Multiple Myeloma RESEARCH REVIEW™

Making Education Easy

Issue 8 – 2022

In this issue:

Abbreviations used in this issue
BCMA = B-cell maturation antigen
CAR = chimeric antigen receptor
CTC = circulating tumour cell
EMP = extramedullary plasmacytoma
HCT/SCT = haematopoietic/stem-cell transplant
ISS/R-ISS = (Revised) International Staging System
MM = multiple myeloma
MRD = measurable/minimal residual disease
NGS = next-generation sequencing
OS = overall survival
PFS = progression-free survival
VTE = venous thromboembolism

Welcome to issue 8 of Multiple Myeloma Research Review.

A second revision of the ISS that improves stratification of patients with intermediate-risk newly diagnosed MM begins this issue. Another included study evaluated the impact that autologous HCT has on MM burden, assessed by NGS, for a cohort of clinical trial participants treated with quadruplet induction, autologous HCT and then MRD-adapted consolidation. There is also research on vaccination against SARS-COV-2 in patients with MM that reports several implications for booster vaccines in immunocompromised patients. We also ask if the US predictive model for early mortality in patients with newly diagnosed MM is applicable locally. The issue concludes with research reporting that adding daratumumab to RVd (lenalidomide, bortezomib, dexamethasone) did not increase VTEs, although antithrombotic prophylaxis use was suboptimal and the cumulative incidence of VTE was relatively high.

Thank you for your feedback, which helps us find research to include that is important to you, so please keep sending us your comments.

Kind regards,

Dr Nicole Chien
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Second revision of the International Staging System (R2-ISS) for overall survival in multiple myeloma

Authors: D'Agostino M et al.

Summary: This report from the HARMONY project of the European Myeloma Network outlined a second revision to the ISS for MM to improve stratification of intermediate-risk disease. Analysis of data from >10,000 patients with newly diagnosed MM from 16 clinical trials identified five factors as having the greatest influence on OS and PFS: ISS, del(17p), lactate dehydrogenase level, t(4;14) and chromosome 1q gain/amplification. A prognostic model was created based on the presence of each factor with weighting according to degree of impact on outcomes that stratified patients into four discrete risk categories: low, low-to-intermediate, intermediate-to-high and high. The model retained prognostic significance for both OS and PFS in training and independent validation sets with median survival in the four risk groups of not reached, 109.2 months, 68.5 months and 37.9 months, respectively.

Comment: This is an update of the R-ISS prognostic score which aims to subclassify the large proportion of patients in the intermediate-risk group. The main difference is taking into consideration the additive effect of the high-risk cytogenetic abnormalities. t(14;16) has been excluded as it only affects PFS in multivariant analysis and not OS. Gain/amplification of 1q21 has been included, but unfortunately the data do not have the granularity to differentiate the two. In some studies, amplification has a more significant impact on survival outcome. The only additional variable required for R2-ISS is Ch1q21 abnormality, which makes it easy to use in clinics. It is worth noting the study population comprised a high proportion of younger and transplant-eligible patients and all patients were enrolled in clinical trials; therefore, further validation in the real-world population will be required.

Reference: J Clin Oncol 2022;40:3406–18
Abstract

Circulating tumor cells for the staging of patients with newly diagnosed transplant-eligible multiple myeloma

Authors: Garcés J-J et al.

Summary: In this Spanish cohort study of 374 adults with newly diagnosed MM, CTCs were detected in peripheral blood by next-generation flow cytometry before treatment in 92%. An inverse relationship was noted between percentage of CTCs and PFS. Multivariable analysis adjusted for ISS, lactate dehydrogenase level and cytogenetics identified a threshold value of 0.01% CTCs as an independent adverse prognostic factor for PFS associated with a doubled risk of disease progression (hazard ratio 2.02 [95% CI 1.3, 3.1]). Irrespective of complete remission or MRD status, undetectable CTCs correlated with favourable PFS.

