Multiple Myeloma RESEARCH REVIEW™

Making Education Easy

Issue 4 – 2022

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Abbreviations used in this issue
BCMA = B-cell maturation antigen
CR/PR/VGPR = complete/(very good) partial response
CRS = cytokine-release syndrome
HR = hazard ratio
MM = multiple myeloma
ORR = overall response rate
OS = overall survival
PD-1/PD-L1 = programmed cell death (ligand)-1
PFS = progression-free survival
SCT = stem-cell transplantation

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Welcome to issue 4 of Multiple Myeloma Research Review.

Although the BCL-2 inhibitor venetoclax has been shown to be effective for treating MM in clinical trials, particularly for patients harbouring the t(11;14) translocation, data outside of clinical trials are lacking – the first paper addresses this limitation by reporting on patients treated with venetoclax at the Mayo Clinic. The Mayo Clinic also provides us with information on the optimal duration of lenalidomide maintenance following autologous SCT in MM, and choice of therapy for relapsed disease following maintenance therapy. As COVID-19 case numbers increase, information on the impact of COVID-19 for our myeloma patients is important. We include two such papers in this issue, one reporting on the incidence and course of COVID-19 infections for outpatients with MM treated with novel drugs in the Czech Republic, and the other reporting reduced humoral responses to COVID-19 vaccines (including BioNTech-Pfizer's BNT162b2) in patients with MM, particularly those receiving anti-CD38 therapy. The issue concludes with a predictive model derived via machine learning for predicting survival in MM.

We hope this issue helps to keep you up to date. We appreciate your comments and feedback, so please keep sending them.

Kind regards,

Dr Ahmed Kolkeila
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Venetoclax for the treatment of multiple myeloma

Authors: Sidiqi MH et al.

Summary: The medical records of 56 patients who had received venetoclax outside of clinical trials at the Mayo Clinic for relapsed/refractory MM were reviewed. The patients had received a median of six prior therapies, with 14% having received ≥10, and 95% were refractory to an immunomodulatory drug and proteasome inhibitor. Venetoclax was administered as a doublet with dexamethasone in 55% of the patients and as triplet or quadruplet therapy in 45%. There were no cases of tumour lysis syndrome recorded. Among evaluable patients (n=52), the ORR was 44%, with a median of 2 months for time to best response and a median response duration of 13.6 months. The respective median PFS and OS durations across the entire cohort were 5.8 months and 28.4 months, with both these outcomes significantly better in the presence of t(11;14) translocation.

Comment (KR): Venetoclax has become a hot topic of interest because of its increased efficacy when used in myeloma patients harbouring the t(11;14) translocation. This is a small study from the Mayo Clinic and 25% did not actually have the translocation, but they were wanting to describe the efficacy of the drug outside of a clinical trial. The group of patients was very heavily pretreated, so the ORR rate was on the low side at 44%. The median PFS for the whole group was 5.8 months, but the presence of the translocation gave an improved PFS of 9.7 months and the OS for venetoclax not reached as yet. This study does demonstrate some encouraging activity for venetoclax in the t(11;14) group with relapsed/refractory disease. A study has recently opened at Middlemore Hospital for this group, and I understand that patients from other DHBs may be able to participate.

Reference: Am J Hematol 2021;96:1131–6
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.

Teclistamab, a B-cell maturation antigen × CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MajesTEC-1)

Authors: Usmani SZ et al.

Summary: This was a preliminary report from the ongoing open-label, phase 1, first-in-human MajesTEC-1 study investigating the BCMA and CD3-bispecific antibody teclistamab in 157 adults with relapsed/refractory MM (ECOG performance status 0–1). In the dose escalation part of the trial, participants received step-up teclistamab doses intravenously (n=84) or subcutaneously (n=73), with the phase 2 recommended dose established to be 1500 µg/kg each week administered subcutaneously after 60 µg/kg and 300 µg/kg step-up doses. The ORR at this dose was 65% (evaluable n=40) at a median follow-up of 6.1 months, with 58% achieving a VGPR or better and median response duration not reached. There was also consistent T-cell activation and deepening of response over time. Grade 1–2 CRS was reported in 70% of participants and neutropenia was reported in 65% (40% grade 3–4).

