Multiple Myeloma RESEARCH REVIEW™

Making Education Easy

Issue 39 – 2021

In this issue:

Abbreviations used in this issue

EFS = event-free survival
HR = hazard ratio
MM = multiple myeloma
MRD = minimal residual disease
ORR = overall response rate
OS = overall survival
PCD/PD = pomalidomide, (cyclophosphamide), dexamethasone
PFS = progression-free survival
Rd = lenalidomide, dexamethasone

Welcome to issue 39 of Multiple Myeloma Research Review.

This issue's selection includes research reporting that switching elderly intermediate-fit patients with MM to reduced-dose lenalidomide maintenance without dexamethasone after nine cycles of Rd was both feasible and provided outcomes similar to those associated with continuing Rd. Two separate but complimentary papers from the Eur J Haematol provide an assessment of how costs and healthcare usage have changed over time in two Scandinavian countries, namely Denmark and Sweden. Other included research reports that a formulation of daratumumab with recombinant human hyaluronidase PH20 for subcutaneous administration was well tolerated with fewer infusion-related reactions and similar trough concentrations compared with intravenous administration. We have also included the final OS analysis of the TOURMALINE-MM1 trial of ixazomib-lenalidomide-dexamethasone for relapsed/refractory MM, which included some participants from NZ.

Thank you for your comments and suggestions – they are always appreciated, so please keep sending them.

Kind regards,

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Dose/schedule-adjusted Rd-R vs continuous Rd for elderly, intermediate-fit patients with newly diagnosed multiple myeloma

Authors: Larocca A et al.

Summary: This Italian phase 3 trial enrolled 199 newly diagnosed patients aged >65 years with symptomatic, measurable MM and clinical signs of frailty to receive nine cycles of lenalidomide 25 mg/day and dexamethasone 20mg once-weekly (Rd) followed by either single-agent low-dose lenalidomide (10 mg/day for three of each four-week cycle; n=101) or continuous Rd (n=98). The primary outcome measure of EFS was superior in the single-agent maintenance lenalidomide arm, with a 3.5-month extension of median EFS and a 30% reduced risk of disease progression/death from any cause, lenalidomide discontinuation or grade 4 haematological or grade 3–4 nonhaematological adverse events (10.4 vs. 6.9 months; HR 0.7 [95% CI 0.51, 0.95]). There was no significant difference in the secondary outcome measures of PFS (20.2 vs. 18.3; HR 0.78 [95% CI 0.55, 1.10]) or 3-year OS (74% vs. 63%; 0262 [0.37, 1.03]). The grade ≥3 nonhaematological adverse event incidence was lower in the lenalidomide maintenance arm (33% vs. 43%).

Comment (HC): The primary objective of this study was EFS, which was superior in the Rd-R arm, where the dose of lenalidomide was reduced and dexamethasone was stopped after 36 weeks of induction. This was primarily driven by the difference in nonhaematological toxicities, in particular, the frequency of fatigue and other undefined constitutional symptoms between the two arms. As this was an open-label study, this could potentially be subject to bias. Albeit the fact that the study was not sufficiently powered for PFS and OS, no obvious difference in either was seen between the two arms. In addition, even though the dose of lenalidomide was also reduced to 10mg during maintenance, no sudden separation of the survival curves was noted at that timepoint. These results are consistent with the data from the EMN01 trial where no benefit was noted with the addition of prednisone to lenalidomide maintenance following an initial induction with lenalidomide-dexamethasone with or without an alkylator. Based on these data, it is reasonable to discontinue dexamethasone after initial induction. It would be interesting to see the survival data between the two arms stratified according to their depth of response at the 36-week mark, as potentially a response-adapted approach may be a better way in determining the right timing and patients for treatment de-escalation.

Reference: Blood 2021;137:3027–36
Abstract

Independent commentary by Dr Henry Chan

Dr Henry Chan is a consultant haematologist at North Shore Hospital in Auckland. Following completion of specialist training in clinical and laboratory haematology, he completed a clinical fellowship in multiple myeloma and lymphoma at Princess Margaret Cancer Centre in Toronto. He is currently actively involved in clinical research, registrar teaching and patient education.

