Multiple Myeloma RESEARCH REVIEW™

Making Education Easy

Issue 37 – 2021

In this issue:

Abbreviations used in this issue
BCMA = B-cell maturation antigen
COVID = coronavirus disease
FISH = fluorescence *in situ* hybridisation
HR = hazard ratio
MGUS = monoclonal gammopathy of undetermined significance
MM = multiple myeloma
OS = overall survival
PFS = progression-free survival
QOL = quality of life
SARS-COV-2 = severe acute respiratory syndrome coronavirus
SCT = stem-cell transplantation

NZMA New Zealand Medical Association

Welcome to issue 37 of Multiple Myeloma Research Review.

This issue begins with a retrospective, multinational report describing the clinical features associated with outcomes of patients with MM who had acquired SARS-COV-2 infection. There is also research demonstrating that autologous HSCT is an important therapy among patients with MM, even our elderly patients. Researchers from the US have performed some elaborate analyses of trial and real-world data to conduct indirect treatment comparisons between D-Rd (daratumumab, lenalidomide, dexamethasone; MAIA trial) and other standard-of-care regimens used for treating transplant-ineligible patients with newly diagnosed MM in community-based oncology practices in the US. The issue concludes with a health-related QOL analysis of the CASSIOPEIA randomised trial comparing VTd (bortezomib, thalidomide, dexamethasone) with versus without daratumumab in newly diagnosed, transplant-eligible MM.

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

Kind regards,

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Clinical features associated with COVID-19 outcome in multiple myeloma

Authors: Chari A et al.

Summary: These researchers reported outcomes from a group of 650 patients (median age 69 years) with plasma cell disorders (96% with MM) entered in the International Myeloma Society dataset who had acquired SARS-COV-2 infection. This retrospective analysis was limited to hospitalised patients with MM, for whom ~36% were diagnosed with MM during 2019–2020 and 54% were receiving first-line therapy. One third of the patients had died. Risk factors for mortality were age, International Staging System stage 3, high-risk disease, renal disease, suboptimal myeloma control (active or progressive disease) and the presence of ≥1 comorbidity; of these, age, high-risk MM, renal disease and suboptimal MM control remained independent predictors after multivariate adjustments. Prior transplant (including within a year of COVID diagnosis) and treatment for MM were not associated with outcome.

Comment (HC): Although NZ has been much less affected by COVID-19 than elsewhere in the world, the threat of this pandemic remains ever-present for our vulnerable patients with myeloma. The data from this study came from several European countries, the US and Brazil. The mortality rate from COVID increased from 4% for those who were managed as outpatients to 31% in hospitalised patients and 80% amongst those who required ventilation. Amongst those hospitalised, the probability of dying was estimated at 18% for a 40-year-old, 31% for a 60-year-old, and 49% for an 80-year-old. Interestingly, recent transplantation (within 6 months before COVID diagnosis) and the type of active myeloma treatment received just before contracting the virus were not prognostic on multivariate analysis. Only age, high-risk cytogenetics, uncontrolled myeloma and renal dysfunction were predictive of dying from COVID. This study provides a useful backdrop for managing myeloma patients with COVID, but hopefully, none of us would ever need to use it.

Reference: Blood 2020;136:3033–40
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.

For more information, please go to http://www.medsafe.govt.nz

Normalization of serum B-cell maturation antigen levels predicts overall survival among multiple myeloma patients starting treatment

Authors: Jew S et al.

Summary: These researchers reported that patients with MM who had normal serum BCMA levels when they started a new treatment for MM had significantly better PFS and OS than those with abnormal levels. They also reported that patients who started treatment with an elevated serum BCMA level (≥82.59 ng/mL) had significantly better OS and overall response rate if their serum BCMA level normalised. Serum BCMA normalisation was seen in all patients who achieved complete remission, with normalisation occurring in a median of 0.9 months, compared with a median time to complete remission of 5.0 months (p=0.0036).