Comment (HC): Several phase 1 trials using bispecific antibodies in patients with heavily pretreated MM are currently underway, and these include teclistamab (Janssen), elranatamab (Pfizer), REGN5458 (Regeneron) and cevostamab (Roche). With the exception of the latter, which is a FcRH5xCD3 bispecific antibody, all of the others are BCMAxCD3 bispecific antibodies. Although data from all of these studies have been published in abstracts, teclistamab is one of the first to have its data published in a peer-reviewed journal. Albeit this being a phase 1 study, the ORR of 70% at the recommended phase 2 dose is impressive in this heavily pretreated triple class exposed patient group, where published data in the past, with the exception of CAR T-cell therapy, only achieved response rates of around 30%. However, bispecific antibodies are not without their drawbacks. Although this teclistamab study introduced a split-dose ramp-up before cycle one day one to reduce CRS, this was still seen in 70% of the patients who received the recommended phase 2 dose. It is worth noting that although all of these were grade 1 and 2 only, grade 2 CRS would encompass someone needing <40% FiO_2 or vasopressor support for hypotension according to the Lee et al. criteria. These patients could potentially require tocilizumab and high-dependency unit support, making it difficult to be used in smaller or less experienced centres, at least during the first cycle when CRS mostly occurs.

Reference: Lancet 2021;398:665-74
Abstract

Outcome of COVID-19 infection in 50 multiple myeloma patients treated with novel drugs

Authors: Krejci M et al.

Summary: These authors reported on the incidence and course of COVID-19 for a retrospective cohort of 351 outpatients with MM from a single centre; 50 of the patients (32 males, median age 68 years) had a diagnosis of COVID-19 recorded (positive PCR test), of whom 19, 20 and 11 were ISS stage I–III, respectively, and 15, 12 and 17 had received daratumumab- lenalidomide- and bortezomib-based treatment, respectively. All patients had their antimyeloma treatment interrupted, 56% required hospitalisation for COVID-19 pneumonia (36% and 20% standard unit and ICU, respectively) and 18% died. Factors significantly associated with COVID-19 hospitalisation were nonresponsive (versus responsive) disease, ECOG performance status ≥3 vs. 0–2 and having ≥2 vs. 0–1 comorbidities, and factors significantly associated with COVID-19- related mortality were ECOG performance status ≥3 vs. 0–2, having ≥2 vs. 0–1 comorbidities and a serious COVID-19 course with ICU admission; age, gender, ISS stage, immunoparesis and antimyeloma treatment type were not predictors of a worse outcome. Complete recovery from COVID-19 was recorded for 82% of the patients, occurring in a median of 32 days.

Comment (KR): This was a study from the Czech republic where they detected COVID-19 disease in 14% of a group of 351 patients. There was a high rate of hospitalisation for pneumonia and 20% needed intensive care. It was interesting, however, that full recovery was able to be achieved in 82% of the patients, but still a high rate of death at 18%. There was also a high rate of comorbidities in the group. The interruption of MM therapy with symptomatic COVID-19 disease is strongly recommended.

Reference: Ann Hematol 2021;100:2541–6
Abstract

Phase 2 study of venetoclax plus carfilzomib and dexamethasone in patients with relapsed/refractory multiple myeloma

Authors: Costa LJ et al.

Summary: This phase 2 dose-escalation study in 49 adults with relapsed/refractory MM investigated oral venetoclax 400mg or 800mg combined with intravenous carfilzomib 27, 56 or 70 mg/m^2 and oral dexamethasone 20mg or 40mg in four dose-finding cohorts; an expansion cohort received venetoclax 800mg, carfilzomib 70 mg/m^2 and dexamethasone 40mg. Diarrhoea (65%), fatigue (47%), nausea (47%) and lymphopenia (35%) were the most common treatment-emergent adverse events. The serious adverse event incidence was 53%, and one of three treatment-emergent deaths was deemed to be treatment-related. The ORR was 80%, with respective rates of 92% and 75% in patients with (n=103) and without (n=36) t(11;14) translocations. The CR or better rate was 41% and the median PFS duration was 22.8 months.

Comment (HC): Following the publication of the BELLINI data (Moreau et al. ASH 2019 abstract; Kumar et al. Lancet Oncol 2020), where an unfavourable risk-to-benefit ratio was noted for non-t(11;14) patients receiving venetoclax with bortezomib and dexamethasone, the majority of the commentary on the role of venetoclax is primarily focused on those with t(11;14). This study was started before the publication of the BELLINI data, which would explain why it included non-t(11;14) patients. Although the study mandated antibiotic prophylaxis later on, given the BELLINI data, infection was still common in this not-so-heavily pretreated patient group, with 12% of the patients experiencing grade 3 or 4 pneumonia. Unfortunately, the authors did not indicate whether these respiratory tract infections occurred before or after the antibiotic mandate. Despite this, it is worth noting that an ORR of 80% (92% for those with t[11;14]) is still a good result in the relapsed/refractory setting. The authors plan to focus on t(11;14) patients in the future and compare the weekly venetoclax with bortezomib and dexamethasone regimen against bortezomib plus dexamethasone, which will hopefully give the combination more positive traction than what happened in the BELLINI study.

