Welcome to issue 32 of Multiple Myeloma Research Review.

This issue begins with research investigating the influence of SNPs (single nucleotide polymorphisms) of the CRBN gene on the risk of adverse effects associated with thalidomide-based chemotherapy for MM. We have also included important real-life research supporting the VRD (bortezomib, lenalidomide, dexamethasone) induction regimen with high OS rates compared with VCD (bortezomib, cyclophosphamide, dexamethasone), but unfortunately, we are still not able to offer VRD to our patients. There is also research on response kinetics for MM in the era of novel agents showing that slow and gradual responses are more favourable. Results from the KEYNOTE-183 and -185 trials of pembrolizumab, pomalidomide and dexamethasone in MM are also presented. We would also like to express great thanks to Dr David Simpson for his valuable expertise and input into Multiple Myeloma Research Review over the years. It was a privilege to be associated with David over 31 issues, and we wish him well in his new role.

Please remember, your comments and feedback are always welcome.

Kind regards,

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Polymorphisms in the promotor region of the CRBN gene as a predictive factor for peripheral neuropathy in the course of thalidomide-based chemotherapy in multiple myeloma patients

Authors: Mlak R et al.

Summary: This research investigated the influence of specific genetic factors on treatment complications to thalidomide-based chemotherapy for MM. Adverse effects to front-line thalidomide, cyclophosphamide and dexamethasone treatment were analysed for 82 patients and correlated to SNPs of the CRBN gene. A multivariate analysis showed a significant correlation between the presence of the CRBN CC genotype (rs1672753) and significantly increased risks for peripheral polyneuropathy and diarrhoea (respective odds ratios 14.29 and 16.67). CRBN genotypes AA (rs6768972) and TT (rs1672753) showed a protective effect against the risk of constipation (respective odds ratios 0.003 and 0.004).

Comment (KR): In our clinical practice, we have all seen patients who seem to develop neuropathy on thalidomide within a very short time and often under 6 months. This elegant study shows us the genetic factors that predispose patients to this early neuropathy and also gastric side effects. We will hopefully be able to pretest our patients for this abnormality in the future, but it is likely to be some time before it becomes an available test. The trend is for thalidomide to be used for much shorter durations.

Reference: Br J Haematol 2019;186:695–705

Abstract

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Research Review publications are intended for New Zealand health professionals.

Independent commentary by Dr Ken Romeril, FRACP, FRCPath

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.
Clinical efficacy of daratumumab, pomalidomide, and dexamethasone in patients with relapsed or refractory myeloma: utility of re-treatment with daratumumab among refractory patients

Authors: Nooka AK et al.

Summary: The utility of retreatment with daratumumab among refractory patients, as well as in naïve patients, was retrospectively analysed in 34 patients with MM treated with combination daratumumab, pomalidomide and dexamethasone. All the patients had received prior therapy with immunomodulatory drugs and proteasome inhibitors, and they were divided into cohorts based on their prior exposure to daratumumab and pomalidomide. Cohort 1 (n=12) was comprised of patients naïve to both daratumumab and pomalidomide. Cohort 2 (n=22) included patients who were refractory to daratumumab and/or pomalidomide when treatments were received individually, and included a subgroup (cohort 3) of 12 patients who were refractory to both agents. Patients naïve to daratumumab and pomalidomide treatment had an ORR of 91.7% and included four stringent complete responses. At a median 41 months of follow-up, this group had not reached median PFS duration. Cohort 2 had an ORR of 40.9% and a median PFS duration of 3.2 months. Cohort 3 had an ORR of 33.3% to the combination therapy, with a PFS duration of 2.5 months.

Comment (KR): This is a small study that has been around for a while and was actually first presented at ASH 2016 in San Diego. The extremely good PFS benefit certainly shows the benefit of adding a monoclonal antibody to any regimen, and this even worked in people who had exhibited prior refractoriness to both daratumumab and pomalidomide. It is an attractive triplet that may mean that a quadruplet regimen may not be required.

Reference: Cancer 2019;125:2991–3000

Response to first cycle is the major predictor of long-term response to lenalidomide and dexamethasone therapy in relapsed and refractory multiple myeloma: can we spare patients the toxicity and costs of additional agents?

Authors: Gassiot S et al.

Summary: Patients with relapsed or refractory MM who had a good response (PFS >24 months) to lenalidomide plus dexamethasone salvage therapy were identified and characterised in this research; 227 patients with evaluable data from three tertiary-care hospitals were identified. A multivariate analysis revealed that the main independent predictor of PFS >24 months was achieving a partial response after the first therapy cycle, which, along with standard-risk cytogenetics, also predicted a higher complete response rate. The only baseline characteristic associated with long-lasting response was prior plasma-cell dyscrasia. Significant prognostic factors for poorer OS were high-risk cytogenetics and no history of monoclonal gammapathy of undetermined significance, whereas there was a trend for improved OS in patients who had received only one prior therapy.

