Multiple Myeloma Research Review™

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Abbreviations used in this issue

ASO-RQ-PCR = allelic-specific oligonucleotide real-time quantitative polymerase chain reaction
AUC = area under the curve
BCMA = B-cell maturation antigen
CAR = chimeric antigen receptor
CR = complete response
HCT/SCT = haematopoietic/stem-cell transplantation
HR = hazard ratio
MGUS = monoclonal gammopathy of undetermined significance
MM = multiple myeloma
MRD = minimal residual disease
ORR = overall response rate
OS = overall survival
PFS = progression-free survival
PR/VGPR = (very good) partial response

Welcome to the thirtieth issue of Multiple Myeloma Research Review.

This issue begins with research comparing ASO-RQ-PCR (allelic-specific oligonucleotide real-time quantitative polymerase chain reaction) with multiparameter flow cytometry for assessing MRD status in patients with newly diagnosed MM being treated with lenalidomide maintenance. Other included research has looked at the initial toxicity of a BCMA-directed CAR T-cell therapy in patients with relapsed or refractory MM. A small but valuable phase 2 study has investigated the use of an all-oral regimen of ixazomib, cyclophosphamide and dexamethasone for the treatment of relapsed/refractory MM. This issue concludes with a large US analysis of the considerable real-world costs of peripheral neuropathy associated with treatment of MM.

We hope you find our latest update in myeloma research informative. Please feel free to send us your comments and suggestions.

Kind regards,

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Minimal residual disease by flow cytometry and allelic-specific oligonucleotide real-time quantitative polymerase chain reaction in patients with myeloma receiving lenalidomide maintenance

Authors: Gambella M et al.

Summary: This was a pooled analysis of data from 73 participants from two phase 3 trials who had achieved VGPR or better following intensification/consolidation; all had received lenalidomide maintenance until disease progression. MRD was evaluated on bone marrow after intensification/consolidation, again after six courses of maintenance and every 6 months thereafter until clinical relapse with both ASO-RQ-PCR (sensitivity 10^{-5}) and multiparameter flow cytometry (sensitivity 10^{-4} to 10^{-5}). The respective molecular and flow CR rates after intensification/consolidation were 46% and 63%. Around a quarter of MRD-positive participants after consolidation became MRD-negative during maintenance. At median follow-up of 38 months, participants who were MRD-negative on both ASO-RQ-PCR and multiparameter flow cytometry had prolonged PFS (respective HRs 0.29 [95% CI 0.14, 0.62] and 0.19 [0.09, 0.41]); the impact of MRD-negative status on PFS was similar in all autologous SCT status, ISS stage and cytogenetic risk subgroups. Correlation between ASO-RQ-PCR and multiparameter flow cytometry was high.

Comment (DS): This study compared two methods of MRD testing, ASO-RQ-PCR and multicolour flow. ASO-RQ-PCR was more sensitive and found more MRD-positive cases, but the MRD-negative cases did better than those who were MRD-negative on flow. ASO-RQ-PCR is too labour intensive and has been surpassed by next-generation sequencing. The failure rates of MRD testing were high at 30%, but the outcomes add to the growing volume of literature that lower MRD levels are better and it does not matter how they are measured.

Reference: Cancer 2019;125:750–60
Abstract

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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.

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Long-term follow up of tandem autologous-allogeneic hematopoietic cell transplantation for multiple myeloma

Authors: Maffini E et al.

Summary: These researchers reported long-term clinical outcomes for 102 previously reported patients and 142 additional patients with MM treated with sequential high-dose melphalan and autologous HCT, followed by total body irradiation 200 cGy with or without fludarabine 90 mg/m^2 and allogeneic HCT. Median follow-up was 8.3 years. Donors included 179 HLA-identical siblings and 65 matched unrelated donors. Upfront tandem autologous-allogeneic HCT was performed in 209 patients, while 35 patients had failed prior autologous HCT before the planned autologous-allogeneic HCT. Maintenance treatment was provided for 31 patients a median of 86 days after allogeneic HCT. The respective 5-year OS and PFS rates were 54% and 31%, and the respective 10-year OS and PFS rates were 41% and 19%. The 100-day and 5-year overall nonrelapse mortality rates were 2% and 14%, respectively. Shorter OS and PFS was seen in patients with induction-refractory disease and those with high-risk biological features. Among 152 patients who relapsed, 117 received salvage treatment, and of these, 83 had a clinical response with median survival duration of 7.8 years. Patients who became MRD-negative had a significantly lower relapse rate than MRD-positive patients.

