Multiple Myeloma Research Review™

Making Education Easy

Issue 25 – 2018

In this issue:

Abbreviations used in this issue

CR = complete response
HR = hazard ratio
Ig = immunoglobulin
MGUS = monoclonal gammopathy of undetermined significance
MM = multiple myeloma
ORR = overall response rate
OS = overall survival
PFS = progression-free survival
SCT = stem-cell transplantation
SFLC = serum-free light chain
VGPR = very good partial response

NZMA New Zealand Medical Association

myeloma new zealand

Myeloma NZ is a new foundation in NZ to provide a deeper level of support for those who affected by multiple myeloma. If patients or their loved one have been diagnosed with multiple myeloma, Myeloma NZ can help them learn about treatment options and point them to information and services to help them cope with the disease. www.multiplemyeloma.org.nz/

Welcome to issue 25 of Multiple Myeloma Research Review.

This issue begins with the final survival analysis of the FIRST trial, which compared continuous Rd (lenalidomide, low-dose dexamethasone), 18 cycles of Rd and MPT (melphalan, prednisone, thalidomide) in patients with SCT-ineligible, newly diagnosed MM. Other research included suggests that autologous SCT can be safely performed for selected individuals with MM in an outpatient setting. The ALCYONE Trial Investigators have conducted an interim analysis that suggests that the risk of disease progression or death is lowered by adding daratumumab to VMP (bortezomib, melphalan, prednisone) in patients with newly diagnosed MM who are ineligible for SCT. This issue concludes with research suggesting venetoclax monotherapy has an acceptable safety profile and antimyeloma activity in patients with relapsed/refractory MM.

Your comments and suggestions are always welcome, so please keep sending them.

Kind regards,

Dr David Simpson
davidsimpson@researchreview.co.nz

Dr Ken Romeril
kennethromeril@researchreview.co.nz

Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma

Authors: Facon T et al.

Summary: The phase 3 FIRST trial recruited 1623 autologous SCT-ineligible patients with newly diagnosed MM to receive continuous Rd until disease progression (n=535), 18 cycles of Rd (n=541) or 21 cycles of MPT (n=547). This paper described outcomes at median follow-up of 67 months. Continuous Rd was associated with improved PFS, with a lower risk of progression or death compared with MPT (HR 0.69 [95% CI 0.59, 0.79]) and a similar benefit when compared with 18 cycles of Rd. Compared with MPT, continuous Rd improved median OS duration (59.1 vs. 49.1 months; HR 0.78 [95% CI 0.67, 0.92]) and was similar to the 62.3-month OS duration seen with 18 cycles of Rd. Continuous versus 18 cycles of Rd was associated with a longer median time to next treatment in participants achieving CR or VGPR. Bortezomib was the basis of second-line treatment in >50% of participants who required such treatment, and their outcomes were better if they had previously received one of the Rd regimens rather than MPT. There were no new safety concerns, including secondary malignancy risk.

Comment (KR): There appears to be a succession of papers emanating from the FIRST trial, which was considered pivotal when first presented at ASH by Facon. This one is the final analysis of survival outcomes and shows that the median OS on treatment with continuous Rd is around 5 years, which is certainly significant in newly diagnosed MM patients. Bortezomib at relapse also appeared to have utility, as the patients did not get this drug up front.

Reference: Blood 2018;131:301–10
Abstract

Phase II study of bortezomib, cyclophosphamide and dexamethasone as induction therapy in multiple myeloma

Authors: Einsele H et al.

Summary: Treatment-naïve patients with MM (n=414) received three 21-day cycles of VCD (bortezomib, cyclophosphamide, dexamethasone) as induction therapy prior to autologous SCT in the DSMM XI trial. The most common grade ≥3 adverse events were leucopenia in 31.4% and thrombocytopenia in 6.8%. The investigator-assessed ORR was 85.4%, with no clinically relevant difference following induction between participants with versus without high-risk cytogenetic abnormalities (86.2% vs. 84.3%) among the 74% with evaluable data. Additional follow-up data for 113 participants who underwent autologous SCT and were included in a prospective consolidation trial showed a median PFS duration of 35.3 months and median OS not reached over median follow-up of 55.5 months. However, their median PFS and OS durations were shorter if they had high- versus standard-risk cytogenetics (19.9 vs. 43.6 months [p<0.0001] and 54.7 months vs. not reached [p=0.0022], respectively).

Comment (KR): This paper by Einsele analyses a large patient group who received a similar induction regimen as our NZ patient population. A subgroup analysis of patients given an autologous SCT reaches a similar conclusion as local data. VCD gives a similar response rate independent of cytogenetics, but if followed long enough then the high-risk group will have a worse OS. This group continues to have an unmet need and requires further treatment with more potent drugs, such as carfilzomib or a new monoclonal antibody.