Reference: Blood Adv 2021;5:3748–59
Abstract

The effect of duration of lenalidomide maintenance and outcomes of different salvage regimens in patients with multiple myeloma (MM)

Authors: Ho M et al.

Summary: This retrospective study from the Mayo Clinic aimed to elucidate the optimum length of lenalidomide maintenance therapy and the efficacy of salvage regimens for 213 patients with MM who underwent autologous SCT and then received maintenance with lenalidomide with or without dexamethasone. The median PFS for the cohort was 4 years from diagnosis, and the 5-year OS rate was 77% with median OS not reached. Superior clinical outcomes were found in patients who received ≥3 vs. <3 years of maintenance therapy, including significantly ($p<0.05$) longer PFS (7.2 vs. 4.4 years) and a higher 5-year OS rate (100% vs. 85%). Patients who were lenalidomide refractory at first relapse had a shorter PFS2 than those without refractoriness (8.1 vs. 19.9 months). Salvage regimens containing daratumumab elicited superior PFS2 (18.4 vs. 8.9 months [$p=0.006$]), whereas combining daratumumab with an immunomodulatory drug resulted in longer PFS2 compared with combining daratumumab with bortezomib (not reached vs. 1 year [$p=0.004$]).

Comment (KR): This study from the Mayo Clinic group analysed a decent number of patients (n=213) who had received lenalidomide maintenance at the institution. Lenalidomide is the current preferred maintenance strategy following autologous SCT, especially in the non-high-risk group, and studies such as CALGB100704, GEMIMA and Myeloma IX have shown improvements in PFS. Only the CALGB study has shown a significant OS improvement with lenalidomide maintenance. There are no prospective data to guide the optimal duration, and the current practice is to continue until progression or toxicity. In this study, patients who got ≥3 years of maintenance had superior 5-year OS of 100% vs. 85% in those who got <3 years of maintenance. This association was significant even after adjusting for high-risk cytogenetics, age and ISS stage 3. Daratumumab-based therapies at relapse result in a significant improvement in PFS2.

Reference: Blood Cancer J 2021;11:158
Abstract

The neutralizing antibody response post COVID-19 vaccination in patients with myeloma is highly dependent on the type of anti-myeloma treatment

Authors: Terpos E et al.

Summary: Data from a Greek study were analysed to investigate the response to COVID vaccines in patients with plasma cell neoplasms; this analysis was based on 213 with active MM, 38 with smouldering MM and 25 with monoclonal gammopathy of undetermined significance, and 226 control patients of comparable age, who received either two doses of the BNT162b2 mRNA vaccine (BioNTech-Pfizer; 76.9%) or one dose of the Oxford-AstraZeneca viral vector vaccine (23.1%). All patients with smouldering MM were naïve to antimyeloma therapy and 12.3% of those with active MM were not receiving therapy at the time of vaccination. A suboptimal humoral response to COVID vaccination was observed in patients with plasma cell neoplasms compared with controls, with significantly lower proportions achieving clinically relevant neutralising antibody titres (≥50%) at postvaccination days 22 and 50 (19.9% vs. 32.3% [$p=0.002$] and 57.3% vs. 81% [$p<0.001$], respectively). A multivariable analysis identified active treatment with either anti-CD38 monoclonal antibodies or belantamab mafodotin as prognostic for suboptimal antibody response to vaccination.

