Multiple Myeloma Research Review™

Making Education Easy

Issue 23 – 2017

In this issue:

Abbreviations used in this issue
CR = complete response
FISH = fluorescence *in situ* hybridisation
HR = hazard ratio
MM = multiple myeloma
ORR = overall response rate
OS = overall survival
PFS = progression-free survival
SCT = stem-cell transplantation
SNP = single-nucleotide polymorphism
VGPR = very good partial response

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Welcome to issue 23 of Multiple Myeloma Research Review.

This issue begins with papers reporting clinical characteristics and outcomes for patients with MM and light-chain deposition disease or IgM myeloma. The clinical applicability of a revised Myeloma Comorbidity Index was evaluated in a comprehensive comorbidity, frailty and disability evaluation. There is also a meta-analysis highlighting the clinical benefits of carfilzomib-containing combinations for newly diagnosed patients with MM. Also on the subject of carfilzomib, this issue concludes with a preplanned subgroup analysis of the ENDEAVOUR trial showing that cytogenetic risk does not impact on the superiority of carfilzomib plus dexamethasone over bortezomib plus dexamethasone.

We hope these and the other papers included in this issue are of interest and helpful to you. As always, your suggestions and feedback are welcome.

Kind regards,

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Clinical characteristics and prognostic factors in multiple myeloma patients with light chain deposition disease

Authors: Mohan M et al.

Summary: These researchers reported on renal and extra-renal involvement for 69 patients with MM and biopsy proven light-chain deposition disease. The 30% of patients with coexisting light-chain amyloidosis or cast nephropathy had shorter survival. One-third of the patients had cardiac involvement by light-chain deposition disease, and this also resulted in shorter OS as well as a significantly increased post-SCT treatment-related mortality risk compared with those without cardiac involvement.

Comment (KR): Light-chain deposition disease is uncommon and usually comes to haematology by way of a diagnostic renal biopsy in patients with significant proteinuria. The proportion of patients with cardiac involvement was surprisingly high and suggests that a thorough cardiac workup is mandatory in staging.

Reference: Am J Hematol 2017;92(8):739–45

Abstract

IgM myeloma: a multicenter retrospective study of 134 patients

Authors: Castillo JJ et al.

Summary: This was a retrospective analysis of 134 patients with IgM myeloma (>10% marrow involvement by monoclonal plasma cells, presence of an IgM monoclonal paraproteinaemia of any size, and anaemia, renal dysfunction, hypercalcemia, lytic lesions and/or t[11;14]); 37%, 43%, 19% and 70% had anaemia, renal dysfunction, hypercalcemia and skeletal lytic lesions, respectively. The patients had a median serum IgM level of 2895 mg/dL, with 19% having levels >6000 mg/dL. The respective proportions with ISS (International Staging System) stages of 1, 2 and 3 were 33%, 44% and 24%. The respective proportions of malignant cells expressing CD20 and cyclin D1 were 58% and 67%, and the most common cytogenetic finding was t(11;14), affecting 39%. Median OS duration was 61 months. A significant association was seen between higher ISS score and worse survival (p=0.02).

Comment (KR): IgM myeloma is rare but is increasingly being recognised as a distinct entity with a specific FISH abnormality. The article does not cite two recent studies that have found venetoclax to have a place in the initial treatment.

Reference: Am J Hematol 2017;92(8):746–51

Abstract

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/

Daratumumab monotherapy compared with historical control data in heavily pretreated and highly refractory patients with multiple myeloma

Authors: Usmani SZ et al.

