on QOL, symptom and psychological health is less. This study does remind us of the importance of screening for psychological health in clinics and ensure that patients can access appropriate support services throughout their treatment for myeloma, which can span many years. It is also crucial to realise that despite extensive counselling, patients' views on their goal of therapy are likely to be different to those of clinicians, and ongoing discussion is important to ensure realistic planning of management goals.

Reference: Cancer 2022;128:1996–2004
Abstract

Incidence and management of CAR-T neurotoxicity in patients with multiple myeloma treated with ciltacabtagene autoleucel in CARTITUDE studies

Authors: Cohen AD et al.

Summary: These researchers examined factors associated with movement and neurocognitive treatment-emergent adverse events for participants from the CARTITUDE-1 trial of ciltacabtagene autoleucel for MM; 5% of the trial's participants reported such events while receiving this BCMA-targeted CAR T-cell therapy. Participants who experienced such movement and neurocognitive adverse events typically had ≥2 of the following: high tumour burden, grade ≥2 cytokine-release syndrome or any-grade ICANS (immune effector cell-associated neurotoxicity syndrome) after ciltacabtagene autoleucel infusion, and high CAR T-cell expansion/persistence. After implementation of strategies to monitor and manage participants with movement and neurocognitive treatment-emergent adverse events, the incidence of such events fell from 5% to <1% across the ciltacabtagene autoleucel programme.

Comment (HC): CAR T-cells are promising treatments for patients with MM, and many early-phase trials are currently underway. The two forerunners in this area are idecabtagene vicleucel (Bristol Myers Squibb) and ciltacabtagene autoleucel (Janssen), and both are US FDA approved. This study evaluated the long-term neurotoxicity of the latter in the drug company-sponsored CARTITUDE-1 study. In addition to the much-reported cytokine-release syndrome and ICANS, which commonly occur within days of CAR T-cell infusion and are of limited duration, a minority of patients (5/97) also experienced late-onset movement and neurocognitive adverse events. Unlike ICANS, movement and neurocognitive adverse events do not appear to respond to treatments such as steroid or anakinra, and may potentially be chronic. The authors have identified that one of the amendable predictors for movement and neurocognitive adverse events is pre-infusion disease burden, highlighting the potential role of bridging chemotherapy in minimising this risk. The pathophysiology for ICANS and other CAR T-cell-related neurotoxicities remains poorly understood. Since movement and neurocognitive adverse events can occur after the patient has been discharged, robust monitoring would be essential for any centre wanting to offer CAR T-cell therapies in the future in NZ.

Reference: Blood Cancer J 2022;12:32
Abstract

Comparison of cilta-cel, an anti-BCMA CAR-T cell therapy, versus conventional treatment in patients with relapsed/refractory multiple myeloma

Authors: Costa LJ et al.

Summary: These researchers compared outcomes for patients with anti-CD38 monoclonal antibody-refractory MM from the MAMMOTH study who would have been eligible for participation in the CARTITUDE-1 trial and had received non-CAR T-cell therapy with those of CARTITUDE-1 participants who underwent apheresis and received ciltacabtagene autoleucel; 95 participants from the CARTITUDE-1 intent-to-treat population and 69 from a modified intent-to-treat population of participants without progression or death within 47 days were propensity score matched to non-CAR T-cell therapy recipients from MAMMOTH. Compared with MAMMOTH participants, CARTITUDE-1 participants had improved overall response rates (84% vs. 28% and 96% vs. 30% for the intent-to-treat and modified intent-to-treat cohorts, respectively [both p<0.001]), longer PFS (respective HRs 0.11 [95% CI 0.05, 0.22] and 0.02 [0.01, 0.14]) and longer OS (0.20 [0.10, 0.39] and 0.05 [0.01, 0.22]).

Comment (NC): The CARTITUDE-1 and MAMMOTH studies both included a group of myeloma patients who were exposed and/or refractory to multiple currently available therapeutic agents. This group of patients often have poorer responses to subsequent lines of therapy and short survival outcomes. There are two anti-BCMA CAR T-cell therapies approved by the FDA for this indication based on single-arm studies showing high response rates and promising PFS data. In the MAMMOTH study, despite all patients being refractory to anti-CD38 antibodies, around a quarter of patients were retreated with the same class of agent, 34% received pomalidomide, 19% received carfilzomib and 35% received cytotoxic therapy. There is perhaps little surprise that ciltacabtagene autoleucel significantly outperformed the other available therapies used in the MAMMOTH study, despite many caveats of a retrospective propensity-matched study. The next question would be how anti-BCMA CAR T-cell therapy compares with off-the-shelf T-cell engagers and new agents/CAR T-cell therapies that target different antigens. We are also likely to see CAR T-cell therapy being moved towards earlier lines of therapy, which may further improve efficacy. Myeloma therapy is becoming increasingly expensive for many countries with publicly funded health systems. It will be imperative for future studies to investigate cost-effective ways of using these agents. NZ will also need to consider how we may be able to introduce these new classes of therapies to our myeloma patients to improve our outcomes and catch up with the rest of the developed world.

Reference: Clin Lymphoma Myeloma Leuk 2022;22:326–35
Abstract

Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM)

Authors: Richardson PG et al.

Summary: This article reported a prespecified updated 24-month OS analysis of the open-label phase 3 ICARIA-MM trial, which had randomised adults with relapsed/refractory MM to receive pomalidomide and dexamethasone with (n=154) or without (n=153) intravenous isatuximab 10 mg/kg on days 1, 8, 15 and 22 of the first 4-week cycle and days 1–15 of subsequent cycles. After a median 35.3 months of follow-up, median OS durations in the respective isatuximab and control arms were 24.6 months and 17.7 months (HR 0.76 [95% CI 0.57, 1.01]). The most common grade ≥3 treatment-emergent adverse events were neutropenia (50% and 35% of isatuximab recipients and nonrecipients, respectively), pneumonia (23% and 21%) and thrombocytopenia (13% and 12%), and the respective serious treatment-emergent adverse event rates were 73% and 60%. There were two treatment-related deaths in each group.

