Multiple Myeloma Research Review™

Making Education Easy

Issue 12 - 2018

In this issue:

Abbreviations used in this issue:

ASCT = autologous hematopoietic stem cell transplantation
BET = bromodomain and extraterminal domain
CI = confidence interval
CrCl = creatinine clearance
DRd = daratumumab plus lenalidomide and dexamethasone
DVd = daratumumab, bortezomib and dexamethasone
eGFR = estimated glomerular filtration rate
ELd = elotuzumab plus lenalidomide and dexamethasone regimen
HR = hazard ratio
IL = interleukin
IMP = ixazomib-melphalan-prednisone
Ld = lenalidomide and dexamethasone
MRD = minimal residual disease
NDMM = newly diagnosed multiple myeloma
NK = natural killer
PFS = progression free survival
RRMM = relapsed/refractory multiple myeloma
SLAMF7 = signaling lymphocytic activation molecule F7
VMP = bortezomib- melphalan-prednisone

Welcome to the October edition of Multiple Myeloma Research Review.

This month we begin with recent updates on the POLLUX, CASTOR and ELOQUENT- 2 studies in RRMM. We also review novel immunological insights into daratumumab resistance and discover a new take on sibling rivalry. From the world of transplantation, we review the impact of impaired renal function on ASCT tolerability as well as German data on the role of allogeneic stem cell transplantation. Lastly we round off this month's edition by examining trends in the management of end of life care in MM.

I hope this month's review proves to be beneficial to your practice and once again I welcome any feedback.

Kind Regards,

Associate Professor Philip Campbell

philip.campbell@researchreview.com.au

Daratumumab plus lenalidomide and dexamethasone versus lenalidomide and dexamethasone in relapsed or refractory multiple myeloma

Authors: Dimopoulos, M et al.

Summary: This updated analysis of the multicenter, open-label, active-controlled phase 3 POLLUX trial (N = 569, median age 65 years, minimum ≥ 1 prior line of therapy) provides additional 12-months follow-up data for daratumumab plus lenalidomide and dexamethasone (DRd) versus lenalidomide and dexamethasone in patients with relapsed or refractory multiple myeloma (RRMM). By all measures of efficacy, and in all subgroups analysed, the addition of daratumumab to a lenalidomide and dexamethasone regime was beneficial and increased survival. Compared to lenalidomide and dexamethasone alone, daratumumab plus lenalidomide and dexamethasone increased progression free survival (PFS; 17.5-months *vs* median not reached; regardless of number of lines of prior therapy), increased the overall response rate (76.4% *vs* 92.9%), increased the complete response rate (21.0% *vs* 51.2%) and increased the minimal residual disease (MRD)-negative at the 10e5 sensitivity threshold rate (6.4% *vs* 26.2%) – all P < 0.0001.

Comment: Combining daratumumab with standard of care regimens induces deeper responses and significant prolongation of PFS. The POLLUX study, first published 2 years ago after just 1 year of follow up, demonstrated a 63% reduction in the risk of disease progression or death and hitherto unprecedented levels of MRD negativity in the RRMM setting. In this further analysis after more than 2 years of follow up, investigators performed a subgroup analysis to identify those patients deriving the greatest benefit from the DRd combination. Their results confirm significant benefit of DRd across all patient groups irrespective of prior treatment, risk status or time since previous treatment. The fourfold increase in MRD negativity is even more remarkable when one considers not all eligible complete response patients had MRD assessments and this observed increase may indeed be conservative.

Reference: Haematologica 2018;Sept 20, epub ahead of print
Abstract

Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma

Authors: Spencer A et al.