Comment (HC): This is an interesting proof-of-concept study that illustrates the potential role of using serum BCMA level to measure and predict treatment response. The advantage of using serum BCMA level over paraprotein is its short half-life (24–36h vs. 21–25 days for IgG and 7–14 days for IgA). The study shows that patients who normalised their serum BCMA level experienced better PFS and OS in both newly diagnosed and relapsed settings. More importantly, those who normalised their serum BCMA level did so after only a median of 1.1 months of treatment. Although this is a single-centre study and the results will need to be validated externally, these findings raise the potential of using serum BCMA level as an early biomarker for predicting treatment failure.

Reference: Br J Haematol 2021;192:272–80
Abstract

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Age no bar: a CIBMTR analysis of elderly patients undergoing autologous hematopoietic cell transplantation for multiple myeloma

Authors: Munshi PN et al.

Summary: This analysis of data from patients with MM assessed outcomes after upfront autologous SCT in elderly patients aged ≥70 years; 15,999 patients were included, of whom 2092 were elderly. The proportion of older patients who received autologous SCT increased from 15% in 2013 to 28% in 2017. There was no significant difference between patients aged ≥70 vs. 60–69 years for nonrecurrence mortality (HR 1.3 [99% CI 10.0, 1.7]), disease recurrence and/or progression (1.03 [0.9, 1.1]), PFS (1.06 [1.0, 1.2]) or OS (1.2 [1.0, 1.4]). Older patients were more likely to receive low-dose melphalan, with 82% of all patients receiving 200 mg/m^2 and 58% of elderly patients receiving 140 mg/m^2), which was a risk factor for the inferior outcomes of 100-day nonrecurrence mortality (1% vs. 0% [p=0.003]), 2-year PFS (64% vs. 69% [p=0.003]) and 2-year OS (85% vs. 89% [p=0.01]).

Comment (HC): This large dataset from the CIBMTR found that nonrecurrence mortality increased with age, but there was no significant difference between those aged 60–69 years and those older than 70 years of age. This was despite those aged above 70 years having a greater proportion with poorer performance status (Karnofsky score <90) and higher Haematopoietic Cell Transplantation Specific Comorbidity Index (>0), both of which were independent prognostic factors for nonrecurrence mortality. This is consistent with other published data that indicate that autologous SCT is feasible for those aged above 70 years. However, as this is a heterogeneous group of patients, the more important question as to who should not be offered transplant in this age group remains unanswered. Unfortunately, the authors did not dissect the over 70-year age group data further, as it would have been useful to know the age distribution within this age group, nonrecurrence mortality outcomes between 70–74, 75–79 and ≥80 years, and nonrecurrence mortality between various performance and comorbidity status; these data would have helped clinicians in selecting the right patient for transplantation.

Reference: Cancer 2020;126:5077–87
Abstract

Ixazomib as postinduction maintenance for patients with newly diagnosed multiple myeloma not undergoing autologous stem cell transplantation

Authors: Dimopoulos MA et al., on behalf of the TOURMALINE-MM4 study group

Summary: The phase 3 TOURMALINE-MM4 trial randomised patients with newly diagnosed MM not undergoing autologous SCT, who had achieved a partial response or better on 6–12 months of standard induction therapy, to receive 28-day maintenance cycles of oral ixazomib 3mg (n=425) or placebo (n=281) on days 1, 8 and 15 for 2 years. Median follow-up was 21.1 months. Compared with placebo, ixazomib was associated with an 8-month extension of PFS and a longer time to disease progression (17.4 vs. 9.4 months; HR 0.659 [95% CI 0.542, 0.801]), with the benefit particularly pronounced in participants who achieved complete response or very good partial response postinduction. The benefit with ixazomib was maintained across all prespecified subgroups. Toxicities were mainly nausea (26.8% vs. 8.0% for ixazomib versus placebo), vomiting (24.2% vs. 4.3%) and diarrhoea (23.2% vs. 12.3%).