Comment (HC): Many recent publications have illustrated the reduced humoral response to COVID vaccines amongst patients with haematological malignancies. This study from Greece specifically analysed those with plasma cell disorders, and evaluated the impact of different stages of the disease and treatment. Amongst patients with myeloma who are on treatment, anti-BCMA therapy appears to dampen humoral response the most, followed by anti-CD38 treatment. Meanwhile, patients on lenalidomide maintenance had a similar response to those who were off treatment. These data support the current recommendation for all myeloma patients to receive the third primary dose of the BioNTech-Pfizer vaccine in NZ, and one could extend that to include those with smouldering myeloma. Meanwhile, the data also reassure patients who are currently on lenalidomide maintenance that a temporary treatment hold is probably unnecessary before getting the COVID-19 vaccine. Questions remain as to the most appropriate management for those who are on anti-BCMA or anti-CD38 treatment. The authors mention the data from a UK study that suggested no reduction in antibody production following influenza, Haemophilus and Streptococcal vaccines in patients more than 2 months out from daratumumab. However, this will certainly need to be balanced against the risk of disease progression once treatment intensity is reduced. Although it may be worrying to see a subdued humoral response in these patients, it is important to note that these patients may still mount a T-cell response, as shown in 74% of lymphoma patients who did not seroconvert following COVID-19 vaccines (Marasco et al. Br J Haematol 2021).

Reference: Blood Cancer J 2021;11:138
Abstract

Maintenance with daratumumab or observation following treatment with bortezomib, thalidomide, and dexamethasone with or without daratumumab and autologous stem-cell transplant in patients with newly diagnosed multiple myeloma (CASSIOPEIA)

Authors: Moreau P et al.

Summary: The phase 3 open-label CASSIOPEIA trial evenly randomised 886 patients aged 18–65 years with newly diagnosed MM (ECOG performance status 0–2) to induction and consolidation with VTd (bortezomib, thalidomide and dexamethasone) with or without daratumumab, after which participants still on study with a PR or better underwent a second randomisation to intravenous daratumumab 16 mg/kg every 8 weeks (n=442) or observation only (n=444) for ≤2 years. After a median 35.4 months of follow-up from second randomisation, daratumumab recipients had longer median PFS than participants assigned to observation alone (not reached vs. 46.7 months; HR 0.53 [95% CI 0.42, 0.68]), with a significant interaction between maintenance and induction and consolidation therapy seen in a prespecified analysis of PFS. The most common grade 3–4 adverse events were lymphopenia (4% and 2% of the daratumumab and observation-only groups, respectively), hypertension (3% and 2%) and neutropenia (2% and 2%), with serious adverse events recorded for 23% and 19% of the daratumumab and observation-only groups, respectively. There were two treatment-related deaths in the daratumumab arm.

Comment (KR): This is an important paper building on the results of CASSIOPEIA part 1, which showed an improved PFS with the use of daratumumab plus VTd versus VTd as induction versus consolidation in patients with newly diagnosed MM who underwent autologous SCT. In part 2, this large study was carried out in 111 European academic and community practice centres. The patients that were still on study were assigned by an interactive web response to daratumumab 16 mg/kg intravenously every 8 weeks (this was a reduced frequency compared with standard daratumumab long-term dosing). Daratumumab maintenance given every 8 weeks for 2 years reduced the risk of progression or death compared with observation. This would be an expensive exercise.

Reference: Lancet Oncol 2021;22:1378–90
Abstract

Baseline serum B-cell maturation antigen levels predict time to disease progression for patients with smoldering multiple myeloma

Authors: Bujarski S et al.

Summary: The utility of baseline serum BCMA level for predicting progression of smouldering MM was investigated in 65 patients with the condition in this research. It was found that the optimal baseline serum BCMA level cutoff for differentiating between a high and low risk of progression from smouldering MM was 137.5 ng/mL, with patients in the high-risk group having a significantly shorter time to transformation. There was also a significantly higher serum BCMA level at the time of transformation compared with baseline. Serum BCMA level was found to be the sole variable significantly predictive of time to transformation, and was also found to be independent of other risk factors.

Comment (HC): This California group has previously evaluated the prognostic impact of serum BCMA level in those receiving frontline antimyeloma treatment and noted that those with a normal serum BCMA level (defined as <82.59 ng/mL in that study) at the beginning or following treatment had better OS (Jew et al. Br J Haematol 2020). In this single-centre study, they applied the same assay on patients with smouldering myeloma. Instead of using the cutoff of 82.59 ng/mL in their previous study, they used a threshold of 137.5 ng/mL for predicting progression within 5 years after reviewing the receiver operating characteristic curve. (Note, the manuscript reported the serum BCMA level as mg/mL and should have been ng/mL as confirmed by my subsequent correspondence with the senior author). The sensitivity and specificity of the test at that cutoff was 84.2% and 62.5%, respectively. Meanwhile, the overall rate of disease progression within 5 years in this cohort was lower than expected at 16%, giving positive and negative predictive values of 43% and 92%, respectively. One can argue that a test with a positive predictive value of around 50% is too low to be used as an indicator to initiate pre-emptive treatment. Given the high negative predictive value, the test is probably more useful in reassuring negative patients that a watch-and-wait approach remains appropriate. Lastly, it is worth noting that some of the authors in this paper have equities in a company called ONCOtracker, which owns the patent for the serum BCMA assay.

