Multiple Myeloma Research Review™

Making Education Easy

Issue 22 – 2017

In this issue:

Abbreviations used in this issue
CR = complete response
CV = cardiovascular
HR = hazard ratio
IV = intravenous
MM = multiple myeloma
ORR = overall response rate
OS = overall survival
PFS = progression-free survival
SCT = stem-cell transplantation
(VG)PR = (very good) partial response

Welcome to issue 22 of Multiple Myeloma Research Review.

This issue begins with a Lancet paper reporting improved outcomes and an acceptable risk-benefit profile for the addition of bortezomib to lenalidomide and dexamethasone (VRD) in patients with newly-diagnosed MM, which is followed by an N Engl J Med paper reporting that VRD with SCT improved PFS compared with continuing VRD and postponing SCT, but did not affect OS, in nonelderly patients with newly diagnosed MM. A paper from Jim Berenson's group in West Hollywood reported better outcomes for patients when they were treated at their specialist MM centre, supporting the call for more such centres in NZ. This issue concludes with a subanalysis of FIRST trial data confirming that continuous lenalidomide plus low-dose dexamethasone was safe and effective in the trial's Asian participants.

We hope you are enjoying your quarterly updates in MM research, and we appreciate receiving your feedback and suggestions.

Kind regards,

Dr David Simpson
davidsimpson@researchreview.co.nz

Dr Ken Romeril
kennethromeril@researchreview.co.nz

Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777)

Authors: Durie BGM et al.

Summary: Adults with newly diagnosed MM were randomised to receive initial treatment with eight 21-day cycles of IV bortezomib 1.3 mg/m^2 on days 1, 4, 8 and 11, oral lenalidomide 25mg on days 1–14 plus oral dexamethasone 20mg on days 1, 2, 4, 5, 8, 9, 11 and 12 (VRD; n=264) or six 28-day cycles of oral lenalidomide 25mg on days 1–21 and oral dexamethasone 40mg on days 1, 8, 15 and 22 (n=261) in this open-label phase 3 trial. Compared with the lenalidomide/dexamethasone only arm, the inclusion of bortezomib was associated with significantly longer median PFS (43 vs. 30 months; stratified HR 0.712 [96% CI 0.56, 0.906]) and median OS (75 vs. 64 months; 0.709 [0.524, 0.959]), with greater PR or better and CR or better rates (82% vs. 72% and 16% vs. 8%, respectively) among assessable participants. The groups with and without bortezomib had respective grade ≥3 adverse event rates of 82% and 75%, and adverse event-related discontinuation rates of 23% and 10%, and there were two treatment-related deaths in the VRD arm versus none in the lenalidomide/dexamethasone only arm.

Comment (DS): This SWOG study showed that adding bortezomib to lenalidomide/dexamethasone improved PFS and OS in untreated myeloma. This survival benefit was realised despite using the old-fashioned regimen of twice weekly IV bortezomib, resulting in a 25% discontinuation rate due to neuropathy. It is hard to recommend either regimen as used in this study, especially without transplant, as initial therapy. The FIRST study showed stopping the lenalidomide early was not a good idea, and this was done in both arms. There were no differences in outcomes in those with poor-risk cytogenetics, but the numbers were too small to read too much into this. The study does confirm that a triplet is better than a doublet in initial therapy, but times have moved on and now quadruplets with anti-CD38 antibodies are likely to be better again.

Reference: Lancet 2017;389(10,068):519–27
Abstract

Time spent reading this publication has been approved for CME for Royal New Zealand College of General Practitioners (RNZCGP) General Practice Educational Programme Stage 2 (GPEP2) and the Maintenance of Professional Standards (MOPS) purposes, provided that a Learning Reflection Form is completed. Please **CLICK HERE** to download your CPD MOPS Learning Reflection Form. One form per review read would be required.

Time spent reading this publication has been approved for CNE by The College of Nurses Aotearoa (NZ) for RNs and NPs. For more information on how to claim CNE hours please **CLICK HERE**.

Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma

Authors: Attal M et al., for the IFM 2009 Study

Summary: These researchers randomised patients with MM to three cycles of induction VRD and then either five cycles of consolidation VRD (n=350) or high-dose melphalan plus SCT followed by two additional cycles of VRD (n=350); maintenance lenalidomide was given for 1 year in both study arms. Compared with the VRD only arm, the transplantation arm had a significantly longer median PFS duration (primary endpoint; 50 vs. 36 months; adjusted HR 0.65 [p<0.001]), with all patient subgroups benefiting, and greater proportions of participants achieving a CR (59% vs. 48% [p=0.03]) and no detection of minimal residual disease (79% vs. 65% [p<0.001]), but with a similar 4-year OS rate (81% vs. 82%) and higher rates of grade 3 or 4 neutropenia (92% vs. 47%), grade 3 or 4 gastrointestinal disorders (28% vs. 7%) and infections (20% vs. 9%). There was no significant between-group difference for treatment-related mortality, second primary cancers, thromboembolic events or peripheral neuropathy.

Comment (DS): This study looked at VRD (using the same old-fashioned twice weekly IV bortezomib and 2 weeks of lenalidomide) for a paltry three cycles pretransplant or postponing transplant until later. The addition of transplantation improved depth and duration of response, with an impressive 88% achieving at least VGPR, but OS was the same in both arms. Delayed transplantation was carried out in 79% of those who progressed in the nontransplant arm. This study supports the *status quo* with early transplantation, but shows that delayed transplants are not unreasonable. The triplet induction was successful even if not optimal.

Reference: N Engl J Med 2017;376(14):1311–20
Abstract

Carfilzomib, lenalidomide, and dexamethasone in patients with relapsed multiple myeloma categorised by age

Authors: Dimopoulos MA et al.

Summary: This was a secondary *post hoc* analysis of ASPIRE trial data in participants categorised by age; the phase 3 trial previously reported improved PFS by adding carfilzomib to lenalidomide and dexamethasone in patients with relapsed MM. Of the 396 participants in each study group, 103 and 115 from the respective carfilzomib and control groups were aged ≥70 years. Median PFS remained longer in the carfilzomib versus control group for participants aged <70 years (28.6 vs. 17.6 months; HR 0.701) and for those aged ≥70 years (23.8 vs. 16.0; HR 0.753), and the ORRs were also greater with carfilzomib for these respective age groups (86.0% vs. 66.9% and 90.3% vs. 66.1%). Carfilzomib recipients aged ≥70 years experienced more grade ≥3 CV adverse events than those aged <70 years.

Comment (DS): The ASPIRE study showed that the addition of carfilzomib to lenalidomide and dexamethasone improved PFS and OS of relapsed myeloma. This *post hoc* analysis looked at whether age >70 years impacted on results. The response rates were the same in the young and older cohorts, but despite no difference in risk groups, PFS was less in the older group. However, the addition of carfilzomib improved outcomes by the same margin regardless of age. The elderly paid a higher price in terms of CV toxicity, with all of the increase in heart failure, myocardial infarction and embolic events seen in those over age 70 years. The mechanism for the CV toxicity remains elusive, and increased prophylaxis, especially when carfilzomib is combined with an immunomodulatory drug, seems prudent, although unproven.

Reference: Br J Haematol 2017;177(3):404–13
Abstract

Independent commentary by Dr Ken Romeril, FRACP, FRCPA Haematologist specialising in malignant haematology, Wellington Hospital. He trained in Christchurch, Sydney and Southampton, and is currently at the Wellington Blood and Cancer Centre and Aotea Laboratory. 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 and a former chair of the ALLG Myeloma Sub-Committee.

Independent commentary by Dr David Simpson, MBChB, FRACP, FRCPA, Consultant Haematologist North Shore Hospital. His interests are in malignant haematology. He qualified and specialised in Auckland and had postgraduate training in Vancouver and Toronto. He was Assistant Professor of Bone Marrow Transplant at Rush Cancer Institute in Chicago. He has first authored a number of journal articles, reviews, abstracts, and a textbook chapter. He is active in clinical research. David is also a member of the Pharmacy and Therapeutics Committee at North Shore Hospital and the Tender Subcommittee of PHARMAC.

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***

Upfront lower dose lenalidomide is less toxic and does not compromise efficacy for vulnerable patients with relapsed refractory multiple myeloma

Authors: Quach H et al.

Summary: This paper reported the final analysis of the prospective phase 2 RevLite study, in which 149 patients aged >59 years and/or with renal impairment received lenalidomide 15mg and dexamethasone 20mg for relapsed/refractory MM. The ORR was 71%, with a CR rate of 15%, and the respective median PFS and OS durations were 8.9 and 30.5 months. Neither the PFS nor the OS duration differed significantly from those reported for a matched cohort of participants enrolled in the pivotal phase 3 MM009/MM010 studies, who had received higher doses (lenalidomide 25mg and dexamethasone 40mg), but the lower doses in RevLite were associated with fewer grade 3–4 toxicities, mainly neutropenia (29% vs. 41%), infections (23% vs. 31%) and venous thromboembolism (3% vs. 13%).

