Multiple Myeloma Research Review™

Making Education Easy

Issue 28 – 2018

In this issue:

Abbreviations used in this issue
HR = hazard ratio
MGUS = monoclonal gammopathy of undetermined significance
MM = multiple myeloma
ORR = overall response rate
OS = overall survival
PFS = progression-free survival
QOL = quality of life
SCT = stem-cell transplantation

NZMA New Zealand Medical Association

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/

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Multiple Myeloma Research Review

Welcome to issue 28 of Multiple Myeloma Research Review.

We begin this issue with an interesting paper reporting on a novel agent that targets the micro-RNA cluster miR-17-92, with potential for use in MM and other MYC-driven malignancies. Other included research has identified a close relationship between subclone patterns in AL (light-chain) amyloidosis and other plasma cell dyscrasias. Following on from the earlier report of improved PFS in the TOURMALINE-MM1 trial, we now have participant-reported data on health-related QOL. This issue concludes with research assessing the long-term effects of induction and maintenance thalidomide in patients with recently diagnosed MM.

We do hope these papers provide you with valuable information you can use in your everyday practice. Please don't hesitate to send us your feedback and suggestions.

Kind regards,

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Therapeutic vulnerability of multiple myeloma to MIR17PTi, a first-in-class inhibitor of pri-miR-17-92

Authors: Morelli E et al.

Summary: The micro-RNA cluster miR-17-92 is a valuable therapeutic target in MYC-driven malignancies. This paper reported on MIR17PTi, the most promising novel LNA (locked nucleic acid) gapmeR antisense oligonucleotide developed by the researchers that resulted in the degradation of MIR17HG primary transcripts, thereby preventing biogenesis of miR-17-92 micro-RNA. MIR17PTi was shown to provide better impairment of proliferation of several cancer cell lines, via on-target antisense activity, than miR-17-92 inhibitors. MIR17PTi was also shown to trigger apoptosis via impairment of homeostatic MYC/miR-17-92 feed-forward loops in MM cells derived from patients, and to induce MYC-dependent synthetic lethality. Alteration of a BIM-centred feed-forward loop was shown to be required for MIR17PTi's cytotoxic effects in MM cells. MIR17PTi also resulted in strong antitumor activity in nonobese diabetic severe combined immunodeficient mice with clinically relevant MM models, and its safety and pharmacokinetic profiles in nonhuman primates were encouraging.

Comment (DS): The most commonly dysregulated pathway in myeloma is MYC, and MYC expression is important for myeloma survival. This paper looked at reducing MYC activity by blocking the precursor of the miR-17-92 cluster by using an antisense oligonucleotide. This resulted in upregulation of BID and apoptosis in patient-derived myeloma cells. If lack of toxicity is confirmed, expect to see this trialled in myeloma and other MYC-dependent tumours.

Reference: Blood 2018;132:1050–63
Abstract

Elotuzumab monotherapy in patients with smouldering multiple myeloma

Authors: Jagannath S et al.

Summary: Patients with smouldering MM were treated with intravenous elotuzumab 20 mg/kg on days 1 and 8 of the first cycle and then monthly (n=15) or 10 mg/kg every week for the first two cycles and then every 2 weeks (n=16) in this nonrandomised phase 2 trial; data from both regimens were combined for this report. The relationship between baseline proportion of bone marrow-derived CD56dim natural killer cells and maximal M-protein level reduction (primary endpoint) was negative. At ≥28 months' follow-up, the ORR was 10% and the 2-year PFS rate was 69%. Adverse events included upper respiratory tract infections (58%) and grade 1–2 infusion reactions (13%).

Comment (DS): Elotuzumab is an interesting antibody that seems to augment the immune control of myeloma. It had minimal activity as a single agent in relapsed/refractory MM, but was shown to improve survival when given with lenalidomide and dexamethasone in the same population. In this study it was given as monotherapy to patients with smouldering myeloma. It only achieved a response in 10%, and 30% progressed within 2 years on treatment, which is not very convincing. The next trial is to use it in combination with lenalidomide and dexamethasone in smouldering myeloma, when it will probably show more benefit, but this is not the antibody I would like for my myeloma patients.

Reference: Br J Haematol 2018;182:495–503
Abstract

Characterisation of immunoparesis in newly diagnosed myeloma and its impact on progression-free and overall survival in both old and recent myeloma trials

Authors: Heaney JLJ et al.