Reference: Br J Haematol 2017;179:586–97
Abstract

Inpatient vs outpatient autologous hematopoietic stem cell transplantation for multiple myeloma

Authors: Shah N et al.

Summary: These researchers analysed retrospective data from 669 inpatients and 377 outpatients who had undergone autologous SCT for MM. Compared with inpatients, outpatients were significantly younger (58 vs. 62 years [p<0.001]) and were more likely to have an haematopoietic stem-cell comorbidity index score of <2 (p=0.003) and a lower creatinine level (p<0.001). Although there was no between-group difference for treatment-related mortality, inpatients experienced significantly more grade 2–5 and grade 3–5 adverse events (p=0.003 for both). Outpatients also had significantly greater 2-year PFS and OS rates than inpatients (60% vs. 50% [p=0.005] and 83% vs. 77% [p=0.01], respectively]).

Comment (KR): This was a very large US-based study comparing inpatient with outpatient autologous SCT, which is used in only a few NZ centres at the present time. The fact that the inpatient group had more toxicity would suggest that the patients were correctly selected. Careful attention to formulating a haematopoietic stem-cell comorbidity index score seemed important and should be an integral part of the treatment workup.

Reference: Eur J Haematol 2017;99:532–5
Abstract

Prediction of outcome in newly diagnosed myeloma

Authors: Shah V et al., on behalf of the NCRI Haemato-oncology CSG

Summary: These authors performed a meta-analysis of copy number alteration and translocation data from 1036 NCRI Myeloma XI trial participants, linked to OS and PFS, as well as data from the MRC Myeloma IX trial, with a total of 1905 patients with newly diagnosed MM. The analyses confirmed the association of t(4;14), t(14;16), t(14;20), del(17p) and gain(1q21) with worse OS (respective HRs 1.60, 1.74, 1.90, 2.10 and 1.68 [p values ≤0.0089]). Participants with ≥2 adverse lesions had even worse OS (HR 2.67 [$p=8.13\times10^{-27}$]), including those who received intensive treatment (3.19 [$p=1.23\times10^{-18}$]). Comprehensive copy number alteration and translocation profiling in Myeloma XI trial participants also revealed a strong association between t(4;14) and *BIRC2/BIRC3* deletion ($p=8.7\times10^{-15}$), including homozygous deletion. Distinct subgroups of hyperdiploid MM were also described, with either gain(1q21) and *CCND2* overexpression or gain(11q25) and *CCND1* overexpression (p<0.0001 for both).

Comment (KR): This was a very comprehensive analysis and the largest ever done to investigate the additive effects of multiple genetic lesions on subsequent outcomes in newly diagnosed MM. The median PFS of the 'double-hit' group of patients in the Myeloma XI trial was only 19.7 months, meaning that about half of these relapsed 12 months following autologous SCT. These patients would clearly benefit from molecularly targeted therapies where available.

Reference: Leukemia 2018;32:102–10
Abstract

RACP MyCPD Program participants can claim **one credit per hour** (maximum of 50 credits per year) **for reading and evaluating Research Reviews** *FOR MORE INFORMATION* ***CLICK HERE***

CLICK HERE
to read previous issues of
Multiple Myeloma
Research Review

Effect of high-cutoff hemodialysis vs conventional hemodialysis on hemodialysis independence among patients with myeloma cast nephropathy

Authors: Bridoux F et al., for the MYRE Study Group

Summary: Patients with myeloma cast nephropathy who required haemodialysis were randomised to intensive haemodialysis consisting of eight 5-hour sessions over 10 days with either a high-cutoff (n=46) or conventional high-flux (n=48) dialyser; all participants received the same bortezomib and dexamethasone chemotherapy regimens, and 94 were evaluable for a modified intent-to-treat analysis. There was no significant difference between the high-cutoff versus conventional haemodialysis groups for the primary endpoint of 3-month haemodialysis independence rate (41.3% vs. 33.3% [p=0.42]), but the rates at 6 months and 12 months (secondary endpoints) were greater in the high-cutoff group (56.5% vs. 35.4% [p=0.04] and 60.9% vs. 37.5% [p=0.02], respectively). The respective incidences of haemodialysis-related adverse events were 43% and 39% in the high-cutoff and conventional haemodialysis groups, the respective incidences of chemotherapy-related serious adverse events were 39% and 37%, and there had been nine and ten deaths in the respective groups at 12 months.

