Multiple Myeloma RESEARCH REVIEW™

Making Education Easy

Issue 36 – 2020

In this issue:

Abbreviations used in this issue
CR = complete response
HR = hazard ratio
MM = multiple myeloma
OS = overall survival
PFS = progression-free survival
RCT = randomised controlled trial
SCT = stem-cell transplantation
VGPR = very good partial response
VTE = venous thromboembolism

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Welcome to issue 36 of Multiple Myeloma Research Review.

The use of ixazomib-based induction therapy in routine clinical practice is relatively uncommon for several reasons, so the first study for this issue is useful, as it describes the effectiveness and safety of such treatment in a multicentre cohort of real-world patients. US research has confirmed that dialysis inpatients with MM who undergo autologous SCT with high-dose melphalan are at increased risk of dying. Another included study, an RCT, found no benefit of adding cyclophosphamide to bortezomib and dexamethasone in terms of renal recovery for patients with initial myeloma cast nephropathy and acute kidney injury not requiring dialysis. This issue concludes with a report of VTE risk in participants treated with immunomodulatory drugs for MM in the Myeloma IX and XI RCTs.

We hope you find the selected research in this issue interesting and helpful in your everyday practice. Please don't hesitate to send us your thoughts and suggestions.

Kind regards,

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Ixazomib-based frontline therapy in patients with newly diagnosed multiple myeloma in real-life practice showed comparable efficacy and safety profile with those reported in clinical trial

Authors: Li J et al.

Summary: The real-life effectiveness and safety of ixazomib-based induction therapy was reported for an observational cohort of 85 patients with newly diagnosed MM. IRd (ixazomib, lenalidomide, dexamethasone) was used in 44.7% of the patients, ixazomib plus dexamethasone in 29.4%, and ixazomib, dexamethasone plus doxorubicin, cyclophosphamide, thalidomide or daratumumab in 25.9%. The ixazomib induction regimens were given for a median of six cycles (range 1–20). Ten patients also received ixazomib maintenance. The overall response rate was 95.3%, including VGPR or better and CR rates of 65.9% and 29.5%, respectively, with a median time to response of 30 days. The different ixazomib-based regimens were associated with similar response rates. Median PFS was not reached. The grade ≥3 adverse event rate was 29.4%, and the discontinuation rate due to adverse events was 15.3%; there were no cases of grade 3–4 peripheral neuropathy.

Comment (KR): It seems surprising that the use of ixazomib has not been more widely taken up considering the convenience of a once-daily oral regimen. Despite accessing a lot of centres, this study only accrued 85 newly diagnosed MM patients. Similar to the TOURMALINE trial in which a number of us were involved, the drug was well tolerated and there was a low incidence of neuropathy. The drug is a useful alternative option in the newly diagnosed MM group. IRd is a useful combination in the relapsed setting as well.

Reference: Ann Hematol 2020;99:2589–98
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.

Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma

Authors: Voorhees PM et al., for the GRIFFIN Trial Investigators

Summary: Autologous SCT-eligible patients with newly diagnosed MM were randomised to a standard regimen of four cycles of RVd (lenalidomide, bortezomib dexamethasone) induction, autologous SCT, two cycles of RVd consolidation and 26 cycles of lenalidomide maintenance with (n=103) or without (n=103) the addition of daratumumab (induction, consolidation and maintenance) in the phase 2 GRIFFIN trial. The addition of daratumumab to RVd was associated with a significantly greater stringent CR rate at the end of consolidation treatment (42.4% vs. 32.0%; odds ratio 1.57 [95% CI 0.87, 2.82]) and at median follow-up of 22.1 months (62.6% vs. 45.4% [p=0.0177]), and a greater minimal residual disease negativity rate (51.0% vs. 20.4% [p<0.0001]). The respective 24-month PFS rates in the RVd and RVd plus daratumumab arms were 89.8% and 95.8%. There was a greater incidence of grade 3–4 haematological adverse events, but not infections, in the RVd plus daratumumab group.

Comment (KR): The GRIFFIN trial is regarded as a pivotal trial where daratumumab was added to an already effective upfront treatment for transplant-eligible myeloma patients. It showed a statistically significant endpoint reached with a stringent CR by the end of the post-SCT consolidation. It was a phase 2 study, so was not intended to evaluate small patient subgroups such as those with high-risk cytogenetics. The positive results will support the rationale for the ongoing phase 3 PERSEUS study, which will investigate the use of subcutaneous administration.

Reference: Blood 2020;136:936–45
Abstract

Inpatient mortality of patients with multiple myeloma and renal impairment undergoing autologous stem cell transplantation

Authors: Mohyuddin GR et al.

