Multiple Myeloma RESEARCH REVIEW™

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Issue 33 – 2020

In this issue:

Abbreviations used in this issue
CR = complete response
EFS = event-free survival
HR = hazard ratio
IMB = immunomagnetic bead
MM = multiple myeloma
MRD = minimal residual disease
OS = overall survival
PFS = progression-free survival
PI = proteasome inhibitor
PR/VGPR = (very good) partial response
SCT = stem cell transplantation

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Welcome to issue 33 of Multiple Myeloma Research Review.

This first issue of Multiple Myeloma Research Review for the decade begins with a paper reporting the development of a novel risk stratification algorithm for patients with MM who need second-line treatment. Other included research reports outcomes with autologous followed by allogeneic SCT that were better than those with tandem autologous SCT in patients with del13q MM. The interim OS analysis of the ALCYONE trial of daratumumab added to VMP (bortezomib, melphalan, prednisone) also provides encouraging data, as does our final paper from Canada, which reports that autologous SCT in the outpatient setting is safe and feasible with low transplant-related mortality.

We hope you find this update in MM research enlightening, and we look forward to your comments and feedback.

Kind regards,

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Development and validation of a novel risk stratification algorithm for relapsed multiple myeloma

Authors: Hájek R et al.

Summary: A risk stratification algorithm was developed based on independent OS predictors derived from a Cox model applied to data from patients receiving second-line treatment for MM. The patients were stratified into groups 1–4 (low- to high-risk) based on their scores. The median OS durations for patients in groups 1–4 were 61.6, 29.6, 14.2 and 5.9 months, respectively; the between-group differences were statistically significant. On application to an external validation dataset, the algorithm resulted in similar risk stratification.

Comment (HC): Myeloma is a dynamic disease, and relapse is inevitable for many patients despite improvements in frontline treatment. Although commonly used prognostic scoring systems, such as ISS (International Staging System) and R-ISS (revised ISS), have been widely adopted, none of these have been fully validated in the relapsed setting nor do they incorporate clinically relevant factors at the time of relapse. Using registry data, these authors have developed a novel prognostic scoring system that incorporates many of the important clinical factors at relapse, such as duration of first remission, development of new bony lesions, and presence of extramedullary disease; albeit the equation being somewhat complicated to remember. If this can be developed into a smartphone application or an online calculator, then it will greatly improve its usability and become a useful tool for clinicians.

Reference: Br J Haematol 2019;187:447–58

Abstract

Daratumumab added to standard of care in patients with newly diagnosed multiple myeloma

Authors: Xu W et al.

Summary: This was a network meta-analysis of data from six trials (n=5106) investigating daratumumab added to standard care for treatment-naïve myeloma. These regimens were associated with a CR or better rate of 24%, a VGPR or better rate of 67%, an overall response rate of 92%, improved PFS (HR 0.52 [95% CI 0.44, 0.61]) and a trend for improved OS (0.73 [0.52, 1.04]). Among autologous SCT-ineligible patients, D-Rd (daratumumab, lenalidomide, dexamethasone) and D-VMP (daratumumab, bortezomib, melphalan, prednisone) were associated with better PFS than a range of other non-daratumumab first-line regimens. D-Rd was associated with 83.4% and 91.0% likelihoods of reaching the longest PFS and OS, respectively. Myelosuppression was the main toxicity; any-grade nonhaematological adverse events included peripheral sensory neuropathy (41%) and upper respiratory tract infections (39%).