Comment: The use of CTCs as a potential prognostic tool has many advantages, including easily accessible samples and avoidance of patchy disease distribution in bone marrow sampling. As shown in this study and another by Bertamini L et al. (J Clin Oncol 2022;40:3120–31), correlation with bone marrow plasma cell burden is poor, but CTC level correlates better with survival outcomes. Bruinink DHO et al. (J Clin Oncol 2022;40:3132–50) found that in patients with a high CTC level, the CTCs have primary plasma cell leukaemia-like features that may explain the correlation with poor prognosis. The cutoff for 'high CTC level' differs in studies, and further investigation and standardisation of testing method will be imperative. CTC detection requires the use of next-generation flow cytometry, which is only available in a limited number of centres, and the need for fresh samples will likely limit its utility in clinical practice. However, it does provide opportunity for prognostication and further understanding of myeloma disease biology.

Reference: J Clin Oncol 2022;40:3151–61
Abstract

Impact of autologous hematopoietic cell transplantation on disease burden quantified by next-generation sequencing in multiple myeloma treated with quadruplet therapy

Authors: Bal S et al.

Summary: These researchers used NGS to evaluate the impact of autologous HCT on MM burden in 123 participants from a clinical trial of quadruplet induction, autologous HCT and then MRD-adapted consolidation; 109 participants had undergone autologous HCT and had both pre- and post-transplant MRD assessments. MRD $<10^{-5}$ postinduction was achieved by 40% of the participants postinduction, which increased to 70% post-transplant. Among participants who remained MRD-positive postinduction (n=65), autologous HCT led to a reduction in MRD burden in 83%; the median reduction in MRD after autologous HCT was 1.10 $\log_{10}$. The reduction in MRD burden post-transplant was significantly greater in participants with high-risk cytogenetic abnormalities; the respective median relative reductions for participants with 0, 1 and ≥2 high-risk cytogenetic abnormalities were 0.91 $\log_{10}$, 1.26 $\log_{10}$ and 1.34 $\log_{10}$, and the only factor associated with a >1 $\log_{10}$ reduction in MRD burden with autologous HCT was the presence of high-risk cytogenetic abnormalities.

Comment: This analysis is based on patients from the MASTER study, which is a phase 2 trial investigating the use of four cycles of daratumumab-KRd (carfilzomib, lenalidomide, dexamethasone) induction followed by autologous HCT and MRD-directed consolidation therapy (Costa LJ et al. J Clin Oncol 2022;40:2901–12). Participants achieving MRD negativity entered treatment-free observation. This is one of the first published studies to investigate the use of response-adapted therapy in myeloma. The rationale of using this quadruplet combination is to maximise the chance of achieving MRD negativity. The proportion of patients achieving MRD negativity postinduction and autologous HCT is extremely encouraging, given 57% of the patients had ≥1 high-risk cytogenetic abnormality. It appears that despite effective quadruplet therapy, there remains a potential role for autologous HCT. Ongoing follow-up for sustained response and survival outcomes will be important. The role of autologous HCT is well established in the setting of triplet induction. However, autologous HCT is associated with significant toxicity, and in the future whether this is required for all patients and whether it can be replaced by immunotherapy remains to be explored.

Reference: Am J Hematol 2022;97:1170–7
Abstract

Independent commentary by Dr Nicole Chien, MB ChB (Otago); FRACP - Internal Medicine

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.

Paraskeletal and extramedullary plasmacytomas in multiple myeloma at diagnosis and at first relapse

Authors: Jiménez-Segura R et al.

Summary: These authors reported on their institution's experience with managing paraskeletal and EMPs (extramedullary plasmacytomas) in 1304 patients with MM; 17.6% and 1.9% had paraskeletal and EMPs, respectively. Plasmacytomas were associated with lower serum M-protein levels and less advanced ISS stage. At first relapse, 19.8% of the patients had developed plasmacytomas (14.6% paraskeletal, 5.1% EMPs). Plasmacytomas at diagnosis was the only factor significantly associated with the development of plasmacytomas at relapse (46% vs 13% [p<0.00001]). For patients without plasmacytomas, paraskeletal plasmacytomas and EMPs, the respective median OS durations were 45, 44 and 20 months (p=0.013), and for those who underwent autologous SCT, OS was similar between those with paraskeletal plasmacytomas versus those without but significantly longer (p=0.006) than for those with EMPs (98 vs. 113 and 47 months, respectively). In SCT-ineligible patients, those with paraskeletal plasmacytomas and those with EMPs had shorter OS than those without plasmacytomas (32 and 24 vs. 6 months [p=0.009]). Among patients who relapsed, survival was significantly better after the year 2000, but significant differences persisted among patients without plasmacytomas, paraskeletal plasmacytomas and EMPs (37 vs. 22 vs. 16 months [p=0.003]). Rescue therapy (proteasome inhibitors plus immunomodulatory drugs) was associated with prolonged OS from first relapse, even for patients with EMPs.