Comment (HC): Although pomalidomide-dexamethasone was the standard of care for relapsed myeloma when the study was designed, it is a relatively weak comparator by today's standard. As such, it should not come as a surprise that the addition of isatuximab had led to an improved survival outcome in this follow-up study. However, what is interesting are the PFS2 data (PFS during the subsequent line of therapy), where those who received isatuximab continued to be superior, even when compared with those who received daratumumab as the subsequent treatment in the control arm. This highlights the potentially detrimental effect of not using a triplet combination and saving an efficacious agent for later.

Reference: Lancet Oncol 2022;23:416–27
Abstract

Melflufen or pomalidomide plus dexamethasone for patients with multiple myeloma refractory to lenalidomide (OCEAN)

Authors: Schjesvold FH et al., on behalf of the OCEAN (OP-103) Investigators

Summary: OCEAN was a randomised open-label phase 3 study of melflufen (melphalan flufenamide; n=246) versus pomalidomide (n=249), both administered as a doublet with dexamethasone, in patients with relapsed/refractory MM; median follow-up periods were 15.5 months and 16.3 months in the two respective arms. Compared with the pomalidomide combination, the melflufen combination was associated with a small but significant prolongation of median PFS (6.8 vs. 4.9 months; HR 0.79 [95% CI 0.64, 0.98]), but a shorter median OS duration in the intent-to-treat population (19.8 vs. 25.0 months; HR 1.10 [0.85, 1.44]). The fatal treatment-emergent adverse event rates in the melflufen and pomalidomide arms were 12% and 13%, respectively, with two and four from the respective arms deemed possibly treatment-related.

Comment (NC): While at first glance melflufen appears to be a promising new version of the well-known melphalan, the result of this trial has not quite lived up to its initial expectation. All the patients were refractory to lenalidomide, but only two-thirds of patients were double refractory and 18% of the patients were refractory to daratumumab. The comparator arm is an immunomodulatory drug-based doublet, which is suboptimal in this group of patients where triplets with anti-CD38 antibody and/or proteasome inhibitor-based regimens are likely to be preferred by most clinicians. With this in mind, the investigational arm only showed a modest improvement in PFS by 2 months. More importantly, not mentioned in the abstract, is that OS was lower in the melflufen/dexamethasone arm compared with the pomalidomide/dexamethasone arm, although this was not statistically significant. Close watch of long-term follow-up results will be important. In fact, the FDA has put a hold on all melflufen trial recruitment due to the preliminary OS result from this trial, and the company has subsequently withdrawn melflufen from the US market. The exploratory analysis does raise an interesting point that patients who had not received previous autologous SCT (50%) seemed to have better PFS and OS outcomes when treated with the melflufen/dexamethasone combination.

Reference: Lancet Haematol 2022;9:e98–110
Abstract

Real-world long-term outcomes in multiple myeloma with VRD induction, Mel200-conditioned auto-HCT, and lenalidomide maintenance

Authors: Gaballa MR et al.

Summary: These researchers reported outcomes for a retrospective series of 187 patients with MM treated with RVD induction followed by melphalan 200 mg/m^2-conditioned autologous SCT and lenalidomide maintenance at their institution. The 100-day nonrelapse mortality rate was 0%, the respective pretransplant CR and VGPR or better rates were 9.6% and 52.9%, the respective 100-day post-transplant CR/stringent CR and VGPR or better rates were 29.4% and 74.9%, the respective CR/stringent CR and VGPR or better rates at last evaluation were 57.2% and 87.1%, and after median follow-up of 63.2 months, the respective median PFS and OS durations were 50 and 101.7 months, with respective 5-year PFS and OS rates of 43.1% and 79%. Outcomes were worse for patients with high-risk cytogenetics.

Comment (HC): RVD is considered the standard induction regimen for transplant-eligible patients in many countries, including Australia and the US. This is preliminary based on data showing the improved outcome over Rd (lenalidomide, dexamethasone) induction. However, direct comparisons with VTD (bortezomib, thalidomide, dexamethasone) or CyBorD (cyclophosphamide, bortezomib, dexamethasone) induction are limited, with only data showing a deeper response with RVD and no long-term survival comparison. This study evaluated the real-world outcome of RVD induction followed by autologous SCT in the era of lenalidomide maintenance. The result is, in some ways, underwhelming, with a median PFS of 50 months and OS of 101.7 months, which is not dissimilar to the Canadian data where the majority of patients received CyBorD before autologous SCT and lenalidomide maintenance (median PFS 58.2 months and OS 98.3 months; Cherniawsky HM et al. Haematologica 2021;106:1733–6). However, several caveats are worth noting. This study by Gaballa et al. measured survival from the time of autologous SCT, whereas the starting timepoint was not explicitly mentioned in the Canadian data. Secondly, as these studies only included patients who had undergone autologous SCT and maintenance, some degree of selection bias can exist. Thirdly, as RVD can induce a deeper response, it could have potentially allowed more high-risk patients to have a sufficient response to proceed to autologous SCT, which is a benefit of RVD that has not been evaluated in these studies.

Reference: Leuk Lymphoma 2022;63:710–21
Abstract

Independent commentary by Dr Henry Chan

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Independent commentary by Dr Nicole Chien,
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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.