Comment (HC): It is not surprising to see that the daratumumab-containing regimens (D-VMP and D-Rd) were found to be superior, as has been demonstrated repeatedly in many prospective randomised controlled trials. The rate of infusion reactions at 30% and upper respiratory tract infections at 39% are also consistent with other published data. What is interesting is their results comparing D-Rd with D-VMP, as there has never been a head-to-head comparison between these two regimens. Although D-Rd did not have any significant PFS advantage over D-VMP (HR 0.77 [95% CI 0.46, 1.29]), it showed a trend for better OS (0.56 [0.31, 1.00]). This is a somewhat unusual observation and one may argue that the trend for better OS may potentially be due to differences in relapse treatment. However, the other way to interpret this is to look at the work done by the Italian group, where their cross-study comparison using patient level data found that VMP had a better PFS initially due to more profound tumour reduction, but the PFS curve crosses over just after 30 months when the long-term administration of Rd led to better disease control (Gentile et al. Am J Hematol 2017). Therefore, D-Rd may perhaps show better PFS and OS than D-VMP if follow-up is longer.

Reference: Eur J Haematol 2019;103:542–51
Abstract

Response-adapted intensification with cyclophosphamide, bortezomib, and dexamethasone versus no intensification in patients with newly diagnosed multiple myeloma (Myeloma XI)

Authors: Jackson GH et al., for the UK NCRI Haematological Oncology Clinical Studies Group

Summary: This paper reported on the phase 3 Myeloma XI trial's randomisation to open-label intensification treatment with oral cyclophosphamide 500mg on days 1, 8 and 15, subcutaneous or intravenous bortezomib 1.3 mg/m^2 on days 1, 4, 8 and 11, and oral dexamethasone 20mg on days 1, 2, 4, 5, 8, 9, 11 and 12 (n=289) or no treatment (n=294). Study participants were adults with symptomatic or nonsecretory newly diagnosed MM who had achieved PR or minimal response after induction therapy. Median follow-up was 29.7 months. Compared with no treatment, the active treatment group had longer median PFS duration (30 vs. 20 months; HR 0.60 [95% CI 0.48, 0.75]) but a similar 3-year OS rate (77.3% vs. 78.5%; 0.98 [0.67, 1.43]). The most frequent grade 3–4 adverse events in the active treatment group were haematological and included neutropenia (7%), thrombocytopenia (7%) and anaemia (3%). There were no treatment-related deaths in the active treatment group.

Comment (HC): In this part of the UK MRC XI study, the researchers show that treatment intensification after induction can lead to an improved PFS for those who achieved a PR or less, irrespective of transplant status. However, it is difficult to know whether this benefit is due to exposure to both an immunomodulatory drug and a PI in the intensification arm, deepening of treatment response, or because of a longer duration of induction. For those in the transplant-eligible group, the other question is whether postinduction is the most appropriate timepoint for deciding whether to intensify. Data from the Spanish group found that pretransplant MRD status was not prognostic as long as the patient achieved MRD negativity after transplantation (Lahuerta et al. J Clin Oncol 2017). It is also worth noting that their results are different to the data from the CIBMTR where they found no benefit in salvage chemotherapy prior to transplantation; albeit this was in patients who achieved less than a PR (Vij et al. Biol Blood Marrow Transplant 2015). Regardless, the group should be congratulated for incorporating a response-adapted strategy in their study design, as more of these are needed in order to help clinicians rationalise treatment.

Reference: Lancet Haematol 2019;6:616–29
Abstract

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Multiple Myeloma Research Review

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.

Impact of last lenalidomide dose, duration, and IMiD-free interval in patients with myeloma treated with pomalidomide/dexamethasone

Authors: Kastritis E et al.

Summary: Outcomes from 147 consecutive patients with relapsed/refractory MM homogeneously treated with pomalidomide and dexamethasone were evaluated, with specific focus on the effect of the lenalidomide dose at which resistance developed, the duration of lenalidomide exposure and the lenalidomide-free interval. The PR or better rate was 33%, with respective rates of 32% and 37% when the combination was administered immediately after lenalidomide and immediately after bortezomib. No significant difference in response rate was seen between patients who received lenalidomide 5–15mg vs. 25mg (38.5% vs. 30.5% [p=0.329]), but response rates were higher for those who had received ≥12 months of lenalidomide (44% vs. 27%) and those with a ≥18-month period between their last lenalidomide dose and their first pomalidomide dose (65% vs. 23%). The respective median PFS and OS durations were 5 and 12.1 months, with no significant difference according to receipt of lenalidomide, bortezomib or other regimen just prior to pomalidomide plus dexamethasone, or according to different lenalidomide doses. An immunomodulatory imide drug-free interval of ≥18 months was associated with longer PFS and OS durations (10.3 vs. 3.9 months [p=0.003] and 27.1 vs. 9.3 months [p=0.008], respectively) as was a ≥12-month period since last lenalidomide therapy (7.8 vs. 3.2 months [p=0.023] and 16.5 vs. 7.9 months [p=0.005]); these differences persisted after adjustments for the number of prior therapies, duration of disease and last lenalidomide dose.