Summary: This report provides an updated post-hoc analysis of the phase III CASTOR trial (N = 498) which compared a regimen of daratumumab, bortezomib and dexamethasone (DVd) to a control regimen of bortezomib and dexamethasone in RRMM patients with a history of at least one prior therapy. At a median follow-up of 19.4-months the DVd regimen showed superiority over control in both progression free survival rates (16.7-months *vs* 7.1-months; hazard ratio [HR] 0.31; 95% confidence interval [CI], P< 0.001) and overall response rates (83.8% *vs* 63.2%; P<0.0001). Subgroup analysis showed the greatest benefit in terms of survival for patients receiving DVd at first relapse (median: not reached *vs* 7.9 months; HR 0.19; 95% CI, 0.12-0.29; P <0.0001), however the benefits of DVd regimen were seen in all subgroups irrespective of prior treatment exposure, lenalidomide-refractory status, time since last therapy or cytogenetic risk.

Comment: This update from the CASTOR investigators is almost a mirror image of the POLLUX study described above. Once again we see consistent clinical benefit across all subgroups as well as a deepening of response with a further 12 months of follow up (≥ CR 28.8% compared with 19.2% in the first analysis). Both CASTOR and POLLUX continue to demonstrate the significant clinical benefit seen when daratumumab is combined with a standard of care regimen in RRMM, particularly after 1 previous line of therapy. No new safety concerns have been highlighted and it's likely with longer term follow, the impressive rates of MRD negativity seen in both studies will translate into an overall survival benefit, hopefully increasing the likelihood of reimbursement.

Reference: Haematologica 2018; Sept 20, epub ahead of print
Abstract

Elotuzumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma

Authors: Dimopoulos M et al.

Summary: This report provides extended 4-year follow-up and analysis of relative progression-free survival from the randomized ELOQUENT-2 trial. The phase 3, randomised, open-label ELOQUENT-2 trial enrolled 646 RRMM patients (median age 66-years, median 2 lines of prior therapy) and randomised them 1:1 to either an elotuzumab plus lenalidomide and dexamethasone regimen (ELd) or a control group that received lenalidomide and dexamethasone (Ld). Primary endpoints of PFS and overall response rate showed similar results to 2- and 3-year follow-up data with the ELd regimen decreasing the risk of disease progression/death by 29% compared to Ld (HR 0.71). Subgroup analysis showed that RRMM patients ≥ 3.5-years from diagnosis with 1 prior line of therapy had the greatest PFS benefit from ELd treatment (44% decreased risk of progression/death compared to Ld). PFS benefit was maintained beyond 50-months.

Comment: This 4-year update of the Eloquent-2 study continues to demonstrate a sustained improvement in PFS in favour of ELd and has the longest follow up of all the monoclonal antibody-based studies in RRMM to date. Unlike POLLUX and CASTOR however, the greatest clinical benefit appeared in patients with more indolent and less heavily treated disease which may reflect the distinct anti-tumour profile of signaling lymphocytic activation molecule F7 (SLAMF7) targeting. The authors also performed an indirect cross-trial comparison using data derived from ASPIRE, TOURMALINE and POLLUX, and although the longer follow up in eloquent-2 translated to the greatest relative PFS benefit overall, the 12 month relative PFS benefit was doubled with DRd in POLLUX. Selection and sequencing of monoclonal antibodies in MM remains contentious although daratumumab's potency across all patient subgroups including those with high risk disease make it a more attractive option in those patients with aggressive disease biology.

Reference: Cancer 2018;Sept 11, epub ahead of print
Abstract

Fratricide of NK cells in daratumumab therapy for Multiple Myeloma overcome by *ex vivo*–expanded autologous NK cells

Authors: Wang Y et al.

Summary: This pre-clinical study investigated the mechanisms underlying daratumumab resistance in patients with MM and proposes a way to prevent it. Using flow cytometry, natural killer (NK) cells from peripheral blood and/or bone marrow of MM patients was quantified and compared to healthy donors. MM patients treated with daratumumab had severely depleted $CD38^{+}$ NK-cell populations but normal levels of $CD38^{-/low}$ NK-cells. Immunoblotting analysis showed that the depletion of $CD38^{+}$ NK-cells was due to daratumumab-induced NK-cell fratricide via antibody-dependent cell toxicity. Examination of cell expansion and daratumumab treatment in a MM.1S xenograft animal model showed that expanded $CD38^{-/low}$ NK-cells to be cytotoxic against MM cells and therefore daratumumab resistance in daratumumab-treated MM patients may be overcome by an infusion of *ex-vivo*-expanded autologous NK cells from daratumumab-treated patients.

