Multiple Myeloma Research Review™

Making Education Easy

Issue 31 – 2019

In this issue:

Abbreviations used in this issue
CR = complete response
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
PI = proteosome inhibitor
RCT = randomised controlled trial

Welcome to issue 31 of Multiple Myeloma Research Review.

In 2011, frontline bortezomib became available and thalidomide availability was expanded in NZ, and the impact this has had on MM survival is the focus of the first paper in this issue. Results from two phase 3 trials in transplant-ineligible patients with newly diagnosed MM are also included: the encouraging ongoing MAIA trial, which is investigating the addition of the monoclonal immunotherapeutic daratumumab to standard lenalidomide/dexamethasone; and the CLARION trial, which has compared carfilzomib versus bortezomib, both combined with melphalan and prednisone, but has failed to deliver promising results, possibly due to limitations of the trial's design. This issue concludes with research reporting on the impact of pre-existing monoclonal gammopathies on MM outcomes.

We hope you enjoy this issue, and we welcome your comments and feedback.

Kind regards,

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Impact of increased access to novel agents on the survival of multiple myeloma patients treated at a single New Zealand centre

Authors: Hock BD et al.

Summary: The impact of changes in novel agent usage on MM survival was reported for a retrospective cohort of real-world patients treated at Christchurch Hospital. Patients treated during 2000–2009 (n=237) were compared with those treated during 2011–2017 (n=343); frontline bortezomib became available and thalidomide availability was expanded in 2011. Compared with patients treated in the earlier cohort, those treated in the later cohort were significantly more likely to be treated with novel agents (85% vs. 55%) and had longer median OS duration (56 vs. 44 months) and a greater proportion of patients aged <70 years underwent autologous stem-cell transplantation (74% vs. 49%). In older patients, those treated in the later cohort had significantly longer median OS duration (28 vs. 17 months), but the 5-year relative survival rate remained <50%. In younger patients, those from the later cohort also had significantly increased initial OS duration with the survival curves converging at 5 years. While OS durations did not differ significantly between cohorts for patients who underwent autologous stem-cell transplantation, their median PFS duration was significantly longer in the later cohort (40 vs. 20 months).

Comment (KR): This Christchurch single-centre study adds to the real-world data from the two other recent papers that looked at the total NZ myeloma population. This was the Dunedin study (Sneyd *et al.*) and the Burden of disease study by Milne and Chan now published in Br J Haematol. The results are interesting in that although the median OS of the whole cohort study has improved, this does not translate into an improved OS in the post- (later) cohort transplant group. The use of novel agents seems to have impact on the increased proportion of patients getting to transplant in the post-cohort group and 74% is a very good number, which hopefully will translate to improved survival with a longer follow-up.

Reference: Interm Med J 2019;49:598–606
Abstract

Impact of acquired del(17p) in multiple myeloma

Authors: Lakshman A et al.

Summary: This was a comparison of 76 patients with MM without del(17p) at diagnosis but with subsequent acquisition of this mutation (at median of 35.6 months and after a median of two lines of therapy) versus 152 del(17p)-negative control patients without later acquisition at comparable timepoints. Compared with controls, patients who acquired del(17p) had shorter median PFS and OS durations (30.1 vs. 23.0 months [p=0.032] and 106.1 vs. 68.2 months [p<0.001], respectively). The respective median PFS and OS durations following del(17p) detection were 5.4 and 18.1 months. Predictors of del(17p) acquisition were an elevated LDH level (odds ratio 3.69 [95% CI 1.11, 12.24]) and presence of t(4;14) mutation or any high-risk translocation (2.66 [1.09, 6.48] and 2.23 [1.00, 4.95], respectively) at diagnosis. After del(17p) detection, shorter OS was predicted by a high rate of plasma cell proliferation (HR 2.28 [95% CI 1.31, 3.96]).

Comment (KR): This small study illustrates the adverse effect that acquisition of a del(17p) has on survival in myeloma. It is not a common practice in NZ to revisit FISH (fluorescence *in situ* hybridisation) studies at progression of disease. This study also shows that high risk features tend to co-aggregate to give a double hit scenario that does not bode well.

Reference: Blood Adv 2019;3:1930–8
Abstract

Pomalidomide-based regimens for treatment of relapsed and relapsed/refractory multiple myeloma

Authors: Mushtaq A et al.