Comment (HC): The median PFS of 5 months seen in this real-world cohort with pomalidomide and dexamethasone is consistent with the published data from MM-002 (4.2 months), MM-003 (4 months) and MM-010 (4.6 months); this highlights the fact that using pomalidomide as a doublet with dexamethasone may not be the best way to use the drug. Consistent with the disease biology and the concept of clonal tide, patients who had a longer response with lenalidomide (duration of >12 months) and those who had an immuno-modulatory imide drug-free period of >18 months experienced better PFS and OS with pomalidomide and dexamethasone than otherwise. This observation supports the practice of 'class switch' (i.e. adding in or using a different class of novel agent to the failing regimen) at the time of relapse. However, what if 'class switch' is not possible? Is it still worth going straight from a lenalidomide-based treatment to a pomalidomide-based treatment, or should one try PI-retreatment first before going on to pomalidomide? Unfortunately, there are no published data to guide this, and in practice these decisions are often dictated more by what is funded than clinical evidence.

Reference: Blood Adv 2019;3:4095–103
Abstract

Allogeneic transplantation in multiple myeloma: long-term follow-up and cytogenetic subgroup analysis

Authors: Knop S et al., on behalf of Deutsche Studiengruppe Multiples Myelom

Summary: Patients with newly diagnosed del13q MM (evaluable n=199) underwent tandem autologous SCT or autologous SCT followed by reduced-intensity conditioning allogeneic SCT, according to the availability/absence of an HLA (human leucocyte antigen)-matched-related or matched-unrelated donor, in this phase 3 trial; 126 participants underwent autologous then allogeneic SCT, and 74 received matched-unrelated donor allografts. Median follow-up was 91 months. Compared with tandem autologous SCT recipients, those who underwent autologous then allogenic SCT had a longer PFS duration (primary endpoint; 34.5 vs. 21.8 months; adjusted HR 0.55 [95% CI 0.36, 0.84]) and a greater 2-year nonrelapse mortality rate (14.3% vs. 4.1% [p=0.008]), but a similar median OS duration (70.2 vs. 71.8 months [p=0.856]). For patients with both the del13q and the del17p mutations, both median PFS and OS durations were significantly longer in the autologous then allogenic SCT group (n=19) than in the tandem autologous SCT group (n=6) at 37.5 vs. 6.1 months (p=0.0002) and 61.5 vs. 23.4 months (p=0.032), respectively.

Comment (HC): The induction treatment used in this study, anthracycline and dexamethasone, has now been superseded by regimens containing novel agents. Although this has affected the generalisability of the study's data in today's practice, it still provides some useful insight into the long-term outcomes of those who received tandem autologous/allogeneic SCT. Grade 3/4 acute graft-versus-host disease was seen in 15.2% of the patients, and this was associated with inferior OS duration (19.7 vs. 91.1 months). Chronic graft-versus-host disease was seen in a third of the patients, but this did not translate into any differences in PFS or OS. No significant difference in PFS or OS was noted between matched-sibling and matched-unrelated donor transplants. Although a plateau is noted in the PFS curve with long-term survival without disease relapse at approximately 40%, tandem autologous/allogeneic SCT is also associated with a nonrelapse mortality rate of 14.3%. Whether these numbers justify tandem autologous/allogeneic SCT in selected cases when there is no clear OS benefit remains debatable. As in most cases, the decision regarding allogeneic transplantation in myeloma also depends heavily on other variables, such as the patient's age and the experience of the centre, and the result of this paper is unlikely to change this.