Reference: Eur J Haematol 2021;107:318–23
Abstract

Independent commentary by Dr Henry Chan

Dr Henry Chan is a consultant haematologist at North Shore Hospital in Auckland, New Zealand. 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.

Comparison of monoclonal antibodies targeting CD38, SLAMF7 and PD-1/PD-L1 in combination with bortezomib/immunomodulators plus dexamethasone/prednisone for the treatment of multiple myeloma

Authors: Ye W et al.

Summary: This was an indirect-comparison meta-analysis of data from 11 randomised controlled trials investigating one or more monoclonal antibodies targeting CD38, SLAMF7 or PD-1/PD-L1 in combination with bortezomib/immunomodulators plus dexamethasone/prednisone in 5367 patients with MM. For antibodies targeting CD38 versus SLAMF7, CD38 versus PD-1/PD-L1, and SLAMF7 versus PD-1/PD-L1, the respective HRs for PFS were 0.662 (95% CI 0.543, 0.806), 0.317 (0.221, 0.454) and 0.479 (0.328, 0.699), and for antibodies targeting CD38 versus SLAMF7, the HR for OS was 0.812 (0.584, 1.127) and the respective relative risks for CR or better and neutropenia were 2.253 (1.284, 3.955) and 1.818 (1.41, 2.344).

Comment (KR): This paper claims to be the first meta-analysis comparing the effectiveness and safety of different monoclonal antibodies in combination with other agents in the treatment of patients with MM. There are limitations to this study because the number of included studies that target SLAMF7 and PD-1/PD-L1 was actually insufficient. Despite all this, it does appear that monoclonal antibodies that target CD38 in combination with bortezomib/immunomodulators plus steroids do show a significant therapeutic value. The monoclonal antibodies that target the SLAMF7 group were not as effective as monoclonal antibodies that target CD38 such as daratumumab. It was also apparent that agents targeting PD-1/PD-L1 also tend to have a poor therapeutic effect.

Reference: BMC Cancer 2021;21:994
Abstract

Survival prediction and treatment optimization of multiple myeloma patients using machine-learning models based on clinical and gene expression data

Authors: Orgueira AM et al.

Summary: These researchers applied machine learning algorithms to MM clinical and RNAseq data collected by the CoMMpass consortium to create a 50-variable random forests model (IAC-50) for predicting OS. IAC-50 included patient age, ISS stage, serum β2-microglobulin level, first-line treatment and the expression of 46 genes, and was highly concordant between training and validation datasets. Survival predictions that took first-line treatment for each patient into account found that those treated with the best predicted drug combination were significantly less likely to die than those treated with other regimens, particularly those treated with a bortezomib, immunomodulatory drug and dexamethasone triplet. There was also a trend for IAC-50 to retain its predictivity in patients with high-risk cytogenetics.

Comment (HC): The idea of big data and machine learning could be somewhat foreign to clinicians, but this could potentially change how we view and interpret data in the future. With the ever-expanding data on new treatments, genetic profiling and clinical risk models, it is becoming near-impossible for individuals to incorporate all of this information when making a clinical decision. The idea of machine learning, in essence, is to ask the computer to look for patterns within the large dataset (in this case, data from the CoMMpass consortium) and formulate a model that will best predict outcomes in the cohort. This is not dissimilar to those multivariate analyses that we often see in published papers. However, it is worth noting that the quality of this model is only as good as the input data, and the machine cannot learn about things that have not been included in the training dataset. This means machine learning can be biased if the training cohort is not representative of the population. The model may also discriminate against minorities if appropriate adjustments are not made in the algorithm. It is, therefore, essential to validate these models with external cohorts and population minorities before they are implemented in clinical practice. However, as proof of concept, this study highlights the possibility of tailored, personalised treatment using machine-learning models that incorporate multiple clinical and genetic data. Locally, clinicians can help to ensure that our patient groups are well represented in any future modelling by contributing to large databases, such as the Myeloma and Related Diseases Registry.

Reference: Leukemia 2021;35:2924–35
Abstract