Comment (KR): This is a nice ‘real world’ study that is relevant to our current NZ practice. It clearly shows that the quality of response to the first cycle is a major predictor of a good long-term response. The fact that a high-risk genetic signature is a negative prognostic factor should guide clinicians to looking at some supplementary more active therapy, such as bortezomib. The recent lifting of restrictions on the use of bortezomib may allow clinicians to augment treatment in such high-risk cases as the t(4;14), which we know is more susceptible to bortezomib.

Upfront bortezomib, lenalidomide, and dexamethasone compared to bortezomib, cyclophosphamide, and dexamethasone in multiple myeloma

Authors: Utell K et al.

Summary: This was a retrospective analysis of patients treated with first-line VCD or VRD, with or without subsequent high-dose treatment and autologous SCT; 351 patients received VCD with 213 without high-dose treatment, and 71 received VRD with and 46 without high-dose treatment. Compared with VCD, use of VRD was associated with: i) a higher ORR (98% vs. 88% [p<0.001]), including among those who did not receive high-dose treatment (89% vs. 79% [p<0.001]); ii) a higher 18-month PFS rate overall (88% vs. 63%), in the subgroup who did not receive high-dose treatment (82% vs. 32%) and the subgroup who did (91% vs. 73%); and iii) a higher 18-month OS rate (95% vs. 89% [p=0.048]).

Comment (KB): This is an important comparison because the study compares our standard induction regimen of CyBorD (VCD) with VRD, which is very popular in the US but which we cannot offer to our patients. I understand that VRD has been approved by the PBAC in Australia recently. This quite large study yielded a very impressive ORR of 98%. The 18-month analysis showed that the VRD-treated group had superior survival as well. We need to be able to offer this sort of induction regimen to our patients, and it is yet another unmet clinical need.


Abstract

Once-weekly versus twice-weekly carfilzomib in patients with newly diagnosed multiple myeloma

Authors: Bringen S et al.

Summary: These researchers analysed pooled phase 1–2 trial data to compare efficacy and safety of once-weekly versus twice-weekly dosing of carfilzomib in patients with newly diagnosed MM. The trials comprised 121 transplant-ineligible participants who received nine induction cycles of carfilzomib, cyclophosphamide and dexamethasone (CyCX) and carfilzomib maintenance. Sixty-three participants received a once-weekly schedule of carfilzomib 70 mg/m² and 58 received a twice-weekly dose of 36 mg/m². No significant difference was seen between the once-weekly and twice-weekly dosing for median PFS (35.7 vs. 35.5 months [p=0.26]), 3-year OS (70% vs. 72% [p=0.50]) or grade 3–5 haematological adverse events (24% vs. 30% [p=0.82]).

Comment (KB): This is the ARROW study that has been extensively referred to by speakers at recent meetings. The results clearly show that the more convenient once-weekly approach using a single high dose of carfilzomib prolonged the median PFS of relapsed MM patients. Many clinicians in the US have been using the once-weekly approach for some time now, and the ARROW phase 3 trial confirms that it is a reasonable approach to deliver a more convenient schedule.

Reference: Haematologica 2019;104:1640–7

Abstract

The impact of response kinetics for multiple myeloma in the era of novel agents

Authors: Yan Y et al.

Summary: The relationship between response kinetics and outcome was explored for 626 trial participants with newly diagnosed MM assigned to either immunomodulatory drug-based or PI-based therapy. While there was an association between depth of response and better outcome, survival was significantly worse for participants whose best response was <3 months versus those who responded later, and for those who achieved rapid complete remission versus those who achieved a gradual partial remission. Participants who achieved gradual and sustained remission experienced longer median OS duration than those who achieved a rapid and transient response (126 vs. 30 months). The effects of response patterns on survival were confirmed in participants at different disease stages and cytogenetic risks, including transplant-eligible participants and those achieving a range of response depths.


Abstract
Daratumumab and dexamethasone is safe and effective for triple refractory myeloma patients

Authors: Boyle EM et al., on behalf of the IFM2014-04 investigators

Summary: Final results were reported from the Intergroupe Francophone du Myéloème 2014-04 (Etoile du Nord) trial, in which 57 evaluable patients with triple-relapsed/refractory MM received infusions of daratumumab plus weekly dexamethasone until disease progression or unacceptable toxicity. The respective ORR and clinical benefit rate were 33% and 48%, with a very good partial response or better rate of 8.6%. Median time to response was 4 weeks, and responders had a longer median PFS duration than those with minimal or stable disease (6.6 vs. 3.7 months). The median OS duration for all participants was 16.7 months, for responders it was 23.23 months and for participants with progressive disease it was 2.97 months. Infusion-related reactions occurred at an incidence of 37%, but there were no resultant dose reductions or permanent treatment discontinuations.