Summary: This retrospective analysis used data from MRC Myeloma IX and Cancer Research UK Myeloma XI clinical trials (n=3218; new trials) and MRC myeloma trials (n=2608; old trials) to investigate the effect immunoparesis has on survival in patients with newly diagnosed MM. At diagnosis, 85% of patients had polyclonal immunoglobulin levels below normal. Significantly lower PFS and OS were observed for patients with immunoparesis at diagnosis compared with patients with immunoglobulin levels in the normal range. Analysis of recent trials (excluding MRC myeloma trials where novel agents were not available) showed a median OS of up to 3 years longer in patients without immunoparesis compared with those with immunoparesis. The respective median PFS values for participants with normal IgG, IgA and IgM levels were 39%, 36% and 57% longer than for patients with decreased levels of the individual immunoglobulins. The only immunoglobulin that was proven to be an independent prognostic factor for both OS and PFS was polyclonal IgM. The hazard of death decreased by 36% for each point increase in polyclonal IgM.

Comment (DS): Myeloma patients usually have immune paresis with suppression of normal immunoglobulins (in about 89% using IgM suppression). This is seen even in nonsecretory myeloma and likely reflects the biology of the plasma cell clone, but the mechanisms are imperfectly understood. This study of newly diagnosed myeloma found there was more immune suppression with higher stage and poor-risk disease, and that immunoparesis was associated with decreased survival not explained by increased infections. This backs up previous studies that show reversal of immunoparesis with treatment is associated with better outcomes.

Reference: Leukemia 2018;32:1727–38
Abstract

Cytogenetic intraclonal heterogeneity of plasma cell dyscrasia in AL amyloidosis as compared with multiple myeloma

Authors: Bochtler T et al.

Summary: Clonal and subclonal compositions of underlying plasma cell dyscrasias were compared for 544 patients with systemic AL (light chain) amyloidosis and 519 with MGUS, smouldering MM or symptomatic MM. Interphase FISH was used to stratify subclones into those that were below two thirds of the largest and with an absolute difference of ≥30%. Compared with the non-AL amyloidosis group, a smaller proportion of the AL amyloidosis group had subclones detected (36.6% vs. 51.4% [p<0.001]), and they were not associated with plasma cell dyscrasia stage in either entity. The main clones in both groups were typically t(11;14) translocations, other immunoglobulin heavy-chain translocations and hyperdiploidy, whereas 1q21 gain and 8p21, 13q14, and 17p13 deletions were frequent subclones. MGUS, smouldering MM and MM stage of plasma cell dyscrasia did not impact on subclone/main clone ratio. A multivariate analysis revealed that t(11;14) was associated with a lower rate of subclone formation, whereas hyperdiploidy was associated with a higher rate; AL amyloidosis was not statistically significant, indicating that the lower subclone frequency reflects its high frequency of t(11;14).

Comment (DS): Next-generation sequencing techniques have shed light on the intraclonal heterogeneity of cancers. This paper looked at the malignant plasma cells of patients with AL amyloidosis. Consistent with other data, the frequency of t(11;14) was 60% by interphase FISH. Patients with this were less likely to have subclones, reflecting the different second hits required for malignant transformation. This paper highlights that the biology of myeloma is defined by what augments the original plasma cell mutation, whether this was multiple trisomies, or cyclin D1, cMAF or MMSET translocations.