Comment: As we have seen daratumumab-treated MM patients enjoy substantial clinical benefit but ultimately relapse and the development of therapeutic approaches to overcome resistance will be important. This pre-clinical study from Columbus, Ohio suggests NK-cell fratricide is the mechanism responsible for daratumumab-mediated NK cell depletion. Using a ^{51}Cr release assay they demonstrate NK-NK cellular cytotoxicity in the presence of daratumumab not seen when SLAMF7 is targeted with elotuzumab. In addition, the $CD38^{-/low}$ NK cells left behind can be expanded *ex-vivo* into $CD38^{+}$ cytotoxic NK cells with anti-MM activity. These interesting results will need confirmation as a potential strategy to overcome daratumumab resistance.

Reference: Clinical Cancer Research 2018;24(16):4006-17
Abstract

Lower glomerular filtration rate predicts increased hepatic and mucosal toxicity in myeloma patients treated with high-dose melphalan

Authors: Tamaki M et al.

Summary: This retrospective, single-center study from Saitama Medical Center, Japan, investigated the correlation between renal dysfunction and toxicity of high-dose melphalan followed by autologous hematopoietic stem cell transplantation (ASCT) in patients with MM. 78 MM patients who had undergone high-dose melphalan followed by ASCT were divided into 2 groups; higher estimated glomerular filtration rate (eGFR; eGFR ≥ 60) or lower eGFR (< 60). Although lower eGFR was independently associated with mucositis (OR 10.5, $P=0.032$) and grade 2–4 co-elevation of both aspartate aminotransferase and alanine aminotransferase (OR 21.3, $P=0.016$) it did not correlate with overall survival.

Comment: The International Myeloma Working Group recommends high-dose melphalan dose reductions in patients with a creatinine clearance below 60ml/min although the relationship between renal dysfunction and toxicity is not well defined. Non-renal mechanisms of elimination through hydrolysis is relatively minor due to increased protein binding and yet delayed excretion in renally-impaired patients may potentially enhance anti-tumour activity. This single centre retrospective Japanese study of 78 patients used an eGFR of 60mls/min as a cut-off and they deployed split melphalan dosing. The authors observed higher rates of mucositis, liver dysfunction and engraftment delay but no impact on survival outcomes. Suprisingly, none of the patients received cryotherapy which would be considered routine in many transplant centres and this may have accounted for the higher rates of oral mucositis. Significant inter-individual variation in melphalan clearance and metabolism makes PK monitoring and dosing an attractive way to optimise dosing in this context.

Reference: Int J of Haematol 2018;108(4):423-31
Abstract

Allogeneic transplantation of multiple myeloma patients may allow long-term survival in carefully selected patients with acceptable toxicity and preserved quality of life

Authors: Greil C et al.

Summary: This German retrospective study investigated the efficacy of allogeneic transplantation for patients with MM. 109 MM patients who received reduced-intensity conditioning allogeneic transplantation at the Freiburg University Medical Center between 2000 and 2017 were included in the study. At 71.5-months follow-up, overall response rate was 70%, median OS 39.2% and median PFS 14.2-months. Compared to patients with progressive disease, survival was better in patients with response to previous therapies (median OS 11.5 *vs* 65 months, p=0.003; median PFS 5.1 *vs* 18.4 months, p=0.001) and as a first-line treatment (not relapsed/refractory disease) (median OS not reached *vs* 21.6 months, p<0.001; median PFS 47.7 *vs* 9.6 months, p<0.001). Some level of graft-versus-host disease occurred in 49% of patients.

Comment: The potentially curative capability of allogeneic stem cell transplantation in MM has never been questioned. However, it's role in an era of so many novel, accessible and well tolerated therapies remains unclear. The stubbornly high non-relapse mortality and rates of chronic graft versus host disease continues to be an issue for patients and referring physicians alike. This upbeat assessment of allografting in MM is based on a retrospective single German centre analysis of outcomes over nearly 2 decades. The patient population represents something of a dog's breakfast with multiple conditioning regimens used and no standardisation of transplant timing. Nevertheless, there are long term survivors and quality of life was maintained in some patients reinforcing the importance of careful selection, particularly when applied to high risk patients.