Comment (DS): Allogeneic transplants for myeloma had high treatment-related mortality in the early days, so the Seattle group got around this by separating the high-dose therapy and the allogeneic transplant by doing an autologous HCT followed by a mini-allogeneic transplant. The 100-day mortality rate was 2%. Relapse has been common, especially in those with high or ultrahigh-risk cytogenetics. The long-term outcomes have been good considering the majority of patients received VAD as initial therapy. Extramedullary relapse was common at 25%, often seen in allogeneic transplant series, perhaps due to a graft-versus-myeloma effect in the marrow. Results would be expected to be better with modern induction treatments; however, this approach does not seem good in those with poor-risk disease, which is the group who are most often considered for it.

Reference: Haematologica 2019;104:380–91
Abstract

Conditioning with busulfan plus melphalan versus melphalan alone before autologous haemopoietic cell transplantation for multiple myeloma

Authors: Bashir Q et al.

Summary: Patients aged ≤70 years with newly diagnosed stable or better MM eligible for HCT were randomised to receive busulfan plus melphalan (n=104) or melphalan 200 mg/m^2 on day –2 (n=98) in this open-label phase 3 trial; in the busulfan plus melphalan arm, busulfan 32 mg/m^2 was given followed by adjusted doses on days –7, –6, –5 and –4 to achieve a target daily AUC of 5000 mmol-minute, and melphalan 70 mg/m^2 was given on days –2 and –1. The respective VGPR or better rates at 90 days after transplantation in the busulfan plus melphalan and melphalan alone arms were 98% and 97%. After median follow-up periods of 22.6 months and 20.2 months in the respective busulfan plus melphalan and melphalan alone groups, median PFS duration was longer in the busulfan plus melphalan arm (64.7 vs. 43.5 months; HR 0.53 [95% CI 0.30, 0.91]). No treatment-related deaths were recorded out to day 100. The respective grade 2–3 mucositis rates in the busulfan plus melphalan and melphalan alone groups were 74% and 14%.

Comment (DS): When the best conditioning regimen for myeloma was being selected, melphalan 200 mg/m^2 emerged as the standard as other regimens were inferior or too toxic, including melphalan with oral busulfan. This trial looked at dose-adjusted intravenous busulfan (AUC 5000 mmol-minute) with melphalan 140 mg/m^2 compared with melphalan 200 mg/m^2 in a randomised trial. They found that while early responses were similar, the duration of response improved dramatically from 43.5 to 64.7 months. Patients were well balanced with induction treatment (mostly VRD) and maintenance (mostly lenalidomide alone). Delaying the need for retreatment in myeloma has an added bonus, as it means there is more time for novel options to become available. The cost benefits of this approach need to be weighed up with other options, such as adding daratumumab. With many new drugs for treating myeloma, changing the conditioning regimen deserves another look.

Reference: Lancet Haematol 2019;6:E266–75
Abstract

Risk of MGUS in relatives of multiple myeloma cases by clinical and tumor characteristics

Authors: Clay-Gilmour AI et al.

Summary: These researchers compared age- and sex-specific MGUS rates among 1179 first-degree relatives, aged >40 years, of 430 MM or smouldering MM cases with a population-based sample. Fluorescence *in situ* hybridisation was used to classify cytogenetic subtypes. The age- and sex-adjusted prevalence of MGUS among the first-degree relatives was 5.8%, which is 2.4-fold higher than expected. Familial risk did not differ according to proband's age at diagnosis, gender, isotype, IgH translocation or trisomy.

Comment (DS): While we usually tell patients with myeloma that their relatives are safe, this is not quite true. The study looked at relatives of known myeloma cases and found that incidence rates of MGUS were 2.4-fold greater than expected. It might be predicted that the genetic tendency to develop an initial hit of a translocation or trisomy may be different, so they then looked to see if there were any disease characteristics that correlated with disease in first-degree relatives. Nothing emerged as significant. This means all relatives should worry a little bit.

Reference: Leukemia 2019;33:499–507
Abstract

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Independent commentary by Dr Ken Romeril, FRACP, FRCPA
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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**

Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma

Authors: Raje N et al.