Summary: Inpatient mortality and trends over time were investigated for patients from the US National Inpatient Sample with MM and renal impairment undergoing autologous SCT with high-dose melphalan. From a weighted estimate of 47,253 inpatient admissions, weighted totals of 45 and 1709 patients underwent peritoneal dialysis and haemodialysis, respectively, during autologous SCT with high-dose melphalan. The risk of inpatient mortality was increased by 20.5% and 13.8% for peritoneal and haemodialysis patients undergoing transplantation, respectively, even after other comorbidities were considered (odds ratio 6.193 [CI 3.585, 10.701]). The risk of inpatient mortality decreased significantly from 15.6% in 2009 to 5% in 2014 for patients with end-stage renal disease undergoing autologous SCT with high-dose melphalan.

Comment (KR): It is often a difficult decision to perform an autotransplant on an MM patient with significant renal impairment. A reduction in the melphalan dose is often indicated, but most centres have performed transplants successfully on fully dialysis-dependent patients. The mortality in this paper was quite high peaking at around 20%, which would indicate that careful patient selection is mandatory, as this level of mortality is really unacceptable.

Reference: Eur J Haematol 2020;105:571–7
Abstract

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Different MAF translocations confer similar prognosis in newly diagnosed multiple myeloma patients

Authors: Goldman-Mazur S et al.

Summary: The prognostic impact of the *MAF* translocations t(14;16) and t(14;20) was assessed in 254 patients; 87.8% had the t(14;16) and 12.2% had the t(14;20) translocations. The respective median PFS durations for patients with the t(14;16) and t(14;20) translocations were 16.6 months and 24.9 months (p=0.28), and the respective median OS durations were 54.0 months and 49.0 months (p=0.62). Median OS duration was longer for patients who underwent double autologous SCT than for those who underwent single autologous SCT (107.0 vs. 60.0 months [p<0.001]). Patients with ISS stage 3 had inferior OS (HR 1.89 [95% CI 1.24, 3.19]).

Comment (KR): There have now been several studies that highlight the adverse prognosis related to the *MAF* translocations, and in particular, t(14;16). Personal experience has found very short survivals of <12 months in some patients with this adverse genetic signature. This large group of *MAF* translocation patients indicates that t(14;20) patients should also be considered to have a high-risk signature.

Reference: Leuk Lymphoma 2020;61:1885–93
Abstract

myeloma new zealand

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www.multiplemyeloma.org.nz/

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A phase II study of pomalidomide, daily oral cyclophosphamide, and dexamethasone in relapsed/refractory multiple myeloma

Authors: Van Oekelen O et al.

Summary: This open-label, phase 2 trial examined the addition of metronomic cyclophosphamide to a pomalidomide and dexamethasone regimen in relapsed/refractory MM. A total of 33 patients with lenalidomide-refractory disease (55% also proteasome inhibitor-refractory) received 28-day cycles of pomalidomide 4 mg/day, cyclophosphamide 50mg twice daily and weekly dexamethasone. The overall response rate was 73%, the median PFS duration was 13.3 months, and the median OS duration was 57.2 months. Grade 3–4 toxicities were primarily haematological, but were manageable.

Comment (KR): The prognosis of patients with relapsed/refractory disease is quite limited, and we need to find better strategies for patients already exposed to immunomodulatory drugs and the proteosome inhibitors. Pomalidomide has both tumouricidal and antiangiogenic properties. The addition of cyclophosphamide is known to overcome resistance, and so these triplet regimens have been previously tried with various dosing regimens. Metronomic therapy with daily low-dose cyclophosphamide and a 1-week respite was used to reduce myelosuppression. The results were excellent, with a respectable OS duration of around 57 months.

Reference: Leuk Lymphoma 2020;61:2208–15
Abstract

Lenalidomide maintenance after second autologous stem cell transplant improves overall survival in multiple myeloma

Authors: Modi D et al.

Summary: Outcomes were described for a retrospective group of 111 adults with MM who had undergone a second autologous SCT, after which they had been followed for a median of 58 months. For patients who received no maintenance (n=73), maintenance lenalidomide ≤15mg daily (n=23) and maintenance subcutaneous bortezomib 1.3 mg/m^2 every 2 weeks (n=15), the respective 3-year PFS rates were 11.2%, 29.9% and 0%, and the respective 3-year OS rates were 58.5%, 83.3% and 67.5%; lenalidomide maintenance provided significantly superior PFS and OS compared with no maintenance (respective HRs 0.46 and 0.25 [p=0.009 for both]).