Summary: These researchers performed an adjusted treatment comparison on efficacy data from two studies of daratumumab monotherapy 16 mg/kg and two independent US databases of daratumumab monotherapy (n=148) versus historical data from real-world patients with MM who received ≥3 prior lines of therapy or were double refractory to a proteasome inhibitor and an immunomodulatory drug (n=658). Compared with historical controls, greater proportions of daratumumab recipients had received prior treatment with pomalidomide (55% vs. 15%) or carfilzomib (41% vs. 28%), and a greater proportion was triple/quadruple refractory (64% vs. 14%). For OS, the adjusted HR for daratumumab recipients versus the historical controls was 0.33 (95% CI 0.24, 0.46), compared with an unadjusted value of 0.46 (0.35, 0.59). The effect of the adjustment was due mainly to refractory status and prior pomalidomide/carfilzomib exposure.

Comment (KR): This rather complicated statistical analysis confirms the improved OS of daratumumab monotherapy in very heavily pretreated patients. It is being used as a last resort in this context, but clearly has a more potent effect if used earlier in the disease course together with a potent immunomodulatory drug.

Reference: Am J Hematol 2017;92(8):E146–52
Abstract

A concise revised Myeloma Comorbidity Index as a valid prognostic instrument in a large cohort of 801 multiple myeloma patients

Authors: Engelhardt M et al.

Summary: This analysis set out to develop and validate an easy-to-use myeloma risk score (the revised Myeloma Comorbidity Index) for predicting OS and PFS differences. An assessment was carried out in 801 consecutive elderly patients with MM, including comorbidity risks obtained at diagnosis. A multivariate analysis revealed that renal, lung and Karnofsky Performance Status impairment, frailty and age were significant risk factors for OS. When these were incorporated into a weighted revised Myeloma Comorbidity Index, patients were identified as fit (revised Myeloma Comorbidity Index <3; 30.8%), intermediate-fit (revised Myeloma Comorbidity Index 4–6; 55.7%) or frail patients (revised Myeloma Comorbidity Index >6; 13.5%), with respective median OS durations of 10.1, 4.4 and 1.2 years. When compared with other commonly used comorbidity indices, the revised Myeloma Comorbidity Index, based on 25% and 75% risk quantiles, provided higher HRs, better predictions and Brier scores. The revised Myeloma Comorbidity Index was also accurate in its assessment of patients' physical conditions and had simple clinical applicability.

Comment (KR): This was a large study to attempt to validate a myeloma risk score, which is an instrument gaining favour in clinical trials. Three subgroups were identified and separated out well from the OS point of view. This index would appear to be a useful tool in the clinic and in clinical trials.

Reference: Haematologica 2017;102(5):910–21
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.

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Genetic factors related with early onset of osteonecrosis of the jaw in patients with multiple myeloma under zoledronic acid therapy

Authors: Kastritis E et al.

Summary: These authors screened patients with MM receiving zoledronic acid, including 36 with and 104 without bisphosphonate-related osteonecrosis of the jaw, for *PPARG* and *CYP2C8* SNPs. The risk of bisphosphonate-related osteonecrosis of the jaw developing during the first 2 years of zoledronic acid therapy was increased in patients with SNPs in *PPARG* (59% vs. 16% [p=0.022]) and *CYP2C8* (29% vs. 7% [p=0.07]), with SNPs in both genes significantly associated with a shorter time to develop the complication, independent of poor oral hygiene.

Comment (KR): It has been noted for some time that patients who develop bisphosphonate-related osteonecrosis of the jaw seem to suffer this rather nasty complication early in their disease course. The finding of SNPs in the *PPARG* and *CYP2C8* genes now reveals a genetic association to the clinical observation.

Reference: Leuk Lymphoma 2017;58(10):2304–9
Abstract

Carfilzomib-containing combinations as frontline therapy for multiple myeloma

Authors: Sheng Z et al.

Summary: This was a meta-analysis of 13 trials (n=704) investigating front-line carfilzomib for newly diagnosed MM. Front-line combinations containing carfilzomib were associated with a CR or better rate of 21%, a VGPR or better rate of 68% and an ORR of 94%. The pre-SCT CR or better rate of 18% increased to 43% after SCT, and to 64% after consolidation (p<0001). The quality of responses improved further over time, with CR or better rates of 10%, 20% and 43%, and VGPR or better rates of 29%, 68% and 88%, after the second, fourth and eighth cycles, respectively. The CR or better rate was higher when carfilzomib was combined in a triplet regimen with lenalidomide and dexamethasone than when it was combined with either cyclophosphamide or thalidomide plus dexamethasone (49% vs. 18% and 21%, respectively [p=0.03]).