Comment: EMP at initial presentation is extremely rare as demonstrated in this single-centre series, where over a period of 48 years, only 26 cases were diagnosed. Even at first relapse, only 5% of patients developed EMPs. The introduction of novel agents has led to improvement in survival outcomes for patients with paraskeletal plasmacytomas but not for those with EMPs. The median OS is 4 vs. 8 years for EMPs versus paraskeletal plasmacytomas. Immunotherapies including CAR T-cell therapy, which have shown extremely promising results in myeloma, only have modest effects in patients with EMPs. This paper emphasises the importance of differentiating the two types of plasmacytomas, which likely have different disease biology, to explain differences in response to therapy and survival outcomes.

Reference: Blood Cancer J 2022;12:135
Abstract

Determinants of neutralizing antibody response after SARS CoV-2 vaccination in patients with myeloma

Authors: Nooka AK et al.

Summary: These researchers assessed serological responses to vaccination against SARS-COV-2 and environmental exposure to the virus by analysing the sera of 238 patients with MM who had been vaccinated. They detected vaccine-induced neutralising antibodies at a rate of 54%, which is lower than estimated in previous seroconversion studies in MM, although these earlier studies did not monitor viral neutralisation. One-third of the patients in this study had vaccine-induced antispike receptor-binding domain antibodies that lacked detectable neutralising capacity, including against the B1.617.2 variant of the virus. Race, disease and treatment-related factors were found to affect induction of neutralising antibodies. A significantly greater induction of neutralising antibodies was seen among patients who received Moderna's mRNA1273 vaccine compared with those who received Pfizer's BNT162b2 vaccine (67% vs. 48% [p=0.006]).

Comment: This paper assessed the vaccine response by measuring presence of neutralising antibodies and anti-receptor-binding domain antibodies. Neutralising antibodies are more predictive of vaccine-induced immune protection against symptomatic infection. Eighty-seven percent of patients had detectable anti-receptor-binding domain antibodies, but only 54% had neutralising antibodies. A similar study done by the same group in healthy donors did not show the disparity in induction of these two antibodies. The difference is thought to be due to myeloma-related depletion of naïve B-cells or defective B-cell maturation. There are host, disease and treatment factors that influence vaccine induction of neutralising antibodies. These have been shown in previous studies as well. While autologous SCT and CAR T-cell therapies did not influence vaccine response in multivariant analysis, patients in this trial mostly had autologous SCT more than a year ago and the number of patients treated with CAR T-cell therapy is small. Lastly, myeloma patients appear to respond better to Moderna vaccines, which is intriguing and worth further investigation. Vaccine response in various haematological malignancies has been studied extensively in the last few years due to the COVID-19 pandemic. It furthers our understanding in this field and assists in minimising risk of infection/severe disease while treating these patients.

Reference: J Clin Oncol 2022;40:3057–64
Abstract

Teclistamab in relapsed or refractory multiple myeloma

Authors: Moreau P et al.

Summary: In this phase 1–2 trial, 165 heavily pretreated adults with relapsed or refractory MM disease after ≥3 prior lines of therapy received subcutaneous teclistamab 1.5 mg/kg once per week; 77.5% of participants had triple-refractory disease. The overall response rate after a median 14 months of follow-up was 63%, two-thirds of which were deep responses (complete response or better). The rate of MRD-negativity was 26.7% overall and 46% in patients achieving a complete response or better. The median duration of response exceeded 18 months and the median PFS duration was 11.3 months. Cytokine-release syndrome was common (72.1%) but was predominantly of mild or moderate severity (0.6% grade 3; no grade 4). Other frequent adverse events included haematological events (neutropenia, anaemia and thrombocytopenia) and infections.

