Multiple Myeloma RESEARCH REVIEW™

Making Education Easy

Issue 2 – 2020

In this issue:

Abbreviations used in this issue
BMT = blood/bone marrow transplantation
CR = complete response
HR = hazard ratio
MM = multiple myeloma
MRD = minimal residual disease
OS = overall survival
PFS = progression-free survival
PI = proteasome inhibitor
SCT = stem-cell transplantation

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Welcome to issue 2 of Multiple Myeloma Research Review.

This issue begins with results from the phase 3 GMMG-MM5 trial suggesting that lenalidomide maintenance therapy should be continued for >2 years after CR has been achieved in transplant-eligible patients with MM. Researchers from the US who investigated genomic profiles that predict high risk of progression from smouldering MM to MM report that smouldering MM is a genetically mature entity with most driver genetic alterations having already occurred. Also on the subject of smouldering MM progression, a team of researchers from the Czech Republic have used serum parameters to predict an 80% likelihood of progression over 2 years. The issue concludes with updated results from the EMN01 trial reporting positive outcomes and good safety with lenalidomide-based maintenance regimens in elderly patients with newly diagnosed MM, with different degrees of frailty considered.

We hope you enjoy the update in myeloma research, and we look forward to your comments and feedback.

Kind regards,

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Response-adapted lenalidomide maintenance in newly diagnosed myeloma

Authors: Goldschmidt H et al., for the German-speaking Myeloma Multicenter Group (GMMG)

Summary: Results for lenalidomide maintenance were reported for the phase 3 GMMG-MM5 trial, in which transplant-eligible patients with newly diagnosed MM were randomised to induction PAD (bortezomib, doxorubicin, dexamethasone) or VCD (bortezomib, cyclophosphamide, dexamethasone), after which they all received high-dose melphalan and autologous blood SCT, and lenalidomide consolidation, followed by randomisation to maintenance with lenalidomide either for a 2-year fixed duration (len-2Y; n=251) or achievement of CR (len-CR; n=251); 17.5% of len-CR participants did not start or discontinued lenalidomide maintenance therapy due to CR. Neither PFS nor OS differed significantly among the four study arms. Compared with the pooled len-2Y participants, the pooled len-CR participants had significantly shorter OS (HR 1.42 [p=0.03]) but not PFS (1.15 [p=0.20]); however, PFS was shorter in landmark analyses from the start of lenalidomide maintenance therapy in len-CR recipients achieving CR (1.84 [p=0.02]). Len-CR participants had shorter OS from first progression than len-2Y participants (HR 1.60 [p=0.01]).

Comment (HC): The GMMG-MM5 study had two randomisations. The first was to compare VCD against PAD, and VCD was found to be the more favourable regimen with similar efficacy and a better toxicity profile (Mai EK *et al.* Leukemia 2015;29:1721–9). The second, which was presented in this paper, was to evaluate the idea of following autologous SCT with lenalidomide until CR against continuous maintenance for 2 years. It is worth noting that because of the study design, only participants who achieved less than a CR (~two-thirds) were started on lenalidomide maintenance in the len-CR arm, and these patients had a similar mean duration of maintenance as those in the len-2y arm (16.7 vs. 17.6 months). This would likely explain the lack of PFS difference between len-CR and len-2y (HR 1.15 [95% CI 0.93, 1.44]). Meanwhile, as those in the len-CR arm with CR before randomisation did not receive maintenance as per the study design, the fact that these patients had inferior PFS compared with the corresponding patients in the len-2y arm (HR 1.84 [95% CI 1.08, 3.13]) shows that lenalidomide maintenance remains valuable even in patients who have achieved a good response. This is consistent with the recent data published from the UK MRC XI study, which show a PFS benefit for lenalidomide maintenance even in those who reached MRD negativity following autologous SCT (de Tute RM *et al.* Blood 2017;130(suppl 1):904; ASH 2017). The other interest point noted in the GMMG-MM5 data is the inferior OS from first progression for those in the len-CR arm. This is primarily attributed to the difference in postrelapse treatment, where immunomodulatory drug-based treatment was more common in the len-CR arm and PI-based treatment was common in the len-2y arm. Does this mean that one should use a PI, instead of an immunomodulatory drug, as the immediate subsequent line of treatment in someone who progresses on lenalidomide maintenance? Unfortunately, there are no phase 3 data to help answer this question, but the observation noted in this GMMG-MM5 study does weigh in favour of PIs.