A systematic review and network meta-analysis of randomized data on efficacy of novel therapy combinations in patients with lenalidomide-refractory multiple myeloma

Authors: Mohyuddin GR et al.

Summary: This systematic review with network meta-analysis included seven randomised controlled trials reporting outcomes for patients with lenalidomide-refractory MM. These were linked in two discrete networks with a total of 1698 lenalidomide-refractory patients comparing bortezomib-dexamethasone or dexamethasone versus other treatments. First network: triplets of pomalidomide or daratumumab plus bortezomib-dexamethasone and the daratumumab-carfilzomib doublet were more effective than bortezomib-dexamethasone (respective HRs 0.65 [95% CI 0.50, 0.84], 0.36 [0.21, 0.63] and 0.38 [0.21, 0.69]). Second network: the addition of pomalidomide, isatuximab-pomalidomide and elotuzumab-pomalidomide to dexamethasone were more effective than dexamethasone alone (respective HRs 0.50 [95% CI 0.40, 0.62], 0.30 [0.20, 0.44] and 0.27 [0.16, 0.45]). In both networks, lower HRs and higher P-scores were seen for regimens that included monoclonal antibodies compared with those that didn't.

Comment (KR): The use of lenalidomide both in the relapsed setting and as maintenance after autologous stem-cell transplantation means that many local patients have been exposed to this drug. At present, when patients relapse there are few options available unless they can enter a trial. It is to be fervently hoped that this situation might be remedied by the recent favourable funding criteria in the most recent CATSOP minutes. It was therefore encouraging to see that regimens with pomalidomide and also monoclonal antibody-containing regimens were effective and that the monoclonal antibody regimens in particular had the lower HRs and higher P-scores. My personal bias would be for a monoclonal antibody-containing regimen at relapse after lenalidomide failure.

Reference: Clin Lymphoma Myeloma Leuk 2021;21:489–96
Abstract

Pomalidomide, cyclophosphamide, and dexamethasone for the treatment of relapsed/refractory multiple myeloma

Authors: Rodriguez-Otero P et al.

Summary: This article reported on the real-world experiences from the Spanish Myeloma Group (PETHEMA/GEM) for a cohort of 100 patients with relapsed or refractory MM who had received a median three prior lines of therapy and were treated with PCD (pomalidomide, cyclophosphamide, dexamethasone). The ORR for this cohort was 39%, with a clinical benefit rate of 93%. The respective median PFS and OS durations were 7.6 months and 12.6 months, with consistency seen across different subgroups analysed; patients with responsive disease had particularly prolonged PFS and OS.

Comment (HC): The data from this Spanish retrospective study provide a useful insight into the effectiveness of PCD, especially when there is a lack of prospective phase 3 data for such a regimen. The effect of low-dose cyclophosphamide is thought to be via its ability to augment existing therapies by modifying the immunosuppressive tumour microenvironment. Although a median PFS of just 7.58 months may not seem much at an initial glance, it is still a respectable number for real-world data when the reported median PFS for the PD doublet was only 4.0–7.1 months in phase 3 studies (MM003, OPTIMISMM, ICARIA). The toxicities reported with PCD do not appear to be significantly higher than what has been reported for PD in other studies, and it is a convenient all-oral regimen. However, it is worth noting that there are several different dosing schedules for cyclophosphamide reported in the literature for PCD. In this Spanish study, cyclophosphamide was given at 50mg daily on days 1–21 of a 28-day cycle. In Canada and the Singapore PCD versus PD study, cyclophosphamide was given as 400mg on days 1, 8 and 15 of a 28-day cycle only.

Reference: Clin Lymphoma Myeloma Leuk 2021;21:413–20
Abstract

Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA)

Authors: Moreau P et al., on behalf of the IKEMA study group

Summary: The open-label, phase 3 IKEMA trial randomised patients with MM who had received a median of two prior lines of therapy to receive carfilzomib and dexamethasone with (n=179) or without (n=123) isatuximab. The addition of isatuximab was associated with a longer median PFS (not reached vs. 19.15 months; HR 0.53 [95% CI 0.32, 0.89]). The incidences of serious treatment-emergent adverse events (59% vs. 57%) and deaths (both 3%) were comparable between the isatuximab and control arms, but a higher rate of grade ≥3 treatment-emergent adverse events was seen with isatuximab (77% vs. 67%).