Reference: Blood Adv 2018;2:2607–18
Abstract

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Advances in Immuno-Oncology

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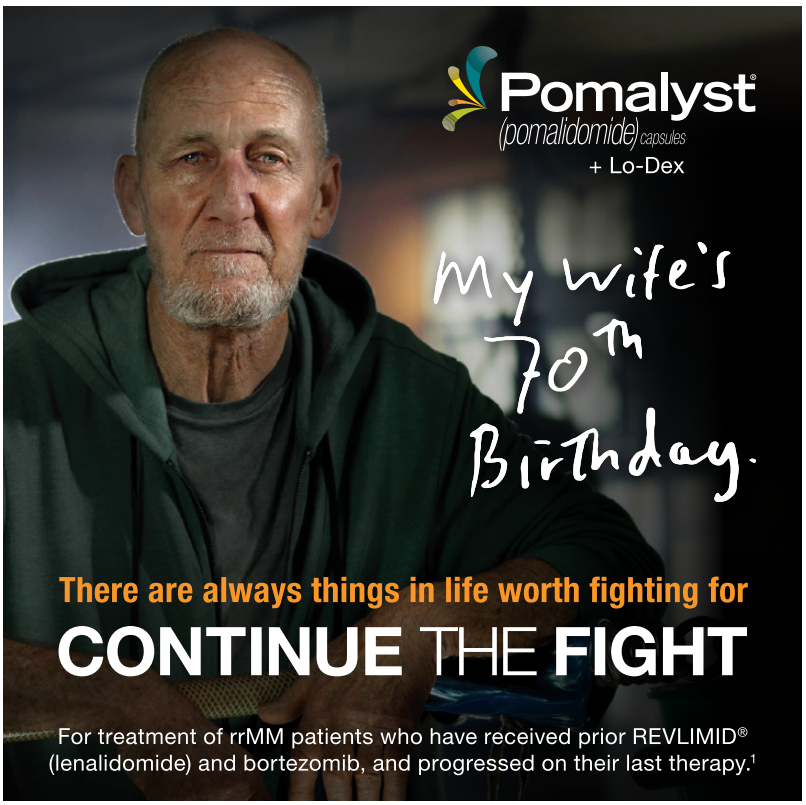
Dr Robert Weinkove, Consultant Haematologist at Wellington Blood and Cancer Centre and Clinical Director at Malaghan Institute of Medical Research introduces the topic of immuno-oncology.



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ABBREVIATIONS: Lo-Dex: low-dose dexamethasone; **rrMM:** relapsed and/or refractory MM.

REFERENCES: 1. POMALYST® Data Sheet.

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Date of preparation: June 2018.

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Elotuzumab plus pomalidomide and dexamethasone for multiple myeloma

Authors: Dimopoulos MA et al.

Summary: Patients with MM refractory or relapsed and refractory to lenalidomide and a proteasome inhibitor were randomised to receive pomalidomide and dexamethasone with (n=60) or without (n=57) elotuzumab and were followed for ≥9.1 months in this trial. Compared with pomalidomide and dexamethasone, the addition of elotuzumab was associated with a significantly longer median PFS duration (primary endpoint; 10.3 vs. 4.7 months; HR for progression or death, 0.54 (95% CI 0.34, 0.86]) and a significantly greater ORR (53% vs. 26%; odds ratio 3.25 [1.49, 7.11]). Common grade 3–4 adverse events were neutropenia (13% and 27% in elotuzumab and control groups, respectively), anaemia (10% and 20%) and hyperglycaemia (8% and 7%). The infection rate for each group was 65%, and infusion reactions occurred in 5% of elotuzumab recipients.

Comment (DS): Patients who are refractory to lenalidomide and a proteasome inhibitor represent a treatment challenge. Pomalidomide and dexamethasone has a modest benefit with a 30% response rate and median PFS of 4 months, confirmed in this trial; although some individuals do very well. The addition of elotuzumab, which has little single drug activity, improved the depth and duration of response. All except 6 of 117 patients had exposure to daratumumab, which is probably the preferred antibody for myeloma, and it would be interesting to see if responses were maintained in patients failing this.

Reference: N Engl J Med 2018;379:1811–22
Abstract

Independent commentary by Dr Ken Romeril, FRACP, FRCPA Haematologist specialising in malignant haematology, Wellington Hospital. He has a particular interest in translational myeloma research and genetics. **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**

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Research Review publications are intended for New Zealand health professionals.

Patient-reported health-related quality of life from the phase III TOURMALINE-MM1 study of ixazomib-lenalidomide-dexamethasone versus placebo-lenalidomide-dexamethasone in relapsed/refractory multiple myeloma

Authors: Leleu X et al.

Summary: Patient-reported health-related QOL (secondary) trial outcomes were reported for participants from the phase 3 TOURMALINE-MM1 trial of lenalidomide and dexamethasone with versus without ixazomib for relapsed/refractory MM after 1–3 prior lines of therapy; the primary endpoint of longer median PFS in the ixazomib arm was met (20.6 vs. 14.7 months [p=0.01]) with limited additional toxicity. Both arms showed that mean Quality of Life Questionnaire Core-30 global health status QOL scores were maintained during median follow-up of ~23 months, with no significant between-group differences, as were function domain scores; the physical, emotional and social function domain scores were also maintained, but with slightly higher mean changes from baseline scores at earlier timepoints in the ixazomib arm.