Reference: Leukemia 2020;34:1853–65
Abstract

Daratumumab monotherapy for patients with intermediate-risk or high-risk smoldering multiple myeloma

Authors: Landgren CO et al.

Summary: The phase 2 CENTAURUS trial randomised 123 patients with intermediate- or high-risk smouldering MM to receive open-label intravenous daratumumab 16 mg/kg on extended intense, extended intermediate or short dosing schedules. At a prespecified primary analysis at median 15.8 months of follow-up, the respective CR rates in the extended-intense, extended-intermediate and short-dosing arms were 2.4%, 4.9% and 0%, with the coprimary endpoint of CR rate >15% not met, and the respective progressive disease/death rates were 0.055, 0.102 and 0.206 per patient-year, translating to median PFS ≥24 months in all arms (respective p values <0.0001, <0.0001 and 0.0213). After median follow-up of 25.9 months, the respective CR rates in the extended-intense, extended-intermediate and short-dosing arms were 4.9%, 9.8% and 0%, and the respective progressive disease/death rates were 0.059, 0.107 and 0.150 per patient-year, also translating to median PFS ≥24 months in all arms (p<0.0001 for all). The respective 24-month PFS rates in the extended-intense, extended-intermediate and short-dosing arms were 89.9%, 82.0% and 75.3%. Pharmacokinetic analyses revealed that intense dosing maintained target-saturating trough concentrations for most participants during the weekly, every-2-week and every-4-week dosing periods. There were no new safety signals detected.

Comment (HC): There has been a series of publications in recent years on treating high-risk smouldering myeloma, ranging from induction treatment with SCT (GEM-CESAR; Mateos M-V *et al.* Blood 2019;134(suppl 1):781; ASH 2019) to combination lenalidomide plus dexamethasone (QUIREDEX, Mateos M-V *et al.* N Engl J Med 2013;369:438–47) and lenalidomide monotherapy (E3A06, Lonial S *et al.* J Clin Oncol 2019;37(15 suppl):8001; ASCO 2019). However, many of these studies included patients that would now be considered as having myeloma based on the SLiM-CRAB criteria. The investigators for this CENTAURUS study specifically excluded those patients, and therefore present a cohort that truly reflects high-risk smouldering myeloma based on the current definition. Although the study reached one of their primary endpoints in achieving a progression/death rate of <0.346 per patient-year, approximately one in five patients still progressed to myeloma after 2 years despite treatment (75–90%). Although this appears to be better than published historical cohorts, it is uncertain if this delay in progression is clinically meaningful in the long run. Further development in this area will depend on the goal of treatment that clinicians are trying to achieve. If the aim of early treatment is to provide better disease control, then we need a better tool than the current clinical model for identifying those with imminent progression who would benefit from early treatment. If the aim of early treatment is eradication, then we will need a better combination than just daratumumab alone.

Reference: Leukemia 2020;34:1840–52
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.

Autologous haematopoietic stem-cell transplantation versus bortezomib-melphalan-prednisone, with or without bortezomib-lenalidomide-dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95)

Authors: Cavo M et al.

Summary: In this phase 3 trial, 1197 patients with newly diagnosed MM received 3–4 cycles of induction bortezomib, cyclophosphamide and dexamethasone and were randomised to melphalan 200 mg/m^2 plus autologous SCT (n=702) or four 42-day cycles of VMP (bortezomib, melphalan, prednisone), after which they were subsequently randomised to no consolidation therapy or two 28-day cycles of VRD (bortezomib, lenalidomide, dexamethasone). All participants received 28-day cycles of maintenance oral lenalidomide. Upfront autologous SCT was associated with longer median PFS than VMP chemotherapy at median follow-up of 60.3 months (56.7 vs. 41.9 months; HR 0.73 [95% CI 0.62, 0.85]), as was consolidation therapy versus no consolidation therapy (median PFS 58.9 vs. 45.5 months; 0.77 [0.63, 0.95]).