Summary: This was a systematic review and meta-analysis of 35 phase 2 and 3 clinical trials (n=4623) reporting outcomes for different pomalidomide regimens for relapsed or refractory MM. The ORR for all 2- and 3-drug pomalidomide regimens was 47.1%. For the most frequently evaluated regimen of pomalidomide plus low-dose dexamethasone, the ORR was 35.7%, PFS duration was 6.1 months and OS duration was 14.37 months. The pooled ORR for triplet regimens was 61.9%. The respective ORRs and PFS durations for bortezomib, pomalidomide plus low-dose dexamethasone were 83.5% and 15.7 months, for carfilzomib, pomalidomide plus low-dose dexamethasone they were 77.1% and 15.3 months, and for pomalidomide, low-dose dexamethasone plus cyclophosphamide they were 59.4% and 9.5 months. The ORR for pomalidomide, low-dose dexamethasone plus bendamustine was 74.2%, for pomalidomide, dexamethasone plus daratumumab it was 64.5% and for pomalidomide, low-dose dexamethasone plus doxorubicin it was 32%. The main adverse events were myelosuppressive, with respective mean incidences of grade ≥3 neutropenia, anaemia and thrombocytopenia of 47.6%, 26.5% and 20.8%. Grade ≥3 nonhaematological adverse events were infections (29.1%), pneumonia (13.8%) and fatigue (10%).

Comment (KR): This is a very large pooled analysis of studies looking at the synergistic activity of pomalidomide with PIs. Personal experience from the time when carfilzomib was available to be used in a compassionate setting has shown that this drug used with pomalidomide gives excellent responses. In Australia, the PBAC does not currently allow the use of doublet regimens in the relapse setting. In NZ, we are now unable to use the combinations either, and we need better access to effective drugs for relapsed disease.

Reference: Clin Lymphoma Myeloma Leuk 2019;19:447–61
Abstract

Daratumumab plus lenalidomide and dexamethasone for untreated myeloma

Authors: Facon T et al., for the MAIA Trial Investigators

Summary: The phase 3 MAIA trial randomised patients with newly diagnosed MM to RD (lenalidomide plus dexamethasone) with (n=368) or without (n=369) daratumumab until disease progression or unacceptable toxicity. This interim analysis after a median follow-up of 28 months found that compared with RD, daratumumab plus RD was associated with a significantly lower proportion of participants who experienced disease progression or death (26.4% vs. 38.8%; HR 0.56 [95% CI 0.43, 0.73]), a greater CR or better rate (47.6% vs. 24.9% [p<0.001]) and a greater proportion of participants below the threshold for MRD (24.2% vs. 7.3%). Grade 3–4 adverse event rates were higher in the daratumumab group, with the most common being neutropenia (50% vs. 35.3% for RD), lymphopenia (15.1% vs. 10.7%) and pneumonia (13.7% vs. 7.9%).

Comment (KR): The MAIA study was presented by Facon at the last ASH meeting in a late-breaker session and is now published. The results in this nontransplant-eligible group certainly show a significant increase in CR over the controls and also an improved PFS. One minor criticism would be that RVD is a more potent comparator arm than RD. Never the less the study highlights the improvement in response that daratumumab offers over standard therapy in the upfront setting.

Comment (DS): Daratumumab continues to do for myeloma what rituximab did for B-cell lymphomas with improved depth of response and better PFS whenever it is added. The MRD-negative rate was increased to nearly 25% in this nontransplant cohort. There was a small price to pay with increased infections and neutropenia. Infusion reactions were common but not often severe. The frequent infusions require commitment, but this will be less of an issue if subcutaneous daratumumab is used. While these results are good, it is likely that adding a PI would give even deeper responses. So the question is not whether to add daratumumab, but to add it to what?

Reference: N Engl J Med 2019;380:2104–15
Abstract

Carfilzomib or bortezomib with melphalan-prednisone for transplant-ineligible patients with newly diagnosed multiple myeloma

Authors: Facon T et al.

Summary: The phase 3 open-label CLARION trial randomised transplant-ineligible patients with newly diagnosed MM to receive nine 42-day cycles of KMP (carfilzomib, melphalan, prednisone; n=478) or VMP (bortezomib, melphalan, prednisone; n=477). No significant difference was seen between the KMP versus VMP arms for any of the endpoints, including PFS (22.3 vs. 22.1 months; HR 0.906 [95% CI 0.746, 1.101]) and ORR (84.3% vs. 78.8% [p=0.218]); grade ≥3 adverse event rates were also similar (74.7% vs. 76.2%).

Comment (KR): The CLARION study was a very large study that also involved several NZ centres. The twice-weekly infusions were a challenge and the cardiac and hypertension side effects have to be carefully monitored. The results are disappointing because there was no improvement in PFS despite the intensive treatment. Regimens such as KRD have been shown to improve CR rates, but carfilzomib has not made an impact in this transplant-ineligible group when compared with VMP.

Comment (DS): The ENDEAVOUR trial (also reviewed in this issue) clearly showed that carfilzomib was better than bortezomib, so it was a surprise that the CLARION trial did not show the same superiority. The dose of carfilzomib was lower in the CLARION trial, but I think the real difference was in the way the PIs were given. In both arms, six of the eight doses of drug were administered with no concomitant steroid or cytotoxic agent, and we know that PIs are not very effective as monotherapy. This study is a good example of how poor trial design using empirically derived therapy can set back drug development.