Summary: Patients with relapsed/refractory MM each received a single infusion of bb2121 (a CAR T-cell therapy) 50×10^6, 150×10^6, 450×10^6 or 800×10^6 in a dose-escalation phase, and $150–450\times10^6$ in an expansion phase in this phase 1 study; results for the first 33 consecutive recipients are reported. At data cutoff (6.2 months after the last infusion), the most common grade ≥3 toxicities were haematological, including neutropenia (85%), leucopenia (58%), anaemia (45%) and thrombocytopenia (45%). The respective grades 1–2 and grade 3 cytokine-release syndrome rates were 70% and 6%, and the respective any-grade and grade 1–2 neurological toxic event rates were 42% and 39% with one case of a reversible grade 4 neurological toxicity. The objective response rate was 85% with a CR rate of 45%; among the 15 participants who achieved CR, six relapsed. Median PFS duration was 11.8 months. All 16 evaluable participants with PR or better were MRD-negative. An association was seen between CAR T-cell expansion and response, and CAR T-cells persisted for up to 1 year postinfusion.

Comment (DS): Once the basics of getting CAR T-cells to work has been sorted, changing the antibody so that another cell type is targeted is a relatively easy step. This study proves the concept of targeting myeloma with BCMA-directed CAR T-cells. The response rate is impressive at >95%, if you received at least 450×10^9 T-cells in patients who had received a median of 7 prior lines of therapy, including about 50% achieving CR. Response and durability seem dependent on cell dose. It seems likely response and duration of effect might be better in less heavily pretreated patients. To improve durability, they have now modified the manufacturing process to include a PI3K inhibitor, and call this BB21217.

Reference: N Engl J Med 2019;380:1726–37
Abstract

Phase 2 study of all-oral ixazomib, cyclophosphamide and low-dose dexamethasone for relapsed/refractory multiple myeloma

Authors: Kumar SK et al.

Summary: Seventy-eight patients with relapsed/refractory MM received 28-day cycles of oral ixazomib 4mg, cyclophosphamide 300 mg/m^2 on days 1, 8 and 15 and dexamethasone 40mg on days 1, 8, 15 and 22 in this phase 2 study. The study participants had received a median of 12 treatment cycles at data cutoff, at which time 31% were still on treatment. The ORR (primary endpoint) was 48%, with a VGPR or better rate of 16%. The respective ORRs in participants aged ≥65 and <65 years were 64% and 32%, with respective VGPR or better rates of 25% and 16%. After median follow-up of 15.2 months, the median PFS duration was 14.2 months, with a trend towards a longer duration in participants aged ≥65 years than those aged <65 years (18.7 vs. 12.0 months; HR 0.62 [p=0.14]). The most common treatment-emergent adverse events being diarrhoea (33%), nausea (24%), upper respiratory tract infection (24%) and thrombocytopenia (22%). The peripheral neuropathy rate was 13%, reaching grade 3 in one participant.

Comment (KR): This phase 2 study was not large but provides useful data on the efficacy and tolerability of an all-oral regimen for relapsed patients. The dropout rate of a third is on the high side, but the ORR was respectable. This is an alternative regimen to lenalidomide, and can be used as a second-line option in NZ by way of a compassionate programme.

Reference: Br J Haematol 2019;184:536–46
Abstract

Daratumumab, bortezomib, cyclophosphamide and dexamethasone in newly diagnosed and relapsed multiple myeloma

Authors: Yimer H et al.

Summary: In the LYRA study, 86 patients with newly diagnosed MM and 14 with relapsed MM received 4–8 induction cycles of bortezomib 1.5 mg/m^2, cyclophosphamide 300 mg/m^2 and dexamethasone 40mg per week, along with intravenous daratumumab 16 mg/kg dosed as approved except for a split first dose in the first cycle. Eligible participants underwent autologous SCT, and all participants received ≤12 daratumumab maintenance doses administered monthly. Among participants with newly diagnosed MM, the respective VGPR or better rate (primary endpoint) and ORR after four induction cycles were 44% and 79%, and at the end of induction they were 56% and 81%, and the 12-month PFS rate was 87%. The regimen was also found to be effective in participants with relapsed MM. The most frequent treatment-emergent adverse event was fatigue (59%) and the most frequent grade 3–4 treatment-emergent adverse event was neutropenia (13%). The infusion reaction rate was 54%, mostly during the first dose, with a grade 3 rate of 2%. The respective median infusion durations for the first and second doses of daratumumab were 4.5 and 3.8 hours.