Comment (HC): The data from this much anticipated study are of high relevance to our practice in NZ. The data show that frontline autologous SCT remains the treatment of choice (HR 0.73 [95% CI 0.62, 0.85]) even in the era of novel agent induction and lenalidomide maintenance. Although PFS appears to be favourable with double autologous SCT, this benefit only applies to those with high-risk cytogenetics (HR 0.59 [95% CI 0.34, 1.03]) and not those with standard-risk disease (0.83 [0.57, 1.22]). The authors specifically presented the subgroup analysis of those with del(17p), showing superior PFS with double autologous SCT (HR 0.24 [95% CI 0.09, 0.66]). Data from other high-risk subgroups were not published. This result provides support for offering double autologous SCT to those with del(17p), while the debate for double autologous SCT in other high-risk groups continues. Lastly, the data presented in this paper show superior PFS with consolidation, but unfortunately the authors did not present the subgroup analysis based on first randomisation (i.e. autologous SCT versus VMP). The interim analysis presented by the same group previously found that RVD consolidation did not appear to significantly improve PFS in high-risk patients and those who had autologous SCT (Sonneveld P *et al.* EHA 2018; abstract S108).

Reference: Lancet Haematol 2020;7:456–68
Abstract

Genomic profiling of smoldering multiple myeloma identifies patients at a high risk of disease progression

Authors: Bustoros M et al.

Summary: Next-generation sequencing was used to study 214 patients with smouldering MM. Whole-exome sequencing on 166 tumours, including five with serial samples, and deep targeted sequencing on 48 tumours revealed that most of the genetic alterations necessary for progression had been acquired by smouldering MM diagnosis. MAPK (mitogen-activated protein kinase) pathway alterations (*KRAS* and *NRAS*), DNA repair pathway alterations (del[17p], *TP53* and *ATM*) and *MYC* translocations or copy number variations independently predicted risk of progression after clinical risk staging was accounted for. Validation in an external smouldering MM cohort confirmed that patients with any of these three features were at higher risk of progressing to MM. In addition, APOBEC (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like)-associated mutations were enriched in patients who experienced progression, and were associated with shorter time to progression.

Comment (HC): Similar to other publications in recent years, these authors have demonstrated that the genetic makeup of smouldering myeloma is similar to that of newly diagnosed myeloma. For some, the process of progression was simply due to ongoing accumulation of malignant plasma cells without marked alterations to their genomic profiles, whilst others were marked by expansion of a subclone following acquisition of new mutations. *MYC* aberrations, mutations in the MAPK pathway and mutations in the DNA repair pathway were found to be independent risk factors for progression on multivariable analysis, and the median time to progression with any of these was only 1.3 years, compared with 3.4 years otherwise. More importantly, their results show that these mutations were more predictive of progression than existing clinical models using paraprotein levels, plasma cell burden and light-chain ratios. The next step would be to confirm this in a larger prospective cohort and determine whether pre-emptive treatment is of clinical benefit.

Reference: J Clin Oncol 2020;38:2380–9
Abstract

Risk of disease recurrence and survival in patients with multiple myeloma

Authors: Schinke M et al.

Summary: These authors reported on 815 consecutive patients with MM through the German Study Group on Multiple Myeloma incentive. Over median follow-up of 10.6 years, median OS duration was 5.1 years. There were substantial differences in prognosis when 5-year conditional survival probabilities derived from data at the time of initial diagnosis were compared with data updated over time. Patients surviving 0–5 years had HRs of 1, 1.68 and 3.17 for those aged <60 years, 60–69 years and >70 years, respectively; these HRs were lower for patients surviving 5 years, those with advanced disease stage and those with unfavourable cytogenetics, whereas progressive disease remained important for patients surviving 1 year, 3 years and 5 years (respective HRs 1.85, 2.11 and 2.14).

Comment (HC): By analysing conditional survival (probability of surviving further after having already survived a predefined length of time), data presented by this group show that the impact of prognostic factors changes over time. Firstly, although anaemia and renal impairment were not prognostic at the time of diagnosis, they did become prognostic as patients survived for longer, and this was independent of other factors, such as disease progression. Meanwhile, as expected, performance status and progression during follow-up remained prognostic throughout the follow-up period. Interestingly, the negative prognostic value of unfavourable cytogenetics at the time of diagnosis (e.g. del[17p], t[4;14], etc.) diminished over time. In fact, after surviving the first 3 years, there was no difference in conditional survival between those with unfavourable and standard-risk cytogenetics. What does this imply? Firstly, this shows that prognosis is a dynamic process and it should be re-assessed throughout the course of the disease. Secondly, these results caution us against reading too much into trial data in the relapsed setting that claim to abrogate the negative prognostic value of high-risk cytogenetics, simply because patients had similar survival to standard-risk.