Comment (KR): This trial is rather similar to the CANDOR trial previously covered that used daratumumab as the monoclonal antibody backbone. The IKEMA trial had some NZ sites recruited but not a lot of patients were enrolled. The results obtained were comparable with the other trial with a significantly improved PFS in the isatuximab arm. It does seem unlikely that we will ever see this combination available locally, although isatuximab is reputedly cheaper in the US.

Reference: Lancet 2021;397:2361–71
Abstract

The impact of changed treatment patterns in multiple myeloma on health-care utilisation and costs, myeloma complications, and survival

Authors: Hannig LH et al.

Summary: Healthcare utilisation and costs, myeloma complications and survival were evaluated for 3518 Danish registrants with MM before (2002–2005) and after (2010–2013) early-line treatments were implemented. Between the earlier and later periods, there was a marked shift from inpatient admissions towards outpatient visits, with 22% and 28% increases in the mean annual number of outpatient visits for those in the <65-year and ≥65-year age brackets, respectively, and corresponding increases in mean annual outpatient service costs from €17,001 to €23,643 in the younger patients and from €11,317 to €16,144 in the elderly. Lower inpatient admission costs outbalanced the increasing outpatient costs, and there was a decrease in adjusted total mean annual costs in younger patients. The 5-year survival rates also increased in both the younger and older groups (respective HRs 0.51 and 0.69).

Reference: Eur J Haematol 2021;107:63–73
Abstract

Healthcare resource utilisation and sickness absence in newly diagnosed multiple myeloma patients who did not undergo autologous stem cell transplantation

Authors: Borgsten F et al.

Summary: Trends in MM survival, healthcare resource utilisation and sickness absence associated with the changing treatment landscape in Sweden were reported for 7012 patients who had not undergone autologous stem-cell transplantation, stratified according to 5-year period of diagnosis. Between the 2001–2005 and 2011–2015 diagnosis periods, median survival duration increased from 2.5 to 3.4 years. Compared with the 2001–2005 and 2006–2010 periods, patients diagnosed during the 2011–2015 period: i) spent a shorter median time receiving inpatient or outpatient healthcare during their first 3 years of follow-up (55 vs. 78 and 63 days, respectively), with less associated inpatient and more associated outpatient healthcare usage; and ii) had a lower average 3-year sickness absence (362 vs. 522 and 410 days, respectively).

Reference: Eur J Haematol 2021;107:92–103
Abstract

Comment (HC): These two studies published in the Eur J Haematol used population-based data to determine the healthcare cost of myeloma in different periods. Even though the data originated from two different countries, both of them demonstrate a shift from inpatient to outpatient care in recent years. More importantly, they both demonstrated a reduction in healthcare utilisation, in terms of the number of hospital admissions and length of inpatient stay in the most recent period analysed, following the introduction of novel agents such as bortezomib and lenalidomide. The Swedish study also found less sickness absence and loss of productivity, and the Danish data showed a reduced total healthcare cost (including the cost of novel agents) in the most recent period. However, the Danish data did also find an increased rate of infection amongst those older than 65 years in the most recent period, which is a known issue with some of the novel agents. These population-based data demonstrate that although novel antimyeloma agents can be costly, they can potentially bring about savings in other parts of the healthcare and tax systems that can potentially make them cost-neutral, if not better, overall.

Subcutaneous daratumumab in patients with relapsed or refractory multiple myeloma

Authors: San-Miguel J et al.

Summary: This article reported on part 2 of the open-label, phase 1b PAVO study, which investigated subcutaneous administration of 15mL of a concentrated, premixed coformulation of daratumumab 1800mg and recombinant human hyaluronidase PH20 30,000U, infused over 3–5 minutes, in 25 patients who had received ≥2 prior lines of therapy for MM, including a proteasome inhibitor and an immunomodulatory drug; part 1 of the study reported that the formulation was well tolerated. The treatment was associated with daratumumab trough concentrations similar to or greater than intravenous administration of daratumumab 16 mg/kg, and its adverse event profile was consistent with intravenous daratumumab with no new safety concerns and fewer infusion-related reactions. After median follow-up of 14.2 months, the ORR was 52%, the median response duration was 15.7 months and median PFS duration was 12.0 months.