Reference: Haematologica 2018;Sept 20, epub ahead of print
Abstract

Lenalidomide and dexamethasone in patients with relapsed multiple myeloma and impaired renal function: PrE1003, a PrECOG study

Authors: Mikhael J et al.

Summary: This real world, multi-centre US phase I/II trial evaluated the efficacy and safety of lenalidomide with dexamethasone in patients with relapsed MM and renal insufficiency. 62 patients (median age 71.5-years, 84% Caucasian, 50% female) from 12 institutions were divided into 3 study groups based on their renal function; creatinine clearance (CrCl) 30-60cc/hour (n = 29), CrCl < 30 cc/hr and not on dialysis (n = 14) and patients on dialysis (n =14). Patients received doses of between 10-25mg lenalidomide daily for 21/28 days plus 40mg oral desamethasone on days 1, 8, 15 and 22 of a 28-day cycle. No dose-limiting toxicities were observed in phase 1. The most common adverse events noted were anaemia, diarrhea and fatigue. The overall response rate was 54%, PFS 7.5-months and OS 19.7-months. The authors concluded that lenalidomide 25mg daily 21/28 days is effective however patients with CrCl < 30 could be given a reduced dose of 15mg daily.

Comment: Lenalidomide dosing in MM patients with impaired renal function is a significant issue and data around the maximum tolerated dose in this situation is lacking. This small phase I/II study from the Mayo Clinic suggests that perhaps we may be too cautious in our dosing of renal-impaired MM patients and that doses above 15mg daily can be delivered safely in patients with severe renal insufficiency.

Reference: Blood Cancer J 2018;8(9):86
Abstract

Meaningful changes in end-of-life care among patients with myeloma

Authors: Odejlide O et al.

Summary: These researchers from the Dana-Farber Cancer Institute used the Surveillance, Epidemiology, and End-Results-Medicare database to investigate end-of-life care including trends in hospice use amongst patients with MM. 12,686 patients (≥ 65-years) diagnosed with MM between 2000-2013 who died by December 31, 2013 were included in the analysis. 48.2% of patients entered hospice, 17.2% of those were a "late" enrolment (≤ 3 days before death). Between 2000 to 2013 hospice use increased from 28.5% to 56.5% (P_{trend} <0.001) whilst late enrolment use remained relatively stable (12.2% in 2000 to 16.3% in 2013, P_{trend} =0.19). Aggressive medical care at end-of-life was most commonly seen in patients who were transfusion-dependent or on dialysis. The authors concluded that meaningful improvements in end-of-life care for this population was seen.

Comment: In comparison to patients with solid tumours, referral to palliative care and hospice services for symptom control and end of life care is underutilised in haematological malignancies. MM shares many clinical features with advanced solid tumours including high rates of pain and incurability and evidence exists to support early palliative care as a means of improving outcomes in solid tumour patients, particularly lung cancer. This study from the Boston group examined patterns of end of life care in elderly MM patients. Using the NCI's SEER database, they identified almost 13,000 MM patients with a median age of 77 and a significant number were still receiving regular transfusions or on dialysis. These patients were more likely to experience delayed admission to palliative care or receive inappropriately aggressive end of life care. On a positive note however, there was evidence of improved engagement with palliative care over the 13- year period during a time of major advances in the treatment of MM. Early discussion and documentation of both goals of care and advanced care plans will deliver improved management of end-of-life care in MM patients.

Reference: Haematologica 2018;103(8):1380-89
Abstract

A phase I/II dose-escalation study investigating all-oral ixazomib-melphalan-prednisone induction followed by single-agent ixazomib maintenance in transplant-ineligible newly diagnosed multiple myeloma

Authors: San-Miguel J et al.