Reference: Cancer 2020;126:3504–15
Abstract

Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR)

Authors: Dimopoulos M et al.

Summary: Patients with relapsed/refractory MM (n=433) were randomised in a 2:1 ratio to receive carfilzomib plus dexamethasone with or without daratumumab in this open-label phase 3 trial. Median follow-up was ~17 months, after which the median duration of treatment was longer in the daratumumab group (70.1 vs. 40.3 weeks) and their PFS duration was longer (not reached vs. 15.8 months; HR 0.63 [95% CI 0.46, 0.85]). The respective grade ≥3 adverse event rates in the daratumumab and non-daratumumab arms were 82% and 74%, and the respective discontinuation rates due to adverse events were 22% and 25%.

Comment (KR): The increasing use of lenalidomide in the upfront situation has meant that there needs to be an effective combination in the relapsed/refractory setting. This study was a large multicentre phase 3 trial showing that the addition of the monoclonal antibody daratumumab at a relatively early stage in the disease course was able to significantly improve treatment duration to well over 1 year. There did seem to be a high rate of grade 3 adverse events however.

Reference: Lancet 2020;396:186–97
Abstract

Prolonged lenalidomide maintenance therapy improves the depth of response in multiple myeloma

Authors: Alonso R et al.

Summary: These authors reported retrospectively on 139 real-world patients with newly diagnosed MM who received lenalidomide maintenance therapy and whose MRD status (sensitivity $\geq 10^{-4}$) was evaluated. A correlation was seen between lenalidomide maintenance and increased depth of response, with 38.1% of the patients achieving maximal response during lenalidomide maintenance. Moreover, 34.3% of MRD-positive patients after induction became MRD-negative during maintenance, with improved PFS. Sequential MRD assessments were able to identify patients with progressively decreasing MRD levels who also had better PFS outcomes, versus those who did not show a decreasing MRD pattern.

Comment (KR): In NZ we have recently been able to offer our patients lenalidomide maintenance to the transplant-eligible group following autologous SCT. This retrospective study looked at the kinetics of MRD in a small patient group. They were able to show a progressive reduction in MRD by two methods to a high degree of sensitivity over a period of time, and this then correlated with better PFS outcomes as expected. These data are additional support that the maintenance approach should be encouraged to obtain a PFS and also OS benefit.

Reference: Blood Adv 2020;4:2163–71
Abstract

Identification of patients with smouldering multiple myeloma at ultra-high risk of progression using serum parameters

Authors: Hájek R et al.

Summary: These researchers from the Czech Republic used only serum parameters to attempt to identify patients with smouldering MM who had an 80% risk of progression to MM within 2 years; training and validation cohorts consisted of 287 and 240 patients with smouldering MM, respectively. After median follow-up of 2.4–2.5 years, the respective progression to MM rates in the training and validation cohorts were 51.9% and 38.8%, and the median annual risks of progression were 11.0% and 9.7% during the 5 years after diagnosis. A univariate Cox regression analysis revealed that predictors of 2-year progression included a serum involved/uninvolved free light-chain ratio >30, immunoparesis and serum monoclonal protein level ≥2.3 g/dL (respective HRs 2.49 [95% CI 1.49, 4.1], 2.01 [1.36, 2.96] and 2.00 [1.44, 2.79]). Using these parameters, the respective 2-year risks of progression for the training and validation cohorts were 78.7% (HR 6.8 [p<0.001]) and 81.3% (38.63 [p<0.001]).

Comment (KR): The area of smouldering MM is still a contentious subject in relation to initiation of therapy, and there is no agreed consensus. The group that has an 80% risk of progression is one that would be of interest for following closely and considering early treatment. This study used serum parameters such as the serum free light-chain ratio and immunoparesis, as well as serum monoclonal protein level, and identified smouldering MM patients with a 2-year risk of progression of 78.7%. This approach would seem to be a useful one.