Comment (KR): The use of subcutaneous daratumumab is an attractive option for ease of delivery and also reducing day-stay times. This paper shows that the subcutaneous route can achieve similar trough concentrations to the intravenous route. There is also a lower infusion related reaction rate, suggesting that the subcutaneous route has to be the preferred option. I understand that a handful of local patients are already getting this product.

Reference: Haematologica 2021;106:1725–32
Abstract

Dynamics of minimal residual disease in patients with multiple myeloma on continuous lenalidomide maintenance

Authors: Diamond B et al.

Summary: Adults with newly diagnosed MM who had received unrestricted front-line therapy received 28-day maintenance cycles of lenalidomide 10mg for 21 days until progression or unacceptable toxicity, for ≤5 years, in this phase 2 trial. After median follow-up of 40.7 months, the primary endpoint of 60-month PFS (evaluable n=100) was 64% with the median PFS duration not reached. Thirty-four of 103 evaluable participants who sustained MRD negativity for 2 years had not progressed after a median of 19.8 months after the 2-year maintenance landmark, whereas the ten who lost their MRD-negative responses were more likely to progress than those with sustained MRD negativity (HR ∞ [p<0.0001]) and those with persistent MRD positivity (HR 5.88 [95% CI 1.18, 33.33]) at the 2-year landmark. The incidence of haematological and nonhaematological serious adverse events was 18%, and the most frequent grade ≥3 adverse events were decreased lymphocyte count (44%) and decreased neutrophil count (44%). The only on-study death was not considered to be related to the study drug.

Comment (HC): End-of-treatment MRD status has long been known to be prognostic with fixed-duration strategies. However, with the shift towards continuous treatment, the right timing of MRD assessment has been a topic of debate. The data from this study and others published in recent years show that the value of MRD assessment is most significant when done serially. In this study from Memorial Sloan Kettering, patients who lost their MRD-negative status during maintenance were at the highest risk of progression with a median time to progression of around 1.5 years from the time of conversion. Unsurprisingly, patients who had sustained MRD negativity had the best long-term outcomes, with none having progressed or died during the follow-up of this study. Similar positive long-term outcomes were also noted amongst those who were initially MRD-positive at the start of maintenance and later converted to MRD-negative. Surprisingly, patients who were persistently MRD positive did not fare as badly as one would suspect; the 5-year PFS calculated from the 2-year landmark timepoint was close to 70%. Although there are still no prospective data to guide clinicians on the right course of action with the various MRD dynamics, read-outs from some of the MRD-direct trials will be expected in the coming years. Meanwhile, hopefully, recent advances in liquid biopsy and mass spectrometry may potentially provide a less invasive alternative to bone marrow biopsy for MRD assessment in the future.

Reference: Lancet Haematol 2021;8:e422–32
Abstract

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Final overall survival analysis of the TOURMALINE-MM1 phase III trial of ixazomib, lenalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma

Authors: Richardson PG et al.

Summary: Patients with relapsed or refractory MM were randomised to receive Rd (lenalidomide, dexamethasone) with ixazomib (n=360) or placebo (n=362) in the phase 3 TOURMALINE-MM1 trial. After median follow-up of 85 months, there was no significant difference between the ixazomib-Rd versus placebo-RD arms for median OS duration (53.6 vs. 51.6 months [p=0.495]), but there was OS benefit seen with ixazomib-Rd for the following prespecified subgroups: refractory to any or last treatment line (respective HRs 0.794 and 0.742), aged >65–75 years (0.757), ISS stage III disease (0.779), 2/3 prior therapies (0.845), high-risk cytogenetics (0.870) and high-risk cytogenetics and/or 1q21 amplification (0.862). The respective proportions of ixazomib-Rd and placebo-Rd recipients who received ≥1 anticancer therapy after study treatment were 71.7% and 69.9%, with 24.7% and 33.9% receiving daratumumab and 71.8% and 76.9% receiving proteasome inhibitors. There were similar rates of new primary malignancies in the ixazomib-Rd and placebo-Rd groups (10.3% and 11.9%, respectively), and no new or additional safety concerns emerged.