Reference: Leukemia 2019;33:2710–9
Abstract

Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE)

Authors: Mateos M-V et al.

Summary: Patients with newly diagnosed MM ineligible for high-dose chemotherapy with autologous SCT were randomised to receive up to nine 6-week cycles of bortezomib, melphalan and prednisone with (D-VMP; n=350) or without (VMP; n=356) intravenous daratumumab 16 mg/kg once weekly during the first cycle and then once every 3 weeks, followed by every 4 weeks as maintenance until disease progression or unacceptable toxicity, in the open-label, phase 3 ALCYONE trial. This paper reported results from a prespecified interim OS analysis; PFS results (primary endpoint) have been reported previously. After a median follow-up period of 40.1 months, D-VMP recipients had superior OS compared with VMP recipients (HR for death, 0.60 [95% CI 0.46, 0.80]) with a greater estimated 36-month OS rate (78.0% vs. 67.9%); PFS remained significantly better among D-VMP recipients (HR 0.42 [0.34, 0.51]). In the D-VMP group, the most frequent adverse events during maintenance daratumumab monotherapy were respiratory infections (19%, 15% and 12% for upper respiratory tract infections, bronchitis and viral upper respiratory tract infections, respectively), cough (12%) and diarrhoea (10%).

Comment (KR): This is an important paper because there is now a definite OS survival advantage in a daratumumab-containing quadruplet, where before there was only an improvement in PFS that had been demonstrated. There was a 10% improvement in survival obtained, and a 78% 3-year OS rate is very good. This figure could well improve with an immunomodulatory drug-containing induction partner. We must hope that this sort of improved OS data will find favour with funding bodies.

Reference: Lancet 2020;395:132–41
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.

Enrichment of circulating myeloma cells by immunomagnetic beads combined with flow cytometry for monitoring minimal residual disease and relapse in patients with multiple myeloma

Authors: Wang N et al.

Summary: These researchers developed methods for enrichment of circulating myeloma cells by using IMBs (immunomagnetic beads) combined with flow cytometry, based on CD38-APC/CD138-APC antibodies in U266-spiked samples and in 122 samples from patients. Compared with flow cytometry alone, CD38/CD138-IMBs with flow cytometry increased U266 cell capture efficiency 6- and 2-fold; the respective sensitivity values of flow cytometry alone and with IMBs were 0.01% and 0.001%. Compared with flow cytometry alone, flow cytometry with IMBs significantly increased the positive circulating myeloma cell rate from 60.5–70.0% to 85–87.2% in patients with newly diagnosed/relapsed MM and those in partial remission. Two patients with complete remission had measurable circulating myeloma cells on flow cytometry with IMBs, with none seen on flow cytometry alone. Compared with newly diagnosed/relapsed patients, those achieving PR or CR during treatment had significantly lower circulating and marrow myeloma cell counts. In patients with relapsed MM and those who achieved partial remission, flow cytometry-positive bone marrow samples were accompanied by IMB-flow cytometry-positive results in 88% of paired peripheral blood samples. Significant associations were seen between circulating myeloma cells and other disease burden biomarkers; a logistic regression analysis revealed that elevated β2-microglobulin levels and moderate or more severe anaemia were significantly associated with the presence of circulating myeloma cells.

Comment (KR): Analysis of myeloma cells has always been a difficult area, with problems of enrichment and variable sampling from bone marrow samples. The issue of MRD analysis is becoming more important, and a method that could give more accurate results but do it by 'liquid biopsy' testing is very compelling. The circulating myeloma cell positivity also correlates well with clinical biomarkers of disease burden.

Reference: Ann Hematol 2019;98:2769–80
Abstract

Peripheral neuropathy following bortezomib therapy in multiple myeloma patients: association with cumulative dose, heparanase, and TNF-α

Authors: Zhao W et al.