Comment (HC): The data from this single centre retrospective review are interesting. Firstly, they revealed an increasing number of patients undergoing second autologous SCT in more recent years (2012–2018). This is somewhat surprising, as published data on the effectiveness of second autologous SCT at the time of relapse are not that much better than novel drug combinations after one prior line of treatment: Rd, median PFS 14.1 months (MM009 and MM010); KRd, median PFS 29.6 months (ASPIRE); DRd, median PFS not reached (POLLUX); DVd, median PFS not reached (CASTOR). Secondly, the study manages to show a survival benefit for lenalidomide maintenance over no maintenance after second transplantation. This is consistent with the published data in the frontline setting, and reinforces the benefit of continuous treatment over fixed-period strategies. Lastly, the benefit of bortezomib maintenance appears to be only modest on multivariate analysis, even after adjusting for the second-line therapy used.

Reference: Leuk Lymphoma 2020;61:1877–84
Abstract

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Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE)

Authors: Kumar SK et al.

Summary: The open-label, phase 3 ENDURANCE trial randomised patients with standard- or intermediate-risk MM to receive 12 3-week induction cycles of KRd (carfilzomib, lenalidomide, dexamethasone; n=545) or VRd (bortezomib, lenalidomide, dexamethasone; n=542), after which they underwent a second randomisation stratified by induction therapy to divide them into ongoing maintenance or fixed-duration 2-year maintenance lenalidomide regimens. The primary outcome of PFS did not differ significantly between the KRd versus VRd arms after median follow-up of 9 months (34.6 vs. 34.4 months; HR 1.04 [95% CI 0.83, 1.31]); median OS had not been reached in either group. KRd induction was associated with more grade 3–4 treatment-related nonhaematological adverse events than VRd, including hyperglycaemia, dyspnoea and thromboembolic events, and also more treatment-related deaths (11 vs. 2).

Comment (HC): To fully appreciate the results from this study, one must also review the supplementary data in depth. On the surface, it appears that KRd was no better than VRd in the frontline setting with similar PFS and OS. However, the study design and data interpretation may have muddied the water. Firstly, only about half of the patients completed the 36-week induction (61.6% in the KRd arm and 43.3% in the VRd arm). There was a numerically greater number of patients in the VRd arm who stopped treatment due to adverse events/complications, whilst the reported grade 3–4 toxicities were actually fewer in the VRd arm. There was also a higher number of patients in the VRd arm who withdrew to go on to alternative therapy (17.7% vs. 13.7%), including autologous SCT, which could certainly affect the survival data. Although the authors did attempt to address this by censoring these patients at the time of alternative therapy in a sensitivity analysis (supplementary data), this is unlikely to be able to fully compensate for any potential bias. Lastly, although the authors also presented the data specifically for those under the age of 70 years (similar to the overall results), as the study design did not mandate frontline transplantation, this result may not be applicable to other centres where frontline autologous SCT is the standard of care for transplant-eligible patients.

Reference: Lancet Oncol 2020;21:1317–30
Abstract

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Randomized trial comparing double versus triple bortezomib-based regimen in patients with multiple myeloma and acute kidney injury due to cast nephropathy

Authors: Bridoux F et al., for the MYRE study group

Summary: After receiving symptomatic measures and high-dose dexamethasone, patients with initial myeloma cast nephropathy and acute kidney injury not requiring dialysis were randomised to receive bortezomib plus dexamethasone with (n=92) or without (n=92) cyclophosphamide; participants with a <50% reduction in serum free light chain levels after three cycles could have their chemotherapy reinforced. Compared with bortezomib plus dexamethasone, the addition of cyclophosphamide did not significantly change the 3-month renal response rate (primary endpoint; relative risk 0.87 [p=0.46]) or the VGPR or better rate (0.76 [p=0.10]), and the numbers of participants who achieved a serum free light chain level of ≤500 mg/L after the first cycle of chemotherapy were similar (67 vs. 69 participants). Serious adverse events occurred in 30 bortezomib plus dexamethasone recipients and 40 bortezomib, dexamethasone plus cyclophosphamide recipients, and at 12 months, nine and ten from the respective arms had died (six and four from myeloma progression and zero and three from infections).