Comment (KR): There seems to be a number of papers being published that highlight the use of ixazomib, which has been moderately popular because of its oral formulation. Many NZ centres contributed to this trial and I note some local names in the author list. The median OS values at 53.6 months were quite good, but in the end this did not translate into a statistically significant OS benefit on an intent-to-treat analysis. This study was also confounded by issues with subsequent treatments, making it hard to form a meaningful conclusion over the real benefits of this oral triplet regimen. I think it is going to be difficult for this drug to find a niche in the era of monoclonal antibody therapies.

Reference: J Clin Oncol 2021;39:2430–42
Abstract

Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO)

Authors: Dimopoulos MA et al. for the APOLLO Trial Investigators

Summary: The ongoing open-label phase 3 APOLLO trial randomised heavily pretreated adults with relapsed or refractory MM to receive pomalidomide and dexamethasone with (n=151) or without (n=153) the addition of daratumumab. At median follow-up of 16.9 months, the inclusion of daratumumab prolonged PFS by 5.5 months over pomalidomide-dexamethasone and conferred a reduced risk of disease progression or death (12.4 vs. 6.9 months; HR 0.63 [95% CI 0.47, 0.85]). Neutropenia, anaemia and thrombocytopenia were the most common grade 3–4 adverse events. Eleven patients in each trial arm died from treatment-emergent adverse events.

Comment (HC): This is the first subcutaneous daratumumab combination study in the relapsed/refractory myeloma setting. Not surprisingly, the triplet combination with daratumumab was more efficacious than pomalidomide-dexamethasone doublet in terms of depth of response, MRD-negative rate and PFS without significantly increasing toxicity. Focusing on those who are lenalidomide-refractory in their last line, which is one of the most urgent unmet needs in NZ, the median PFS was only 6.1 and 8.3 months in the doublet and triplet arms, respectively. This is similar to the data from the CASTOR trial with a median PFS of 4.4 and 9.3 in the bortezomib-dexamethasone and daratumumab-bortezomib-dexamethasone arms, respectively (Spencer A et al. Haematologica 2018). Better results were noted in the CANDOR trial where patients who were refractory to lenalidomide, but not necessarily as their last line of treatment, had not yet reached the median PFS in the daratumumab-carfilzomib-dexamethasone arm (Quach et al. Br J Haematol 2021). These results indicate that the more effective strategy in managing patients who progress on lenalidomide would be to introduce a new class of medication as a triplet and not just simply move from one immunomodulatory drug to another.

Reference: Lancet Oncol 2021;22:801–12
Abstract

Safety and effectiveness of weekly carfilzomib, lenalidomide, dexamethasone, and daratumumab combination therapy for patients with newly diagnosed multiple myeloma

Authors: Landgren O et al.

Summary: The MANHATTAN nonrandomised trial assessed a daratumumab-based quadruplet regimen in 41 patients with newly diagnosed MM; the regimen consisted of 28-day cycles of carfilzomib, lenalidomide, dexamethasone and daratumumab. The MRD-negativity rate (10^{-5} sensitivity) was 71%, achieved in a median of six cycles (range 1–8). The ORR was 100% with 95% of participants achieving a very good partial response or better. The 1-year PFS rate was 98%. There were no deaths during the trial.

Comment (KR): This is a unique paper in that Ola Landgren, when he was at Sloan Kettering, wanted to see if one could achieve very high rates of MRD negativity by using a quadruplet regimen. It was a relatively short follow-up interval, but the OS rate of 100% at 11 months is impressive as is the 70% MRD negativity rate in the treated group of only 41 evaluable patients. I think the main take-away message is what can be achieved with an aggressive quadruplet regimen, which would be extremely expensive and would never become a standard of care anywhere.

Reference: JAMA Oncol 2021;7:862–8
Abstract

Independent commentary by Dr Ken Romeril, FRACP, FRCPA

Ken is a haematologist specialising in malignant haematology. He trained in Christchurch, Sydney and Southampton, and is currently at the Bowen Icon Cancer Centre. 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, a former chair of the ALLG Myeloma Sub-Committee, and is the NZ representative on the International Myeloma Working Group, which has around 200 members.

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