Summary: This Spanish phase I/II trial assessed the efficacy of an all oral induction regimen of ixazomib-melphalan-prednisone (IMP) followed by maintenance ixazomib in elderly (≥ 65-years) newly diagnosed MM transplant-ineligible patients. Patients (N = 61) were divided into 4 arms and all received ixazomib doses of 3.0 – 5.5mg, melphalan 6mg/ml (Arm A) or 9 mg/ml (Arms B, C & D) and prednisone 60mg/m^2 (melphalan/ prednisone days 1-4 in each treatment cycle). Arm A (n = 11) patients received up to 9, 42-day cycles of twice-weekly ixazomib, Arm B (n = 34) up to 13, 28-day cycles of weekly ixazomib and Arms C & D (n = 10 and 6, respectively) up to 9, 42-day cycles of weekly ixazomib. Patients with stable disease after induction also received maintenance single-agent ixazomib therapy, at induction doses, for up to 12, 28-day cycles, disease progression or unacceptable toxicity. The recommended phase II dose was determined to be weekly ixazomib 4.0mg [days 1, 8, 15] in 28-day cycles. At the end of the study the complete response and very good partial response rate was 48% (including 28% ≥ complete response). 34% of patients also had a deepening of responses during maintenance. Progression free survival, at a median follow-up of 43.6-months, was 22.1-months. Some adverse events were noted.

Comment: The VISTA study led to the bortezomib- melphalan-prednisone (VMP) regimen being widely adopted across Europe in transplant-ineligible patients. The observed high CR rate and significant activity in high risk patients supports further investigation of a proteasome inhibitor and melphalan combination. This early phase study evaluated the oral 'VMP-like' regimen of ixazomib, melphalan and prednisone in elderly MM patients, but rather than stopping at 9 cycles, patients went on to ixazomib maintenance. Almost half of patients had a very good partial response or more and a third of patients deepened their responses during the maintenance phase. A well tolerated and active maintenance approach using ixazomib and the lack of dexamethasone makes this regimen a particularly attractive option in this cohort of patients.

Reference: Haematologica 2018;103(9):1518-26
Abstract

The novel bromodomain and extraterminal domain inhibitor INCB054329 induces vulnerabilities in myeloma cells that inform rational combination strategies

Authors: Stubbs M et al.

Summary: This report from The Incyte Corporation gives pre-clinical data on the bromodomain and extraterminal domain (BET) –inhibitor INCB054329. In MM models INCB054329 has been shown to decrease expression of the oncogenes *FGFR3* and *NSD2/MMSET/WHSC1* and suppression of interleukin (IL)-6 Janus kinase-signal transducers and activators of transcription (JAK-STAT) signalling. *In vivo* and *in vitro* studies also show an inhibition of myeloma cell growth by a combination treatment of INCB054329 with JAK-inhibitors ruxolitinib or itacitinib.

Comment: BET proteins bind to 'super-enhancer regions' of DNA promoting the expression of a number of influential oncogenes including c-myc which is activated in a significant proportion of MM patients. A number of BET inhibitors are in the early stages of clinical development across a range of haematological and solid tumours. These investigators report significant activity of the novel BET inhibitor INCB054329 by sensitising MM cells to JAK inhibition as well as t(4;14) MM cells to *FGFR* inhibitors. Phase I studies with this agent in MM are underway

Reference: Clin Cancer Research 2018;Sept 11; 10.1158/1078-0432.CCR-18-0098
Abstract

Multiple Myeloma Research Review™

Independent commentary by Philip Campbell

MB ChB FRCP FRACP FRCPath FRCPA

Philip Campbell is Head of Clinical Haematology and Director of Cancer Services at University Hospital Geelong, and Clinical Associate Professor at Deakin University School of Medicine. His main clinical interests are malignant haematology and clinical research, particularly multicentre collaborative research in malignant haematology. Philip is a member of the Haematology Society of Australia and New Zealand, British Society of Haematology, Australasian Leukaemia and Lymphoma Group, Australasian Society of Thrombosis and Haemostasis, Australasian Society of Blood Transfusion, Australasian Society of Bone Marrow Transplantation and American Society of Hematology.