Comment (DS): NZ sites contributed large numbers of patients to this study of lower dose lenalidomide. This analysis compared outcomes with other randomised studies in a similar population. While there are caveats with this approach, the results show that the response rates are comparable, but these results are achieved with less haematological toxicity and fewer venous thromboembolic events. The study shows that 15mg of lenalidomide is a reasonable strategy, but most doctors would start people without renal impairment at 25mg and reduce if there was toxicity. Given the results of the ASPIRE study and many other triplet versus doublet studies, we should be trying to add a third drug. With the additional toxicity of a third drug, the reduced haematological toxicity makes lower dose lenalidomide more compelling.

Reference: Br J Haematol 2017;177(3):441–8
Abstract

Systematic literature review and network meta-analysis of treatment outcomes in relapsed and/or refractory multiple myeloma

Authors: van Beurden-Tan CHY et al.

Summary: These authors identified 17 phase 3 randomised controlled trials that included 18 treatment options for inclusion in their systematic review and network meta-analysis, with the aim of comparing all current treatments for relapsed/refractory MM. They reported that the best combination treatment was daratumumab, lenalidomide and dexamethasone, being the most favourable in terms of PFS (HR 0.13 [95% credible interval 0.09, 0.19]) and the likelihood of being the best (99% of simulations). This combination reduced the risk of progression or death by 87%, 81% and 63% when compared with dexamethasone alone, bortezomib plus dexamethasone and lenalidomide plus dexamethasone, respectively.

Comment (DS): Continuing the theme of inter-trial analysis, this meta-analysis tried to 'pick-a-winner' of 18 different treatment options used in 17 randomised studies. Not surprisingly perhaps, daratumumab with lenalidomide and dexamethasone was the runaway winner, with a 63% reduction in death compared with lenalidomide and dexamethasone alone. They also showed that lenalidomide and dexamethasone was consistently better than bortezomib and dexamethasone, which is anticipated as proteasome inhibitors work best as a triplet. Daratumumab added more to lenalidomide/dexamethasone than elotuzumab, ixazomib or carfilzomib, but no quadruplet regimens were studied. The body of evidence is accumulating that anti-CD38 antibodies are an important component of myeloma therapy and it should be a priority to get access to these for our patients.

Reference: J Clin Oncol 2017;35(12):1312–9
Abstract

A phase 2 safety study of accelerated elotuzumab infusion, over less than 1 h, in combination with lenalidomide and dexamethasone, in patients with multiple myeloma

Authors: Berenson J et al.

Summary: Seventy patients with newly diagnosed or relapsed/refractory MM received 28-day cycles of IV elotuzumab 10 mg/kg weekly for cycles 1–2 and then biweekly, lenalidomide 25mg on days 1–21 and dexamethasone 28mg orally and 8mg IV weekly for cycles 1–2 and then 40mg orally weekly in this phase 2 trial; premedication consisted of diphenhydramine, paracetamol (acetaminophen) and ranitidine or their equivalents. In the absence of infusion reactions during the first dose in cycle one, the infusion rate was increased from 0.5–2 mL/min to 5 mL/min for the entire infusion by the third dose and subsequent infusions. A median six cycles were delivered. There were no grade 3 or 4 infusion reactions (primary endpoint). There was a single grade 1 and a single grade 2 infusion reaction, both of which occurred during first infusions.

Comment (KR): The long infusion times of between 3 to 6 hours in the delivery of the myeloma-related monoclonal antibodies are a problem in busy haematology day-stay units. This accelerated approach with low toxicity could well prove to be helpful in improving ease of access to our MM patients when we can eventually achieve access to these additional agents to our armamentarium.

Reference: Am J Hematol 2017;92(5):460–6
Abstract

Bortezomib-containing regimens (BCR) for the treatment of non-transplant eligible multiple myeloma

Authors: Jimenez-Zepeda VH et al.

Summary: The impact of different bortezomib-containing regimens for transplant-ineligible MM was investigated in consecutive patients who received a median of six cycles of such treatment. The respective ORRs for CyBorD (cyclophosphamide, bortezomib, dexamethasone), bortezomib, melphalan plus prednisone, and bortezomib plus dexamethasone were 95.2%, 80.9% and 76.3% (p=0.03), their median OS rates were similar, and there was a trend for better PFS for CyBorD.