Comment (DS): Carfilzomib is a more potent proteasome inhibitor than bortezomib. This meta-analysis shows that in phase 2 trials in newly diagnosed MM, carfilzomib triplets achieve very high response rates. The responses when combined with lenalidomide (KRd) are higher than when used with cyclophosphamide, showing that immunomodulatory drugs should be part of front-line therapy. Responses deepened with post-transplant consolidation and high rates of minimal residual disease negativity are obtained. The CLARION study, the only randomised trial, showed no benefit for carfilzomib, but this is the only study that did not show superiority and likely reflects that melphalan and prednisone are not the optimal partners.

Reference: Eur J Haematol 2017;98(6):601–7
Abstract

Lenalidomide maintenance after autologous stem-cell transplantation in newly diagnosed multiple myeloma

Authors: McCarthy PL et al.

Summary: Three RCTs were included in this meta-analysis, which compared lenalidomide maintenance therapy (n=605) with placebo or observation (n=603) in participants with newly diagnosed MM who had undergone autologous SCT; median follow-up was 79.5 months for surviving participants. Compared with placebo/observation, lenalidomide maintenance was associated with significantly longer median PFS (52.8 vs. 23.5 months; HR 0.48 [95% CI 0.41, 0.55]) and OS (not reached vs. 86.0 months; 0.75 [0.63, 0.90]). The cumulative incidence of second primary malignancies before disease progression was higher in the lenalidomide arms, whereas the cumulative incidences of progression, death or death due to myeloma were higher in the placebo/observation arms.

Comment (DS): There have been several studies that have shown the benefit of maintenance lenalidomide but were underpowered to show a survival benefit. This meta-analysis shows PFS was more than doubled from 23.5 to 53 months. There was also a 75% reduction in death. There were 66% who took lenalidomide for at least 1 year and 39% for at least 2 years, but only 16% for more than 3 years. While the treatment received before lenalidomide maintenance varied and the treatment of relapse was not controlled, deferring the need for second-line therapy by 2 years or more is likely to result in better salvage options becoming available. There was a small price to pay in second malignancies, but this was more than outweighed by the reduction in death due to relapse.

Reference: J Clin Oncol; Published online July 25, 2017
Abstract

A phase 1b study of isatuximab plus lenalidomide and dexamethasone for relapsed/refractory multiple myeloma

Authors: Martin T et al.

Summary: Fifty-seven patients with relapsed/refractory MM received 28-day cycles of isatuximab 3, 5 or 10 mg/kg every 2 weeks or 10 or 20 mg/kg every week for 4 weeks and every 2 weeks thereafter, along with lenalidomide 25mg on days 1–21 and dexamethasone 40mg every week, in this phase 1b, open-label, dose-escalation study; 83% of participants had failed to respond to prior lenalidomide therapy. The participants were treated for a median of 36.4 weeks, with 15 patients continuing treatment at data cutoff. There was only one dose-limiting toxicity (grade 3 pneumonia with the highest isatuximab dosage), and the maximum tolerated dose was not reached. Isatuximab-related adverse events included infusion-associated reactions (56%), usually during the first infusion, 84% of which were grade 1 or 2. Among participants with efficacy data (n=52), the ORR was 56%, and was similar among the three highest dosages. Among evaluable lenalidomide-refractory participants (n=42) the ORR was 52%. The overall median PFS duration was 8.5 months. A greater than dose-dependent increase in isatuximab exposure was detected; the pharmacokinetics of isatuximab and lenalidomide appeared to be independent.