Summary: These researchers: i) used total neuropathy scores and electrophysiological examinations to assess treatment-emergent neuropathy associated with bortezomib therapy for MM; ii) evaluated TNF-α and heparanase level expression using enzyme-linked immunosorbent assays; and iii) used rat neurotoxicity models to evaluate the effects of anti-TNF-α agents on the evolution of neuropathy. Their results showed that as the cumulative dose of bortezomib increased, so did the incidence of neuropathy. Moreover, bortezomib administration was associated with increased TNF-α expression, which in turn was associated with exacerbation of neuropathy. TNF-α-induced heparanase expression occurred secondarily to neuropathy development. The researchers commented that a potential neuroprotective effect against bortezomib-induced peripheral neuropathy in rats lies in the co-administration of a TNF-α antagonist with bortezomib.

Comment (KR): Peripheral neuropathy related to bortezomib therapy has been reduced by the use of the subcutaneous route, but is still an issue for some patients who develop the neuropathy quite early in their treatment programme. The place of TNF-α on the pathogenesis is an intriguing idea, and if an effective inhibitor could be found, then this would be most beneficial.

Reference: Ann Hematol 2019;98:2793–803
Abstract

Frontline treatment of elderly non transplant-eligible multiple myeloma patients using CyBorD with or without thalidomide-based consolidation

Authors: Chan H et al.

Summary: These authors conducted a retrospective evaluation of 155 real-world patients aged ≥70 years with newly diagnosed MM treated with ≥1 cycle of CyBorD (cyclophosphamide, bortezomib, dexamethasone) in NZ. The PR or better rate was 79.4% with a VGPR or better rate of 52.9%. After a median follow-up period of 31.9 months, patients aged 70–80 years had longer EFS and OS durations than those aged >80 years (17.7 vs. 8.6 months [p=0.002] and 49.8 vs. 33.3 months [p=0.003], respectively). Among patients who received ≥7 cycles of treatment, median EFS duration was longer for those with a preplanned switch to consolidation VTD (bortezomib, thalidomide, dexamethasone) compared with those who received CyBorD only (25.4 vs. 20.3 months [p=0.028]).

Comment (KR): This paper, recently published in the Br J Haematol by Henry Chan, is a nice example of collaborative work between local centres to provide us with real-world data on myeloma outcomes. The results show that treating elderly patients with CyBorD is worthwhile and probably should be attempted up to the age of 80 years, depending on comorbidities, as significant survival advantages can be obtained. The finding of the benefits of switching to VTD is also interesting, and it is likely that using lenalidomide instead would be even more beneficial.

Reference: Br J Haematol 2019;187:470–7
Abstract

Outpatient autologous stem cell transplants for multiple myeloma

Authors: Kodad SG et al.

Summary: Outcomes were reported for 724 outpatients (median age 60 years; 59.5% male) who underwent 704 first, 44 second and six third autologous SCTs for MM (96.9%), amyloidosis (2.4%) or POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) syndrome (0.7%) at a Canadian tertiary care centre. The patients were transplanted a median of 5 months after diagnosis. Most patients (89.6%) received conditioning with melphalan 200 mg/m^2. Almost one-third of the patients (32.6%) required inpatient admission within the first 30 days post-SCT; the median post-SCT time to admission was 9 days and the median admission duration was 6 days. The respective 100-day all-cause and SCT-related mortality rates were 0.9% and 0.4%.

Comment (KR): This paper from the Vancouver group analyses a large group of autologous SCT patients that had outpatient treatment to reduce waiting times, which is an issue for most transplant units. The median duration of admission was down to 6 days for the third of patients that required re-admission, and so this would have helped with the waiting times. This approach has been followed by several NZ centres, and in an ideal world should become a standard of care. There are centres in NZ, however, where this approach is not always possible because of patients coming from distant peripheral centres, and it is not always deemed safe to discharge straight after the autologous SCT.

Reference: Clin Lymphoma Myeloma Leuk 2019;19:784–90
Abstract

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