Comment (DS): Cast nephropathy is a medical emergency as rapid action has been shown to benefit renal outcomes. Given it is the high levels of SFLCs that are largely responsible for the renal damage, physically removing them from the circulation seems a sensible strategy. This paper reports a subset of a larger trial of myeloma with renal disease. All patients required dialysis, and all were pretreated with 40mg of dexamethasone (or 400mg of intravenous methylprednisolone) for 4 days during screening. They received bortezomib and dexamethasone and were randomised to high-cutoff versus regular dialysis. There was no statistical benefit in the high-cutoff dialysis arm at 3 months, which was the primary endpoint; however, haemodialysis dependence was lower at other timepoints, and was 60.9% vs. 37.5% at 12 months (p=0.02), which is clinically meaningful. In NZ most centres use more effective triple therapy for cast nephropathy; this study will be used to both justify and refute the addition of high-cutoff dialysis. If it is used, then early use seems sensible.

Reference: JAMA 2017;318:2099–110
Abstract

Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma

Authors: Mateos M-V et al., for the ALCYONE Trial Investigators

Summary: The phase 3 ALCYONE trial investigated the addition of daratumumab to the standard-of-care regimen of bortezomib, melphalan and prednisone in patients with SCT-ineligible newly diagnosed MM; 350 and 356 participants received VMP with (D-VMP) and without daratumumab, respectively. A prespecified interim analysis revealed that over median follow-up of 16.5 months, the 18-month PFS rate was significantly higher with D-VMP compared with VMP (71.6% vs. 50.2%; HR for progression or death, 0.50 [95% CI 0.38, 0.65]), as was the ORR (90.9% vs. 73.9% [p<0.001]), CR or better rate, including stringent CR (42.6% vs. 24.4% [p<0.001]) and minimal residual disease negativity rate (22.3% vs. 6.2% [p<0.001]). Grade 3–4 haematological adverse events (D-VMP versus VMP) included neutropenia (39.9% vs. 38.7%), thrombocytopenia (34.4% vs. 37.6%) and anaemia (15.9% vs. 19.8%). The grade 3–4 infection rates were 23.1% and 14.7% in the D-VMP and VMP arms, respectively, with discontinuation rates of 0.9% and 1.4%. The daratumumab-associated infusion-related reaction rate was 27.7%.

Comment (DS): Daratumumab is to myeloma what rituximab is to CD20+ lymphoma; its addition improves the depth and duration of response in all the settings it has been tested. This trial was in transplant-ineligible newly diagnosed MM and used VMP as the chemotherapy in both arms. The 2-year PFS was about 60% on the daratumumab arm compared with about 30% in the control arm. While this difference is impressive and warrants the use of daratumumab in this setting, it still means we need to do better with the chemotherapy. The treatment was well tolerated and there were fewer discontinuations of treatment due to toxicity in the antibody arm, with 79.8 vs. 62.1% completing all nine cycles of planned treatment. The only drawbacks were in increase in grade 3 or 4 infections (23.1% vs. 14.7%), and first-dose infusion reactions in the daratumumab arm.

Reference: N Engl J Med 2018;378:518–28
Abstract

Long-term follow-up of monoclonal gammopathy of undetermined significance

Authors: Kyle RA et al.

Summary: These authors reported outcomes for 1384 patients diagnosed with MGUS during 1960–1994 with median follow-up of 34.1 years (14,130 person-years). The MGUS progression rate for these patients was 11%, which was 6.5-fold greater than seen in a control population. Without accounting for death from competing causes, the respective 10-, 20-, 30-, 35- and 40-year risks of progression were 10%, 18%, 28%, 36% and 36%. In patients with IgM MGUS, the respective 20-year progression risks for those with zero, one and two adverse risk factors (abnormal SFLC ratio and serum M [monoclonal] protein level ≥1.5 g/dL) were 55%, 41% and 19%, and in patients with non-IgM MGUS, the respective 20-year progression risks were 30%, 20% and 7%. Compared with matched controls from the same geographical area, the patients with MGUS had shorter median survival (8.1 vs. 12.4 years [p<0.001]).

Comment (DS): Only a mature physician can write a paper on the 34-year follow-up of their patients. This paper provides an important overview of the natural history of MGUS. While the progression rate of 1% per year holds up over this time, there were four risk groups, with non-IgG, abnormal SFLC ratio, and M-protein >15 g/L all increasing the risk of progression. It also highlights the increased death rate over expected in the absence of progression, something that was also seen in a Swedish registry analysis, opening the door for future approaches to eliminate the plasma cell clones at an early stage.

Reference: N Engl J Med 2018;378:241–9
Abstract

Ixazomib significantly prolongs progression-free survival in high-risk relapsed/refractory myeloma patients

Authors: Avet-Loiseau H et al.