Comment (HC): Albeit with the limitations of a cross-study comparison, the addition of dexamethasone to daratumumab does not appear to yield any substantial improvement in response rate or PFS compared with the published data on daratumumab monotherapy (Loehorst et al., 2015; Lonial et al., 2016; Usmani et al., 2016). Meanwhile, the infection rate was noticeably higher with the addition of daratumumab with 18.5% of the patients experiencing a grade 3 or higher infection despite many patients receiving prophylaxis. Altogether, it is difficult to justify the use of daratumumab-dexamethasone over daratumumab monotherapy.


Abstract

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Bortezomib consolidation following autologous transplant in younger and older patients with newly diagnosed multiple myeloma in two phase III trials

Authors: Straka C et al.

Summary: These authors conducted a post hoc analysis of data from two phase 3 trials in patients with newly diagnosed MM to assess how age and treatment factors influence the efficacy of bortezomib consolidation on PFS after autologous SCT. One of the trials had enrolled 202 participants aged 18–60 years and the other had enrolled 155 participants aged 61–75 years, and both randomised the participants to four 35-day cycles of bortezomib 1.6 mg/m² on days 1, 8, 15 and 22 or observation only. There was no significant difference between the bortezomib consolidation versus observation arms for median PFS duration among participants aged 18–60 years (33.6 vs. 29.0 months (p=0.3599)), but this was significantly longer for bortezomib recipients aged 61–75 years (33.4 vs. 26.4 months (p=0.0073)). Outcomes for the younger and older participants who received prior treatment of differing intensity appeared to be equalised by bortezomib consolidation after autologous SCT.

Comment (HC): As expected, the data from these two phase 3 studies (one for patients aged 18–60 years and the other for patients aged 61–75 years) show an improvement in depth of response with bortezomib consolidation after autologous SCT. Although an improvement in PFS was noted in the 61- to 75-year age group and not the younger cohort, this disparity in observation between the two age groups is likely due to the substantial difference in bortezomib exposure prior to consolidation (70% in the 18- to 60-year group and 22% in the 61- to 75-year group). The final multivariate analysis did however confirm bortezomib consolidation as a positive prognostic factor for PFS, but this did not translate into an OS benefit. With this, the debate regarding the role of post-autologous SCT consolidation continues, but it does appear across the literature that the benefit of consolidation depends on the intensity of induction treatment given.


Abstract

VELCADE is a Prescription Medicine containing bortezomib 1mg or 3.5mg per single dose vial. VELCADE is fully funded, Special Authority criteria apply. Indications: Untreated multiple myeloma unsuitable for high dose chemotherapy, in combination with melphalan and prednisone. Multiple myeloma, received at least one prior therapy with 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. Dose and method of use: 1.3 mg/m² may be administered intravenously at a concentration of 1 mg/mL as a 3-5 mins bolus injection or subcutaneously at a concentration of 1mg/mL, see full Data Sheet for dosing schedule; reduce or withhold dose with haematological toxicity or neuropathy. Renal failure may be considered for patients who had responded to treatment with VELCADE; see full Data Sheet. VELCADE may be intravenous or subcutaneous use only. Intrathelial administration has resulted in death. Contraindications: Hypersensitivity to bortezomib, renal or marrow failure. Precautions: DO NOT ADMINISTER INFRAHEMULLAI; peripheral neuropathy, hypotenison, cardiac disorders, seizures, thrombocytopenia, gastrointestinal adverse events, pulmonary disorder, proctor reversible encephalopathy syndrome, seizures, tumour lysis syndrome, hepatic events, hepatic impairment, renal impairment, fertility, lactation, driving or operating machinery, pregnancy, lactation, children, frequent monitor Complete Blood Counts, see full Data Sheet. Interactions with other drugs: Indicators or inducers of CYP isomeres in particular to CYP 34A1 e.g. Ketocnazole, ritonavir, rifampicin, carbamazepine, phenytoin, phenobarbital, St John’s Wort. Oral hypoglycaemics. Caution patients with concomitant medications that may be associated with peripheral neuropathy (such as amiodarone, anti-virals, isoniazid, nitrofurantion, statins), or with a decrease in blood pressure. Adverse events: Infections, pyrexia, gastrointestinal disorders, haematological disturbances, peripheral neuropathy, hypotenison, cardiac disorders, seizures, thrombocytopenia, gastrointestinal adverse events, pulmonary disorder, proctor reversible encephalopathy syndrome, seizures, tumour lysis syndrome, hepatic events, hepatic impairment, renal impairment, fertility, lactation, driving or operating machinery, pregnancy, lactation, children, increased appetite, general psychiatric disorders, dyspnoea, rash, blurred vision, vertigo, myalgia, fatigue, pyrexia, tumour lysis syndrome (uncommonly), Stevens-Johnson Syndrome, toxic epidermal necrolysis, pulmonary disorders, intestinal obstruction, progressive multifocal leukoencephalopathy, very rare cases with unknown causality of John Cunningham (JC) virus infection resulting in PML and death, anaphylactic reaction, thrombotic microangiopathy, others, see full Data Sheet. Presentation: VELCADE is a Prescription Medicine containing bortezomib 1mg or 3.5 mg per single dose vial. Date of Preparation: 13 November 2018. 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 Preparation Date: Jun 2019. MKT-VEL-NZ-0006. TAPS NA 8996. INSIGHT 9282.