Comment (DS): Isatuximab is the 'other' anti-CD38 antibody. This dose-escalation trial showed it was well tolerated with activity. Infusion reactions were common in the first cycle but were mostly mild. There were four patients who discontinued the drug after the first dose, all due to bronchospasm or anaphylactoid reactions, probably due to the presence of CD38 on mast cells and eosinophils, rather than true allergy. Most occurred at the 250 mg/h rate, which was associated with 84% infusion reactions; this reduced to 50% when the initial infusions were given at 175 mg/h, the current recommended dose. The ORR of 54% in heavily pretreated patients is encouraging, and efficacy will be further defined by phase 3 studies.

Reference: Blood 2017;129(25):3294–303
Abstract

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Recovery of polyclonal immunoglobulins one year after autologous stem cell transplantation as a long-term predictor marker of progression and survival in multiple myeloma

Authors: González-Calle V et al.

Summary: The role of immunoglobulin recovery as a dynamic predictor of progression or survival after autologous SCT was explored in 295 transplant recipients with MM. At 1 year post-transplant, when it is expected that B-cell reconstitution is completed, 52% of 169 participants who were alive and progression-free exhibited immunoglobulin recovery and 48% did not. Compared with those with persistent immunoparesis, participants with immunoglobulin recovery had significantly longer median durations for PFS (60.4 vs. 27.9 months; HR 0.45 [95% CI 0.31, 0.66]) and OS (11.3 vs. 7.3 years; 0.45 [0.27, 0.74]). There was also an association between the percentage of normal plasma cells at post-transplant day 100 and immunoglobulin recovery at that time.

Comment (DS): We routinely check immunoglobulin levels as we monitor patients after induction therapy. This Spanish study shows that recovery of uninvolved immunoglobulin levels above the minimum normal range was associated with improvement in PFS from 28 to 60 months. The data on those who only recovered one antibody level to the normal range were not given. It is likely this is a sign of deep remission, and the authors showed it was associated with lower plasma cell burden. It is hard to know if this also represents a return of normal T-cell function, which may be important for immune surveillance. Recovery of immunoglobulins is something to encourage patients with, as they nervously monitor immunoglobulins as they attend follow-up.

Reference: Haematologica 2017;102(5):922–31
Abstract

Carfilzomib-dexamethasone vs bortezomib-dexamethasone in relapsed or refractory multiple myeloma by cytogenetic risk in the phase 3 study ENDEAVOR

Authors: Chng W-J et al.

Summary: This preplanned subgroup analysis of the ENDEAVOR trial compared carfilzomib versus bortezomib, both with dexamethasone, according to cytogenetic risk; there were 97 and 113 trial participants with high-risk cytogenetics, and 284 and 291 with standard-risk cytogenetics, in the respective arms. For the respective high- and standard-risk groups, carfilzomib versus bortezomib recipients had a longer PFS duration (8.8 vs. 6.0 months; HR 0.65 [95% CI 0.45, 0.92] and not estimable vs. 10.2 months; 0.44 [0.33, 0.58]), higher ORRs (72.2% vs. 58.4% and 79.2% vs. 66.0%) and greater CR or better rates (15.5% vs. 4.4% and 13.0% vs. 7.9%).

Comment (DS): This paper looked at outcomes of the 27% of ENDEAVOUR patients who had poor-risk cytogenetics by FISH, defined as those with t(4;14) or t(14;16) in ≥10% of screened plasma cells or with del(17p) in ≥20%. Although the response rates were the same in high- and standard-risk patients, both favouring carfilzomib, the HR for PFS was 0.66 compared with 0.44 for those with standard-risk disease, highlighting that poor-risk patients relapsed earlier, and while benefiting from carfilzomib, did so less than those with standard risk. The short PFS durations of 8.8 and 6 months in the high-risk patients, treated with carfilzomib or bortezomib, show better treatments are needed.

Reference: Leukemia 2017;31(6):1368–74
Abstract