Comment (HC): Renal impairment is a common complication from myeloma, but there is a lack of published RCT data specifically on this patient group. The data from this French study show that in patients with true cast nephropathy, rather than acute renal impairment from prerenal failure or hypercalcaemia related to myeloma, over 40% of them will still have an estimated glomerular filtration rate of <40 mL/min at 12 months, despite receiving treatment for their myeloma. Unsurprisingly, patients who achieved a deeper response were more likely to experience recovery in renal function, and these patients who had a renal response had a trend towards better OS. The primary aim of this study was to assess renal response, which was not improved with the addition of cyclophosphamide to bortezomib-dexamethasone. However, renal response is just one aspect to consider when managing these patients. The study does also show a trend for better time to next treatment for the triplet arm. The toxicity seen in the triplet arm may be due to the high intravenous dose of cyclophosphamide used, and a lower but greater frequency weekly dosing of cyclophosphamide, like CyBorD, may potentially be more tolerable.

Reference: J Clin Oncol 2020;38:2647–57
Abstract

Maintenance therapy in transplant ineligible adults with newly-diagnosed multiple myeloma

Authors: Balitsky AK et al.

Summary: This systematic review and meta-analysis included five RCTs (n=1139) comparing maintenance therapy with observation for newly-diagnosed transplant-ineligible MM. Compared with observation, maintenance therapy was associated with significantly improved PFS (HR 0.48 [95% CI 0.38, 0.62]), but not OS (0.96 [0.76, 1.2]); the respective certainties for these findings were high and moderate. Maintenance therapy was also associated with more adverse events than observation (very low-to-moderate certainty).

Comment (HC): The result of this study is more about the efficacy of lenalidomide maintenance than anything else, as that was the treatment used in the interventional arm of four of the five included studies. The result is also predominantly influenced by the UK MRC XI study, as it accounts for two-thirds of the patients. Therefore, similar to the published UK MRC XI result last year, the result from this meta-analysis shows improved PFS with maintenance, but no significant difference in OS. However, as most of these studies used immunomodulatory drug-based induction before switching to lenalidomide maintenance, questions remain as to whether lenalidomide maintenance will remain effective after proteasome inhibitor-based induction. Unfortunately, the GERMAIN study (included in this meta-analysis), which evaluated the role of lenalidomide maintenance after VMP induction, failed to recruit a meaningful number of patients to address this issue due to poor accrual and high dropout rates.

Reference: Eur J Haematol 2020;105:626–34
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.

Thrombosis in patients with myeloma treated in the Myeloma IX and Myeloma XI phase 3 randomized controlled trials

Authors: Bradbury CA et al. on behalf of the United Kingdom National Cancer Research Institute Haemato-oncology Clinical Studies Group

Summary: This report provides a pooled prospective evaluation of thrombotic risk in patients with newly diagnosed MM treated with immunomodulatory agent-based induction therapy (thalidomide and lenalidomide) in the Myeloma IX (n=1936) and XI (n=4358) clinical trials. VTE rates were significantly lower in the Myeloma IX trial with CTD (cyclophosphamide, thalidomide, dexamethasone) induction compared with CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone; 16.1% vs. 22.5%), but compared with melphalan/prednisolone induction, the VTE risk was increased 4-fold with attenuated CTD (16% vs. 4.1%, adjusted HR 4.25 [95% CI 2.5, 7.2]). VTE affected up to one fifth of patients, and lenalidomide- or thalidomide-based induction regimens conferred a similar thrombotic risk (Myeloma XI, CRD [cyclophosphamide, lenalidomide, dexamethasone] vs. CTD, 12.2% vs. 13.2%, adjusted HR 0.92 [95% CI 0.72, 1.18]). Although VTE rates dropped between the Myeloma IX and the Myeloma XI trials (CTD regimen, 16.1% vs. 13.2%; attenuated CTD, 16% vs. 10.7%) in response to implementation of an IMWG-guided thromboprophylaxis protocol in Myeloma XI, which meant thromboprophylaxis was used more regularly (80.5% vs. 22.3%), thrombotic events were still frequent. With the exception of an association between arterial events and reduced survival in Myeloma XI (adjusted HR 1.53 [95% CI 1.12, 2.08]), thrombotic events were not found to negatively impact on long-term survival or disease progression outcomes.

Comment (HC): The combined data from these two UK studies show that the risk of thrombosis in patients with myeloma receiving first-line treatment is as high as 13–15%, with the vast majority occurring during the first 6 months. Maintenance did not appear to increase the risk. A cross-study comparison between patients who received the same treatment across the two studies showed a numeric reduction in thrombosis rate in those who received thromboprophylaxis as per the current IMWG guidelines compared with those without mandated thromboprophylaxis (4.3 vs. 5.4 per 100 person-years). However, the rate remains high even with thromboprophylaxis, and further study is needed to see if more intense thromboprophylaxis is required, especially during the initial few months of treatment.

Reference: Blood 2020;136:1091–104
Abstract