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Pembrolizumab plus lenalidomide and dexamethasone for patients with treatment-naive multiple myeloma (KEYNOTE-185)

Authors: Usmani SZ et al., for the KEYNOTE-185 Investigators

Summary: Transplant-eligible adults with newly diagnosed MM (ECOG performance status of 0 or 1) were randomised to receive 28-day cycles of oral lenalidomide 25mg on days 1–21 and oral dexamethasone 40mg on days 1, 8, 15 and 22 with (n=149) or without (n=145) intravenous pembrolizumab 200mg every 3 weeks in the open-label, phase 3 KEYNOTE-185 trial. The trial was terminated early due to a mortality imbalance between the study arms. Median PFS (primary endpoint) was not reached in either group, with no significant between-group difference for the estimated 6-month PFS rates (p=0.75). The respective serious adverse event rates in the pembrolizumab and non-pembrolizumab arms were 54% and 39%, the most common being pneumonia (6%) and pyrexia (5%) in the pembrolizumab arm and pneumonia (6%) and sepsis (1%) in the non-pembrolizumab arm. There were six treatment-related deaths among pembrolizumab recipients and two among lenalidomide and dexamethasone only recipients.


Abstract

Pembrolizumab plus pomalidomide and dexamethasone for patients with relapsed or refractory multiple myeloma (KEYNOTE-183)

Authors: Mateos M-V et al., for the KEYNOTE-183 Investigators

Summary: Adults with MM refractory to ≥2 lines of therapy that excluded pomalidomide (ECOG performance status 0 or 1) were randomised to receive 28-day cycles of oral pomalidomide 4mg on days 1–21 and oral dexamethasone 40mg on days 1, 8, 15 and 22 with (n=125) or without (n=124) intravenous pembrolizumab 200mg every 3 weeks in the open-label, phase 3 KEYNOTE-183 trial. The trial was terminated, with median follow-up of 8.1 months, due to an unfavourable risk-benefit assessment. For the respective pembrolizumab and non-pembrolizumab arms, the median PFS durations were 5.6 months and 8.4 months, with no significant difference for the estimated 6-month PFS rates (p=0.39), and the median OS durations were not reached and 15.2 months (p=0.95). The respective serious adverse event rates in the pembrolizumab and non-pembrolizumab arms were 63% and 46%. There were four treatment-related deaths among pembrolizumab recipients and none among the pomalidomide and dexamethasone only recipients.


Abstract

Comment (HC): These two KEYNOTE studies were halted by the US FDA in July 2017 after noting a risk signal. The published data from both studies show a higher rate of serious adverse events, discontinuations of treatment due to adverse events and treatment-related deaths in the pembrolizumab arm. In KEYNOTE-183, neutropenia and thrombocytopenia were more frequent in the pembrolizumab arm, and the increased treatment-related death rate was due to neutropenic sepsis, myocarditis, Stevens-Johnson syndrome and unknown cause. In KEYNOTE-185, the rates of pyrexia, pneumonia, sepsis, acute renal injury and pulmonary embolism were higher for the pembrolizumab arm, whilst the causes of treatment-related death were cardiac arrest, cardiac failure, myocarditis, large intestine perforation, pneumonia and pulmonary embolism. Despite promising preclinical and early-phase data, PD1/PD-L1 inhibition for the increased treatment-related death rate was due to neutropenic sepsis, myocarditis, Stevens-Johnson syndrome and unknown cause. In KEYNOTE-185, the rates of pyrexia, pneumonia, sepsis, acute renal injury and pulmonary embolism were higher for the pembrolizumab arm, whilst the causes of treatment-related death were cardiac arrest, cardiac failure, myocarditis, large intestine perforation, pneumonia and pulmonary embolism. Despite promising preclinical and early-phase data, PD1/PD-L1 inhibition for the management of myeloma does not appear to be a viable option in the near future.


Abstract