Comment (KR): This is a 'real-world' type of publication that relates to what we can actually do in our current clinical practice. The high response rate and trend to a better PFS suggests that CyBorD is very effective and should be regarded as standard of care in the transplant-ineligible group. The theme of better outcomes with the achievement of high cumulative doses is one that is very familiar.

Reference: Ann Hematol 2017;96(3):431–9
Abstract

Improved clinical outcomes for multiple myeloma patients treated at a single specialty clinic

Authors: Berenson A et al.

Summary: These authors from a single specialist MM clinic reported their experiences for 264 of their patients who presented consecutively. For 1145 treatments overall, including 165 frontline treatments and 980 salvage treatments, the respective PFS durations were 13.9, 4.6 and 5.5 months. Median OS duration was 98 months, with a 5-year survival rate of 74%; OS was markedly improved compared with historical data. OS did not differ significantly across International Staging System stages, but was longer in patients aged <65 years compared with older patients.

Comment (KR): This is a paper from Jim Berenson's group in West Hollywood where they tend to have a low transplant intervention rate. I have personally long been an advocate of a single specialised myeloma clinic model, and this has been a feature in Wellington for well over 10 years to the point that there are now three operating concurrently. The 5-year survival rate of 74% is reasonable and similar to our own experience. I would respectfully encourage other NZ centres to adopt this model to obtain optimal outcomes in this complex disease.

Reference: Ann Hematol 2017;96(3):441–8
Abstract

Bendamustine, lenalidomide and dexamethasone (BRd) has high activity as 2nd-line therapy for relapsed and refractory multiple myeloma

Authors: Mey UJM et al.

Summary: Patients with relapsed/refractory MM following one line of therapy (evaluable n=45) received six 28-day induction cycles of bendamustine 75 mg/m^2 on days 1 and 2, lenalidomide 25mg on days 1–21 and dexamethasone 20mg or 40mg on days 1, 8, 15 and 22, followed by 12 cycles without bendamustine, in this phase 2 trial; the participants also received pegfilgrastim according to protocol-defined criteria. The CR/VGPR rate was 51% (greater than the study's target of 40% postinduction). The respective grade 4 neutropenia and thrombocytopenia rates were 34% and 16%.

Comment (KR): This relatively small European study outlines a more aggressive triplet approach to relapsed patients by adding in bendamustine, which is known to have significant activity in MM. A 51% CR/VGPR rate is a good result in this relapsed/refractory group. Recent breaking news of the advent of subsidised bendamustine is welcome, but as yet MM is not a registered indication.

Reference: Br J Haematol 2017;176(5):770–82
Abstract

Continuous treatment with lenalidomide and low-dose dexamethasone in transplant-ineligible patients with newly diagnosed multiple myeloma in Asia

Authors: Lu J et al.

Summary: This subanalysis of the FIRST trial of 18 cycles of continuous lenalidomide plus low-dose dexamethasone and melphalan, prednisone plus thalidomide examined outcomes in 114 participants of Asian ethnicity. Efficacy and safety outcomes for Asian participants receiving continuous lenalidomide plus dexamethasone were consistent with the overall study population. In the continuous and 18-cycle lenalidomide plus dexamethasone and melphalan, prednisone plus thalidomide arms, the respective ORRs were 77.8%, 65.8% and 57.5%, and the respective 3-year survival rates were 70.2%, 58.1% and 56.4%. Common grade 3/4 adverse events in the respective continuous lenalidomide plus dexamethasone and melphalan, prednisone plus thalidomide arms included neutropenia (25.0% and 43.6%), infection (19.4% and 28.2%) and anaemia (19.4% and 15.4%). There were low rates of thromboembolic events and no second primary malignancies.

Comment (KR): This is yet another publication resulting from the FIRST trial, but concentrating on a subset of Asian patients. Myeloma is known to be less common in Asia but the incidence is increasing in line with Western countries. The results in the Asian patients were fairly similar to the larger cohort and confirmed the efficacy of the continuous lenalidomide plus low-dose dexamethasone approach.

Reference: Br J Haematol 2017;176(5):743–9
Abstract

CLICK HERE to read previous issues of **Multiple Myeloma Research Review**

CONGRATULATIONS TO DR ROBIN RUND who won an iPad mini 3 by taking part in our recent subscriptions update promotion. Robin is an Anaesthetist at the Bay of Plenty District Health Board.