Reference: Blood 2019;133:1953–63
Abstract

Single-agent daratumumab in very advanced relapsed and refractory multiple myeloma patients

Authors: Jullien M et al.

Summary: Outcomes for a series of 41 patients with relapsed or refractory MM treated with single-agent daratumumab from a single centre and outside of clinical trials were reported in the retrospective study. The patients had received a median number of four prior therapies and had been previously received PI and immunomodulatory agents. Most patients were high-risk, including 24% with del17p or t(4,14), 31% with extramedullary disease and 12% with circulating plasmacytosis at the time daratumumab was started. The ORR for these patients was 24%, including a very good partial response or better rate of 5%. All patients relapsed after median follow-up of 6.5 months with a median PFS duration of 1.9 months. At the time of disease progression, 44% of patients had not received subsequent therapy. Median OS duration was 6.5 months. There were no new safety signal detected.

Comment (DS): Daratumumab is an effective agent in myeloma; however, this real-life single-centre experience is sobering as the population mirrors the population who is eligible for the current compassionate access programme in NZ. The treatments were well tolerated but the response rate was lower than trial data with an ORR of 24%, although 39% had at least a minor response. All responses were short lived. The trials have a tail of durable responders and so this series likely reflects a publishing bias of a group who were disappointed in how their patients responded; however, we should not oversell the efficacy of single-agent treatment.

Reference: Ann Hematol 2019;98:1435–40
Abstract

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**

Carfilzomib-dexamethasone versus bortezomib-dexamethasone in relapsed or refractory multiple myeloma

Authors: Orlowski RZ et al.

Summary: Updated OS and safety data and subgroup analyses were reported for the ENDEAVOR trial, which has previously reported significant improvements in PFS and OS with carfilzomib 56 mg/m^2 and dexamethasone versus bortezomib and dexamethasone in patients with relapsed/refractory MM; median follow-up durations for the respective arms were 44.3 months and 43.7 months. Compared with bortezomib plus dexamethasone, carfilzomib plus dexamethasone was associated with longer median OS duration (47.8 vs. 38.8 months; HR 0.76 [95% CI 0.633, 0.915]), a finding that was seen in age and cytogenetic subgroups, and according to number of prior lines of therapy, prior bortezomib or lenalidomide exposure and lenalidomide-refractory status. Exposure-adjusted adverse event incidences for the carfilzomib and bortezomib arms were 1352.07 and 1754.86 per 100 patient-years, with corresponding grade ≥3 adverse event rates of 162.31 and 175.90 per 100 patient-years.

Comment (DS): In this head-to-head study of two PIs, carfilzomib has emerged as the clear winner. The responses were deeper, the durations of response were longer and this translated into a clinically significant survival benefit. The benefit was seen in all subgroups, including low- and high-risk cytogenetics and whether patients had received prior bortezomib treatment or not. Carfilzomib was also better tolerated with exposure-adjusted adverse event rates significantly lower than with bortezomib treatment. There was less neuropathy than seen with bortezomib, but more hypertension and heart failure. The dose of carfilzomib used in this trial was 56 mg/m^2, which is the maximum dose where cardiovascular side effects are more common. While retreatment with bortezomib can be effective, it is not a replacement for carfilzomib in relapsed patients.

Reference: Clin Lymphoma Myeloma Leuk 2019;19:522–30
Abstract

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Impact of prior diagnosis of monoclonal gammopathy on outcomes in newly diagnosed multiple myeloma

Authors: Goyal G et al.

Summary: These researchers compared the prognosis of patients with MM with pre-MM diagnoses of monoclonal gammopathies (MGUS [monoclonal gammopathy of undetermined significance], smouldering myeloma or solitary plasmacytoma) to those without. The analyses included 2322 patients with MM; 774 were diagnosed with monoclonal gammopathies prior to MM and 1548 control patients had no pre-existing monoclonal gammopathy diagnosis. Median follow-up was 81 months. Compared with controls, patients with a pre-MM diagnosis of smouldering myeloma and those with a pre-MM diagnosis of solitary plasmacytoma had longer median OS durations (80 and 95 months, respectively vs. 56 months) and a lower risk of mortality (pooled HR 0.68 [95% CI 0.50, 0.93]), but there were no such differences between those with a pre-MM diagnosis of MGUS and controls.

Comment (DS): We generally think that transformed disease is a poor prognostic factor, so if a patient with a known indolent disease reaches the need for therapy they may do poorly. This study shows that is not the case. Delving deeper, smouldering myeloma that 'catches fire' actually has better survival than *de novo* myeloma. Previous work has shown that all myeloma starts as MGUS, so perhaps it is not surprising that MGUS patients have similar outcomes to *de novo* myeloma where there was no previous blood test.

Reference: Leukemia 2019;33:1273–7
Abstract

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