Comment (KR): This community study confirms previous findings that when daratumumab is added to the standard VCd backbone, there is a good PR rate induced in many patients. It is a tolerable regimen in newly diagnosed MM, regardless of transplant eligibility. The LYRA study is diminished by the small sample size and lack of a control arm. It does show that daratumumab can easily be added to the commonly used VCd regimen, and also did not compromise stem-cell collection.

Reference: Br J Haematol 2019;185:492–502
Abstract

Autologous transplantation, consolidation, and maintenance therapy in multiple myeloma

Authors: Stadtmauer EA et al.

Summary: The phase 3 BMT CTN 0702 trial sought to evaluate the benefit of additional therapy over the standard protocol of induction therapy, melphalan 200 mg/m^2, autologous SCT and lenalidomide maintenance in 758 transplant-eligible patients aged ≤70 years with MM without progression (24% high-risk) who had undergone ≤12 months of induction therapy. The participants were randomised to one of the following three treatment arms: i) autologous SCT (n=257); ii) tandem autologous SCT (n=247); and iii) autologous SCT followed by four consolidation cycles of RVD (lenalidomide, bortezomib, dexamethasone; n=254). All participants received lenalidomide until disease progression. Compared with the standard autologous SCT arm, tandem autologous SCT and autologous SCT plus RVD consolidation did not provide any benefit in terms of PFS rate at 38 months (primary endpoint; 58.5% and 57.8% vs. 53.9%), OS or CR rate.

Comment (KR): This is an important trial and looks at whether the use of additional maintenance or even a second autologous SCT might improve PFS. This was a different approach to the one used in the recently published MRC XI trial looking at the role of lenalidomide maintenance. The results are a little surprising, and even though the OS and PFS rates for the RVD arm appeared superior, they did not reach significance. The conclusion that a single autologous SCT and the use of lenalidomide as maintenance should be the standard approach is understandable, but it would still be reasonable to add RVD as consolidation in high-risk cases.

Reference: J Clin Oncol 2019;37:589–97
Abstract

Multiple myeloma in patients up to 30 years of age

Authors: Jurczyszyn A et al.

Summary: These authors reported a retrospective study of 52 patients from multiple centres diagnosed with MM when aged 8–30 years; 68% of the patients had ISS 1 disease; 22% had light chain-only disease and 48% had elevated serum lactate dehydrogenase levels. Novel agents were used for 85% of the patients, and 62% received front-line autologous SCT. The respective ORRs after front-line treatment and autologous SCT were 71% and 90%. After median follow-up of 86 months, the median OS duration was 166 months with a 5-year OS rate of 77%.

Comment (KR): It has been sometimes stated that very young patients may have more aggressive disease than the rest of the patient population. This group of patients aged under 30 years actually had a very good 5-year OS rate of 77%, suggesting that they have possibly a better prognosis than the general MM population.

Reference: Leuk Lymphoma 2019;60:471–6
Abstract

Cost of peripheral neuropathy in patients receiving treatment for multiple myeloma

Authors: Song X et al.

Summary: These researchers used administrative claims data to evaluate the economic burden attributable to peripheral neuropathy among real-world US adult patients with MM. Among patients meeting study inclusion criteria, 1387 with peripheral neuropathy diagnoses (ICD-9-CM and ICD-10-CM) recorded were matched to 2594 controls. Mean follow-up was 23–26 months. Compared with controls, patients with peripheral neuropathy had higher costs by USD1509 per patient per month, driven by greater rates of hospitalisations (77.4% vs. 67.2% [p<0.001]) and emergency department visits (67.8% vs. 58.4% [p<0.001]), and more outpatient hospital-based visits (13.5 vs. 11.5 per patient per month [p<0.001]).

Comment (KR): This is a very large study, and the extent of peripheral neuropathy is significant and is an unpleasant side effect of the older generation of proteasome inhibitors. It can also sometimes be unpredictable and occur early in the treatment course. The economic cost can be considerable, and overall there is a good case for having access to alternative funded treatments, such as carfilzomib, which is currently not available to NZ patients following the closure of the compassionate access programme.

Reference: Ther Adv Hematol 2019;10:2040620719839025
Abstract