Reference: Br J Haematol 2020;190:189–97
Abstract

Morbidity burden in survivors of multiple myeloma who underwent autologous transplantation

Authors: Arora M et al.

Summary: Severe and/or life-threatening chronic health conditions and subsequent neoplasms were reported for 630 adult 2-year MM survivors who had undergone autologous BMT in the Bone Marrow Transplant Survivor Study; 289 nearest-age siblings were used as comparators. The autologous BMT survivors had a 10-year cumulative incidence of any grade 3–4 chronic health condition of 57.6%, and they were 40% more likely than their siblings to develop such conditions. Solid tumours accounted for 96% of subsequent neoplasms with a 10-year cumulative incidence of 13.6%. The risk of developing a solid tumour was exacerbated by exposure to cyclophosphamide or immunomodulatory drugs prior to BMT (respective HRs 3.5 [95% CI 1.5, 8.1] and 3.9 [1.5, 10.1]). The most common subsequent neoplasms were melanoma and squamous cell carcinoma with respective 10-year cumulative incidences of 3.3% and 5.1%. The risk of melanoma was increased in patients with cyclophosphamide or immunomodulatory drug exposure before BMT (respective HRs 6.02 [95% CI 1.4, 26.1] and 7.9 [0.9, 68.5]).

Comment (KR): Autologous BMT is still considered standard of care for patients, particularly in NZ where we are not able to offer intensive induction therapy, which may include lenalidomide and daratumumab, etc. This large study followed patients for a long time and showed that the cumulative incidence of chronic health conditions was high at 57.6%. There was an increased risk of solid tumours, particularly skin tumours, which may have been related to immunomodulatory drug therapy. There was no mention of myelodysplastic syndrome, which has been an issue in other studies. Close monitoring of survivors would seem a sensible suggestion.

Reference: Cancer 2020;126:3322–9
Abstract

Lenalidomide-based induction and maintenance in elderly newly diagnosed multiple myeloma patients

Authors: Bringhen S et al.

Summary: Results out to median follow-up of 71 months were reported for the EMN01 randomised trial, in which transplant-ineligible patients with MM received melphalan or cyclophosphamide added to induction therapy with lenalidomide plus steroid, after which they were randomised to maintenance lenalidomide with or without continuous prednisone; there were 217 participants who received lenalidomide and dexamethasone, 217 who received melphalan, prednisone and lenalidomide, and 220 who received cyclophosphamide, prednisone and lenalidomide. According to Frailty Score, 43% of the participants were fit, 31% were intermediate-fit and 25% were frail. Lenalidomide maintenance was received by 204 evaluable participants and lenalidomide plus prednisone maintenance was received by 198. After a median of 22.0 months of maintenance therapy, there was no significant difference between the lenalidomide plus prednisone versus lenalidomide arm for PFS duration (22.2 vs. 18.6 months; HR 0.85 [p=0.14]), with no differences among frailty subgroups. Neutropenia, the most frequent grade ≥3 toxicity, affected a lower proportion of lenalidomide plus prednisone recipients than lenalidomide recipients (10% vs. 21% [p=0.001]). Only 15% of participants experienced grade ≥3 nonhaematological adverse events. Among fit participants, melphalan, prednisone plus lenalidomide was associated with significantly longer PFS duration than cyclophosphamide, prednisone plus lenalidomide (HR 0.72 [p=0.05]) and lenalidomide plus dexamethasone (0.72 [p=0.04]), and the two triplet regimens were associated with trends for better OS than lenalidomide plus dexamethasone; there were no apparent differences for the intermediate-fit and frail participants.

Comment (KR): This particular trial focused on transplant-ineligible patients and also segregated patients by a frailty score, which was a novel approach. There were three arms, and one was a melphalan, prednisone plus lenalidomide regimen, which is not often used nowadays, but the results were reasonably good and there was a trend for better survival in this arm than with either cyclophosphamide, prednisone plus lenalidomide or lenalidomide plus dexamethasone. The study shows that fit, older patients can obtain benefit from a full-dose triplet regimen. The more frail patients are best treated with more gentle regimens.

Reference: Haematologica 2020;105:1937–47
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.