Comment (HC): This study included a wide range of patients, including 38% aged 75 years and above, 24% who were deemed frail, and 36% with creatinine clearance between 30 and 60 mL/min. Induction treatment was based on clinician's discretion, and the majority of the patients (82%) received bortezomib-based treatment without any concomitant immunomodulatory imide drugs. Their results showed a superior PFS with ixazomib maintenance, which is consistent with data published in the last decade supporting continuous therapy over those given within a finite period. Despite the anecdotal evidence that proteasome inhibitors may abrogate the negative prognostic impact of adverse cytogenetics, it is disappointing to see that ixazomib maintenance did not appear to have any impact on those with high-risk FISH cytogenetics (HR 1.011 [95% CI 0.631, 1.621]). One of the key competitors to ixazomib maintenance is the more well-studied lenalidomide maintenance. Albeit the limitations of cross-study comparison, it appears that ixazomib maintenance may not be as efficacious, with a median PFS of 17.4 months, compared with the 26 months seen with lenalidomide maintenance in the UK MRC XI study (Jackson GH et al. Lancet Oncol 2019;20:57–73). However, ixazomib does appear to be better tolerated with 22.1% experiencing serious adverse events, compared with 45% in the UK MRC XI study.

Reference: J Clin Oncol 2020;38:4030–41
Abstract

Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI)

Authors: Kumar SK et al.

Summary: Adults with relapsed or refractory MM (ECOG performance status ≤2) were randomised to receive eight 21-day cycles then 35-day cycles of oral venetoclax 800 mg/day (n=194) or placebo (n=97) along with bortezomib and dexamethasone in this phase 3 trial. After median follow-up of 18.7 months, median PFS duration was significantly longer in the venetoclax arm than in the placebo arm (22.4 vs. 11.5 months [p=0.010]). The most common grade ≥3 treatment-emergent adverse events were neutropenia (18% and 7% in the venetoclax and placebo arms, respectively), pneumonia (16% and 9%), thrombocytopenia (15% and 30%), anaemia (15% and 15%) and diarrhoea (15% and 11%). The serious treatment-emergent adverse event rates in the respective venetoclax and placebo arms were 48% and 50%, with treatment-emergent fatal infection rates of 4% and 0%. There were three treatment-related deaths in the venetoclax arm (two from pneumonia and one from septic shock) and none in the placebo arm.

Comment (HC): Despite having a superior PFS and depth of response, the venetoclax arm was associated with an inferior OS. On further analysis, the increased mortality rate was due to infection, especially amongst those who did not respond to treatment, which prompted a protocol amendment mandating *Pneumocystis jiroveci* prophylaxis. It was hypothesised that the increased rate of infection was due to the combined immunosuppressive effect from disease progression and venetoclax. One would wonder whether the same issue with infection would have been a problem if the study mandated *P. jiroveci* prophylaxis initially, or if they adopted fluoroquinolone prophylaxis as demonstrated in the TEAMM study (Drayson MT et al. Lancet Oncol 2019;20:1760–72). Regardless, it is also interesting to point out the marked difference in outcomes between those who had t(11;14) or high BCL2 expression (venetoclax was associated with improved PFS but similar OS) and those without t(11;14) and low BCL2 expression (similar PFS but inferior OS with venetoclax). This result indicates that although venetoclax may not be the right choice for all patients with myeloma, it does appear to be an effective treatment option for those with t(11;14) or high BCL2 expression, paving the way for the future of more tailored molecular-based treatment strategies.

Reference: Lancet Oncol 2020;21:1630–42
Abstract

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Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON)

Authors: Grosicki S et al.

Summary: Patients with relapsed or refractory MM were randomised to receive selinexor 100mg once per week, bortezomib 1.3 mg/m^2 once per week and dexamethasone 20mg twice per week (n=195), or bortezomib 1.3 mg/m^2 twice per week for the first 24 weeks and then once per week and dexamethasone 20mg four times per week for the first 24 weeks and then twice per week (n=207) in the open-label, phase 3 BOSTON trial; median follow-up durations for the respective arms were 13.2 and 16.5 months. Compared with the bortezomib plus dexamethasone doublet regimen, the selinexor-containing triplet regimen was associated with longer median PFS duration (primary endpoint; 13.93 vs. 9.46 months [p=0.0075]). The most frequent grade 3–4 adverse events were thrombocytopenia (39% and 17% with the triplet and doublet regimens, respectively), fatigue (13% and 1%), anaemia (16% and 10%) and pneumonia (11% and 11%). Grade ≥2 peripheral neuropathy affected fewer triplet regimen recipients than doublet regimen recipients (21% vs. 34% [p=0.0013]). The mortality rates in the respective triplet and doublet regimen arms were 24% and 30%.