Comment: Teclistamab has shown promising efficacy in this early-phase trial with results comparable with currently available anti-BCMA CAR T-cell products. The overall response rates were 63%, 73% and 98% and median PFS durations were 11.3 and 10.7 months and not reached for teclistamab, idecabtagene vicleucel and ciltacabtagene autoleucel, respectively. During the trial, the step-up and first doses were given in hospital, but the authors argue this may not be necessary given <1% had grade 3–4 cytokine-release syndrome. The infection rate was high and included 12 deaths due to COVID-19. While this may reflect the period of recruitment, being the beginning and height of the COVID-19 pandemic, the high infection rate will need to be monitored in future trials involving this agent. There are multiple anti-BCMA agents with different modes of actions, including antibody-drug conjugates, CAR T-cells and bispecific antibody, approved by US FDA. The choice of which anti-BCMA agent to offer to patients can be complex and will depend on multiple factors. Another question is whether anti-BCMA agents can be given sequentially. Furthermore, the scene of immunotherapy is moving rapidly in myeloma and agents with promising new targets such as GPRC5D and FCRL5 currently in clinical trials.

Reference: N Engl J Med 2022;387:495–505
Abstract

Daratumumab in first-line therapy is cost-effective in transplant-eligible patients with newly diagnosed myeloma

Authors: Yamamoto C et al.

Summary: This economic analysis utilised Markov modelling with a 10-year time horizon to evaluate the cost effectiveness of adding daratumumab to standard front- and second-line regimens for newly diagnosed transplant-eligible MM. In the absence of long-term data, interim data regarding MRD status following induction therapy with an RVd or VTd (lenalidomide/thalidomide, bortezomib, dexamethasone) triplet regimen with or without daratumumab from the GRIFFIN and CASSIOPEIA trials were used to estimate PFS in the model. Incorporating daratumumab into front-line regimens, as opposed to delaying its use to the second-line setting in combination with carfilzomib/dexamethasone, was reported to be the dominant strategy associated with significantly lower costs and superior clinical outcomes for transplant-eligible patients. In analyses from both Japanese and US payer perspectives, the addition of daratumumab to standard front-line triplet regimens, RVd and VTd, conferred higher QALYs (5.43 vs. 5.18 and 5.67 vs. 5.42, respectively) and approximately 10% lower costs versus the triplet regimen alone.

Comment: The number of antimyeloma agents is rapidly growing, and there is always argument about using the best treatment first versus sequencing the novel agents. The rationale of 'using the best first' is around the concern of development of resistance in the myeloma clones and the attrition rate with each line of therapy. This study makes multiple assumptions zin the analysis. However, in this hypothetical model, the use of daratumumab as part of first-line therapy was shown to be cost effective. Obviously, the analysis will differ depending on the drug cost in each jurisdiction and availability of other agents at disease relapse. The hard question is how to prioritise drug funding in myeloma in countries with public health systems like NZ where overall costs should and need to be considered. The complexity and the rapid change in the field makes funding decisions extremely difficult, especially with the prolonged reviewing process through Pharmac. At the current time there is still no funded immunotherapy option available for myeloma in NZ.

Reference: Blood 2022;140:594–607
Abstract

Predictors of early mortality in multiple myeloma

Authors: McQuilten Z et al., Australian and New Zealand Myeloma and Related Diseases Registry

Summary: In order to assess whether the US predictive model for early mortality in patients with newly diagnosed MM is applicable in the Australasian setting, these researchers explored the frequency and causes of early mortality in a cohort of registrants entered in the MRDR (Myeloma and Related Diseases Registry). The analysis included 2377 patients diagnosed at 36 New Zealand or Australian institutions prior to March 2020 with ≥12 months of follow-up data available. The rate of early mortality, defined as death from any cause within the first 12 months after diagnosis, was 9.1%, half of which occurred in the first 6 months. The primary cause of early mortality was predominantly myeloma (78%). Infection contributed to 38% of deaths and was the primary cause in 7%. Older age, poor ECOG performance status and high serum albumin level were associated with increased likelihoods of 6- and 12-month mortality on adjusted multivariable regression analysis.

Comment: These are important local data showing our early mortality rate is similar to other published population-based studies. Despite recent advances in antimyeloma therapy, the real-world early mortality rate is still around 10%, which is much higher than reported in clinical trials. Disease remains the most common cause. It's worth noting around 45% of patients had infection as the primary or secondary cause of death. Studies have shown antibacterial prophylaxis during the early phase of treatment to be effective in preventing infection in myeloma patients without an increase in bacterial resistance (Drayson MT et al. Lancet Oncol 2019;20:1760–72). However, whether this is necessary for all patients or high-risk individuals only is debatable.