Summary: This preplanned analysis of the phase 3 TOURMALINE-MM1 study, which reported improved PFS with IRd (ixazomib, lenalidomide, dexamethasone) versus Rd (i.e. ixazomib replaced with placebo), evaluated outcomes according to cytogenetic risk assessed by fluorescence *in situ* hybridisation. Among 552 participants with cytogenetic data, 137 had high-risk cytogenetic abnormalities (del[17p], t[4;14] and/or t[14;16]) and 172 had 1q21 amplification alone. Compared with Rd plus placebo, IRd increased median PFS duration in both the high-risk cytogenetics subgroup (21.4 vs. 9.7 months; HR 0.543 [95% CI 0.321, 0.918]) and the standard-risk subgroup (20.6 vs. 15.6 months; 0.640 [0.462, 0.888]). The PFS benefit with IRd versus Rd was consistent across individual high-risk cytogenetic abnormality subgroups, including del(17p) (HR 0.596 [95% CI 0.286, 1.243]), and also in participants with 1q21 amplification (0.781 [0.492, 1.240]) and those in an 'expanded high-risk' subgroup that included high-risk cytogenetic abnormalities and/or 1q21 amplification (0.664 [0.474, 0.928]).

Comment (DS): Many NZ patients were entered into the TOURMALINE study presented here. This paper shows that the high-risk patients defined by the presence of del17p, t(4:14) or t(14;16) had a similar benefit (HR 0.54) to those with normal cytogenetics (HR 0.64). The discussion claims that the addition of ixazomib *"overcomes the poor PFS associated with high-risk cytogenetics"*, which is overstating the results and is not statistically true. The presence of 1q21 amplification was looked at, but oddly there were no outcomes reported for the true high-risk group who have combined high-risk features. Once the price comes down, adding ixazomib to lenalidomide and dexamethasone seems a good option for most patients.

Reference: Blood 2017;130:2610–8
Abstract

Efficacy of venetoclax as targeted therapy for relapsed/refractory t(11;14) multiple myeloma

Authors: Kumar S et al.

Summary: Thirty patients with relapsed/refractory MM received dose-escalated venetoclax (300, 600, 900 or 1200mg) monotherapy in this phase 1 trial, which included a safety expansion phase with venetoclax 1200mg monotherapy in a further 36 patients; the addition of dexamethasone was permitted for disease progression. The participants had received a median of five prior therapies, 61% were double refractory to bortezomib and lenalidomide, and 46% had t(11;14). The most common adverse events were nausea (47%), diarrhoea (36%) and vomiting (21%), and the most common grade 3–4 adverse events were thrombocytopenia (32%), neutropenia (27%), anaemia (23%) and leucopenia (23%). The ORR was 21% with a VGPR or better rate of 15%. Most responses (86%) were in patients with t(11;14), with an ORR of 40% and a VGPR or better rate of 27%. Biomarker analyses confirmed correlations between response to venetoclax and higher BCL2:BCL2L1 and BCL2:MCL1 mRNA expression ratios.

Comment (DS): Despite the title of the paper, this study looked at 66 heavily pretreated patients (median five prior lines of therapy) which included 30 patients with t(11;14) myeloma. Responses were largely limited to those with t(11;14) with only 2/36 responding without this translocation, compared with 12/30 with it. Responses were relatively durable averaging 9.7 months. The number of prior regimens or the addition of other mutations, including del17p present in three of the responders, did not seem to affect outcomes. The dose used was 1200mg, which was the maximum tolerated dose but not necessarily the minimum effective dose. About a quarter of new cases of myeloma carry the t(11;14), but they were enriched in this trial as word got out they were the ones responding. The rates are higher in plasma-cell leukaemia and amyloid light-chain amyloidosis patients, where about 40% harbour this mutation. Venetoclax is clearly effective in t(11;14); it makes sense to use it earlier and probably in combination with conventional agents. Its efficacy may be enhanced when used with other agents that synergise with Bcl2 inhibition, such as idasanutlin. Most NZ centres do not routinely screen myeloma for t(11;14), but now we should.

Reference: Blood 2017;130:2401–9
Abstract

Independent commentary by Dr Ken Romeril, FRACP, FRCPA Haematologist specialising in malignant haematology, Wellington Hospital. He has a particular interest in translational myeloma research and genetics. **For full bio CLICK HERE**

Independent commentary by Dr David Simpson, MBChB, FRACP, FRCPA, Consultant Haematologist North Shore Hospital. His interests are in malignant haematology. **For full bio CLICK HERE**