Comment (KR): Selinexor is a first-in-class exportin-1 inhibitor that has been shown to have good activity in multiple relapsed and refractory patients. It has now been approved by the US FDA for use in this group of patients. This particular study was an open-label trial in many countries, with the usual shortcomings of this type of trial. There was a definite improvement in PFS of around 4.5 months and less peripheral neuropathy. A few patients in NZ have been able to access compassionate supply, and so selinexor is likely to have some role in the relapsed setting as there is a paucity of active agents currently available.

Reference: Lancet 2020;396:1563–73
Abstract

Daratumumab-lenalidomide-dexamethasone vs standard-of-care regimens: efficacy in transplant-ineligible untreated myeloma

Authors: Durie BGM et al.

Summary: MAIA trial participants treated with D-Rd (daratumumab, lenalidomide, dexamethasone) for newly diagnosed MM were compared with patients treated with common standard-of-care primarily at community-based US oncology practices with MAIA inclusion/exclusion criteria and propensity-score weighting applied. Anchored indirect treatment comparisons of D-Rd with VRd (bortezomib-Rd) and Vd, with Rd the common anchor, were undertaken using individual-level patient data from these sources. HRs of direct comparisons of D-Rd versus Rd for PFS within MAIA and of VRd versus Rd and Vd versus Rd within the oncology practices were used to inform indirect treatment comparisons for D-Rd versus VRd and Vd, respectively. D-Rd was associated with a significantly lower risk of progression or death when compared with Rd according to the direct comparison within MAIA (HR 0.54 [95% CI 0.42, 0.71]) and also when compared with VRd and Vd in the indirect treatment comparisons (0.68 [0.48, 0.98] and 0.48 [0.33, 0.69], respectively).

Comment (KR): There are no current trials that have compared D-Rd with standard treatments such as VRd or Vd. Therefore, this analysis was attempting to show that D-Rd as used in the MAIA trial (initially presented at ASH in 2019) could achieve a superior PFS compared with the standard induction regimens. The results confirm the impression from the MAIA trial that the daratumumab combination in transplant-ineligible patients has a significantly lower risk of progression or death and could be regarded as a state-of-the-art regimen in this group of patients.

Reference: Am J Hematol 2020;95:1486–94
Abstract

Independent commentary by Dr Ken Romeril, FRACP, FRCPA

Ken is a haematologist specialising in malignant haematology. He trained in Christchurch, Sydney and Southampton, and is currently at the Bowen Icon Cancer Centre. Ken has a particular interest in translational myeloma research and genetics. He is involved in clinical trials, is the current Chair of Myeloma New Zealand, a former chair of the ALLG Myeloma Sub-Committee, and is the NZ representative on the International Myeloma Working Group, which has around 200 members.

A longitudinal analysis of chromosomal abnormalities in disease progression from MGUS/SMM to newly diagnosed and relapsed multiple myeloma

Authors: Oliva S et al.

Summary: These researchers used FISH to investigate chromosomal abnormality variability in purified bone marrow plasma cells throughout the progression from MGUS or smouldering MM to newly diagnosed MM or plasma cell leukaemia in 139 samples from 144 patients followed for a median of 71 months. High-risk chromosomal abnormalities (presence of at least del[17p], t[4;14] and/or t[14;16], and 1p/1q if available/recorded) were detected at diagnosis of MGUS, smouldering MM or newly diagnosed MM in 28% of samples, and 37–39% harboured high-risk abnormalities at relapse. Among patients with newly diagnosed MM who evolved to relapsed/refractory MM (n=115), three populations were identified, namely: i) gain of new chromosomal abnormalities (27% of these patients); ii) loss of previously identified chromosomal abnormalities (9%); and iii) no changes (64%). Compared with the group with no change, patients with a chromosomal abnormality gain had shorter median OS duration (66 vs. 84 months [p=0.023]).