Comment (KR): NZ centres contributed very well to the TOURMALINE trial and there is a local author on this paper. The final conclusion was that the additional toxicity was fairly mild over the placebo arm, and therefore suggested that the long-term use is feasible. The response rate is lower than such agents as carfilzomib, and if once-weekly dosing becomes widespread, then the take up of ixazomib is likely to struggle. Where it may have a place is the frail elderly where an all oral regimen could be attractive.

Reference: Am J Hematol 2018;93:985–93
Abstract

VELCADE is a funded Prescription Medicine. Special Authority criteria apply. **VELCADE® (bortezomib) - Minimum Data Sheet. Presentation:** VELCADE is a Prescription Medicine containing bortezomib 3.5 mg per single dose vial. **Indications:** Untreated multiple myeloma unsuitable for high dose chemotherapy, in combination with melphalan and prednisone. Multiple myeloma, received at least one prior therapy, have progressive disease. As part of combination therapy, for induction therapy prior to high dose chemotherapy with autologous stem cell rescue for patients under 65 years of age with previously untreated multiple myeloma. **Dosage:** Administer either by IV or SC injection. See datasheet for full details. **Precautions:** DO NOT ADMINISTER INTRATHECALLY, peripheral neuropathy, hypotension, cardiac disorders, seizures, thrombocytopenia, gastrointestinal adverse events, pulmonary disorder, posterior reversible encephalopathy syndrome, tumour lysis syndrome, hepatic events, hepatic impairment, renal impairment, fertility, lactation, driving or operating machinery, pregnancy, lactation, children, frequently monitor Complete Blood Counts, see full Data Sheet. **Interactions with other drugs:** Inhibitors or inducers of CYP isozymes (in particular to CYP3A4) e.g. ketoconazole, ritonavir, rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort. Oral hypoglycaemics. Caution patients with concomitant medications associated with peripheral neuropathy (such as amiodarone, anti-virals, isoniazid, nitrofurantoin, statins), or with a decrease in blood pressure. **Date of Preparation:** 08 March 2017. Please review full Data Sheet before prescribing, available at www.medsafe.govt.nz or on request from Janssen-Cilag (New Zealand) Ltd, PO Box 62185, Sylvia Park 1644, Auckland, New Zealand. Material Date of Preparation Feb 2018. MKT-VEL-NZ-0006. TAPS NA 8996.

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Real-world data on Len/Dex combination at second-line therapy of multiple myeloma: treatment at biochemical relapse is a significant prognostic factor for progression-free survival

Authors: Katodritou E et al.

Summary: Outcomes were reported for 207 consecutive real-world patients who received lenalidomide plus dexamethasone as second-line therapy for MM; first-line treatments had been bortezomib- or immunomodulatory drug-based regimens, and 25% of patients had also undergone autologous SCT. The ORR was 73.4%, with respective complete and very good partial response rates of 17.8% and 23.7%, the median time to best response was 6.7 months, and the median PFS duration was 19.2 months with a 12-month PFS rate of 67.6%. The respective biochemical and clinical relapse rates prior to starting lenalidomide plus dexamethasone were 67.5% and 32.5%, and participants with biochemical relapse had longer median PFS than those with clinical relapse (24 vs. 13.2 months [p=0.006]); this difference retained significance after adjustment for other prognostic factors, and a multivariate analysis confirmed that relapse type was the strongest prognostic factor for PFS.

Comment (KR): These real-world data are a useful addition to our local practice, albeit we have to wait until third line. In reality the use of thalidomide at second line is often short and limited by toxicity. The finding that beginning therapy with lenalidomide plus dexamethasone at biochemical progression confers a significant PFS prognostic factor should encourage clinicians not to delay treatment until clinical progression.

Reference: Ann Hematol 2018;97:1671–82
Abstract

Identification of novel mutational drivers reveals oncogene dependencies in multiple myeloma

Authors: Walker BA et al.

Summary: These researchers identified 63 driver genes using integrated genomics in 1273 patients with newly diagnosed MM, including some novel genes (*IDH1*, *IDH2*, *HUWE1*, *KLHL6* and *PTPN11*). Greater clonality was seen with oncogene mutations than with tumour suppressor mutations, and as such, their selective pressure may be greater. Outcomes were worse with more driver gene abnormalities and also with identified mechanisms of genomic instability. They described a number of oncogenic dependencies identified between mutations in driver genes, common regions of copy number change, and primary translocation and hyperdiploidy events.