Reference: Br J Haematol 2022;198:830–7
Abstract

Isatuximab plus carfilzomib and dexamethasone in relapsed multiple myeloma patients with high-risk cytogenetics

Authors: Spicka I et al.

Summary: The efficacy and safety of isatuximab with (Isa-Kd) or without (Kd) carfilzomib and dexamethasone in patients with high-risk cytogenetic MM was explored in this subgroup analysis from the IKEMA randomised trial; ≥1 high-risk chromosomal abnormality was present in 23.5% and 25.2% of Isa-Kd and Kd recipients, respectively. The addition of isatuximab was associated with a PFS benefit for participants with standard-risk cytogenetics as well as those with high-risk cytogenetics (respective hazard ratios 0.440 [95% CI 0.266, 0.728] and 0.724 [0.361, 1.451]). In participants with high-risk cytogenetics, Isa-Kd recipients had a higher incidence of grade ≥3 treatment-emergent adverse events than Kd recipients (85.7% vs. 63.3%), but a similar incidence of serious treatment-emergent adverse events (64.3% vs. 66.7%).

Comment: Anti-CD38 antibody agents have significantly changed the treatment landscape of myeloma. In this preplanned subgroup analysis of the IKEMA study, there was no difference in depth of response between the two arms in patients with high-risk cytogenetic abnormalities and a trend towards improved PFS, especially in those with t(4;14). This result is similar to that reported in the ICARIA trial, which compared Isa-Pd with Pd (pomalidomide, dexamethasone). While cross-trial comparison is often fraud, the benefit appears less pronounced when compared with the POLLUX and CASTOR trials where daratumumab was added to Rd and Vd, respectively. Interpretation of the effectiveness of a regimen in high-risk cytogenetic abnormalities is often difficult, due to the small numbers of patients included. A randomised trial specifically recruiting high-risk patients would be worthwhile. There is currently a phase 2 trial (GMMG-CONCEPT) examining Isa-KRd in newly diagnosed patients with high-risk cytogenetic abnormalities, and it is showing promising results with a 2-year PFS rate of 75.5% with a median follow-up of 25 months. The IFM 2018-04 study, which examined daratumumab-KRd in a similar patient population, is showing impressive response rates to date.

Reference: Eur J Haematol 2022;109:504–12
Abstract

Daratumumab plus lenalidomide, bortezomib and dexamethasone in newly diagnosed multiple myeloma

Authors: Sborov DW et al.

Summary: These researchers reported vascular thrombotic events in a *post hoc* analysis of the phase 2 GRIFFIN trial. GRIFFIN randomised eligible patients with newly diagnosed MM to receive RVd with or without daratumumab as induction before and consolidation after high-dose therapy and autologous SCT, followed by ≤2 years of lenalidomide maintenance with or without daratumumab. Aspirin ≥162 mg/day was recommended for VTE prophylaxis, and use was similar between the two study arms (84.8% and 83.3% in the daratumumab-RVd and RVd groups, respectively). There were 99 daratumumab-RVd and 102 RVd recipients included in this safety analysis, which revealed VTE incidences of 10.1% and 15.7% of participants from the respective arms, including grade 2–4 VTE incidences in 9.1% and 14.7%, with a significantly longer median time to first onset of VTE in daratumumab-RVd recipients (305 vs. 119 days).

Comment: Myeloma patients are at high risk of VTE. The IMWG guidelines assist clinicians in identifying high-risk patients/thrombogenic therapies and determine appropriate prophylaxis. However, it was published in 2014, and many agents have since become available. This study has not shown an increased risk with the addition of daratumumab to RVd. This has been demonstrated in other daratumumab-containing regimens previously. The VTE rate in this trial is higher than previously reported for the RVd regimen. The proportion of patients in both arms receiving antithrombosis prophylaxis at time of VTE diagnosis is around 60–70%. This is surprisingly low in a clinical trial setting where the protocol recommends prophylaxis as per IMWG guidelines. The reason for this is not clear. While the majority of VTEs occurred during induction, events continue to occur during consolidation and maintenance, and therefore clinical vigilance and ongoing prophylaxis may be required for high-risk individuals.

Reference: Br J Haematol 2022;199:355–65
Abstract