Comment (KR): This study gives further support to the importance of FISH analysis in most types of patients at initial diagnosis, and hopefully no one still doubts the utility of FISH studies. It was not a very large study, but the presence of a high-risk chromosomal abnormality was detected in a surprisingly high 28% as the group did include some MGUS and smouldering MM samples. There were predictive data also gathered, as this high-risk group had a shorter median survival compared with the 74 patients with no changes.

Reference: Ann Hematol 2021;100:437–43
Abstract

Renal response in real-world carfilzomib- vs bortezomib-treated patients with relapsed or refractory multiple myeloma

Authors: Kumar S et al.

Summary: These researchers reported renal responses in real-world patients with relapsed/refractory MM (1–3 prior lines of therapy) and renal impairment treated with either Kd (carfilzomib, dexamethasone; n=543) or Vd (bortezomib, dexamethasone; n=1005). In second-line, Kd was associated with significantly higher renal overall response and renal complete response rates than Vd (51.4% vs. 39.6%; adjusted incidence rate ratio, 1.45 [95% CI 1.18, 1.78] and 26.6% vs. 22.2%; 1.68 [1.24, 2.28], respectively); the renal response benefit associated with Kd persisted out to fourth-line. In a combined analysis of patients receiving Kd and Vd (second-line and second-to-fourth-line), OS and time to next treatment were both longer in renal responders than renal nonresponders.

Comment (KR): Carfilzomib was shown to confer improved survival in the ENDEAVOUR study, which included some NZ centres. This was a real-world study looking at renal response in patients with renal impairment, and this can be a challenging group. It has been shown previously that renal responders tend to fare better and this was borne out here. The patient group was rather small, but there is a strong indication that Kd was a superior regimen for renal rescue. It seems a pity that clinicians in NZ do not currently have access to carfilzomib and the situation is likely to be chronic.

Reference: Blood Adv 2021;5:367–76
Abstract

Bortezomib, thalidomide, and dexamethasone with or without daratumumab for transplantation-eligible patients with newly diagnosed multiple myeloma (CASSIOPEIA)

Authors: Roussel M et al.

Summary: Health-related QOL outcomes were reported for the open-label, phase 3 CASSIOPEIA trial, which randomised transplant-eligible adults with newly diagnosed MM to receive VTd (bortezomib, thalidomide, dexamethasone) with (D-VTd; n=543) or without (n=542) daratumumab, consisting of four 28-day induction cycles before and two 28-day consolidation cycles after HSCT. Health-related QOL questionnaires were completed at baseline by 94% of participants from each arm, and compliance rates after induction were 84% and 80% in the respective D-VTd and VTd arms, and 90% and 88% after consolidation. There was no significant difference between the D-VTd versus VTd groups for mean change in global health status score after induction (3.8 vs. 2.9), or from baseline to post-consolidation (9.7 vs. 8.7 [p=0.45]). Compared with VTd, D-VTd was associated with a significantly greater mean decrease in pain score after consolidation (–23.3 vs. –19.7 [p=0.042]), significantly greater improvements in emotional functioning (13.0 vs. 9.5 [p=0.013]) and constipation (–3.2 vs. 1.8 [p=0.025]), and a significantly smaller reduction in cognitive functioning (–5.0 vs. –7.9 [p=0.036]); between-group differences for changes in all other scales assessed were not statistically significant.

Comment (KR): This study is a follow-up to the large CASSIOPEIA phase 3 trial that showed a significant benefit in obtaining improved rates of stringent complete response using D-VTd prior and after an autologous HSCT. This was a secondary analysis to investigate the QOL by means of sophisticated questionnaires. The improvement in pain scores and lesser reductions in cognitive function were achieved in the D-VTd group compared with the control group. These data would appear to support the use of daratumumab in standard regimens in newly diagnosed transplant-ineligible myeloma, except that lenalidomide would be preferred to thalidomide nowadays.

Reference: Lancet Haematol 2020;7:E874–83
Abstract