Comment (KR): This was a very comprehensive collection of clinical and genomic data from the Arkansas group on a large population, and deserved a commentary in Blood. They show that driver abnormalities include not only mutated driver genes, but also translocations, chromosomal gains and losses and APOBEC mutational signatures. This paper and another by Bolli find that TP53 is the only mutated driver gene that is a strong predictor of clinical outcomes. This impressive collection of data in newly diagnosed MM will be available for other investigators to gain more insights.

Reference: Blood 2018;132:587–97
Abstract

Maintenance treatment and survival in patients with myeloma

Authors: Gay F et al.

Summary: This systematic review and network meta-analysis included 11 randomised trials investigating eight novel agent-based maintenance regimens for patients with newly diagnosed MM (n=5073). Lenalidomide plus prednisone and lenalidomide alone were the most effective maintenance regimens in terms of PFS (respective HRs 0.39 [95% CrI 0.28, 0.53] and 0.47 [0.39, 0.55]), with a 74% probability of being the best; thalidomide plus interferon, thalidomide plus bortezomib, bortezomib plus prednisone and thalidomide alone were also favourable. Lenalidomide alone was found to be the best regimen in terms of OS (HR 0.76 [95% CrI 0.51, 1.16]) with a 38% probability of being the best, followed by bortezomib plus thalidomide and bortezomib plus prednisone. Similar results were seen in the restricted network including transplant trials, in a sensitivity analysis and in most prognostic subgroups.

Comment (KR): This network meta-analysis looked at many trials and confirmed the current clinical consensus that lenalidomide maintenance is the best treatment option. The recent MRC XI trial, which will be in print soon, has found that lenalidomide maintenance confers a significant OS benefit. This option is not currently funded in NZ, and patients have to consider a partial compassionate approach.

Reference: JAMA Oncol 2018;4:1389–97
Abstract

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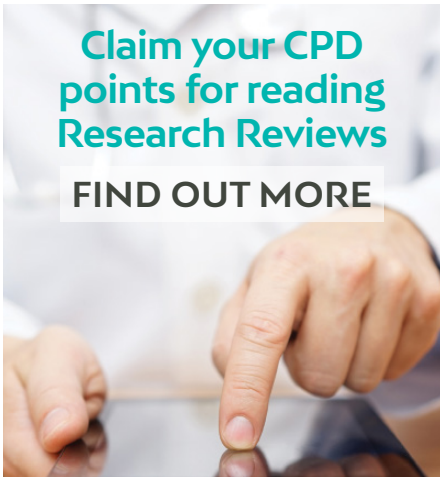
Thalidomide before and after autologous stem cell transplantation in recently diagnosed multiple myeloma (HOVON-50)

Authors: van de Donk NWCJ et al.

Summary: Adults with recently diagnosed Durie-Salmon stage II or III MM were randomised to receive three 28-day cycles of oral thalidomide 200–400mg on days 1–28 (n=268) or intravenous vincristine 0.4mg on days 1–4 (control; n=268), both with intravenous doxorubicin 9 mg/m^2 on days 1–4 and oral dexamethasone 40mg on days 1–4, 9–12 and 17–20 in this open-label, phase 3 trial. The participants were also randomised to one or two courses of intravenous melphalan 200 mg/m^2 with autologous SCT, and those who had a partial response or better after 2–3 months were eligible for maintenance high-dose melphalan. Participants assigned to the vincristine group received maintenance subcutaneous interferon-α 3×10^6 IU 3 times weekly, and those assigned to the thalidomide group received maintenance oral thalidomide 50 mg/day until relapse, progression or adverse events. Outcomes for extended median follow-up of 129 months are reported. Compared with the vincristine-containing regimen, the thalidomide-containing regimen was associated with a significantly longer event-free survival rate censored at SCT (primary endpoint; HR 0.62 [95% CI 0.50, 0.77]). The respective toxicity-related maintenance discontinuation rates were 42% and 27% in the thalidomide and control arms, and the second primary malignancy rates were similar between the two groups. There were 16 and 19 treatment-related deaths in the thalidomide and control groups, respectively.

Comment (KR): This is an interesting although somewhat historical paper, but does indicate that low-dose (50mg) thalidomide maintenance therapy confers an event-free survival advantage. They suggest that it could be an option in countries where there is limited access to lenalidomide, and NZ is a case in point where the drug is not funded after autologous SCT. Toxicity was an issue even at the low dose, and the discontinuation rate was high.

Reference: Lancet Haematol 2018;5:479–92
Abstract



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