Multiple Myeloma
RESEARCH REVIEW™

Making Education Easy

Issue 7 – 2022

In this issue:

Abbreviations used in this issue
BCMA = B-cell maturation antigen
CAR = chimeric antigen receptor
CR/PR/VGPR = complete/(very good) partial response
GVHD = graft-versus-host disease
HR = hazard ratio
MM = multiple myeloma
MRD = minimal residual disease
NRM = nonrelapse mortality
OS = overall survival
PFS = progression-free survival
RCT = randomised controlled trial
SCT = stem-cell transplantation

Welcome to issue 7 of Multiple Myeloma Research Review.

We begin this issue with a phase 3 trial published in N Engl J Med of autologous SCT added to triplet RVD (lenalidomide, bortezomib, dexamethasone) therapy followed by lenalidomide maintenance for newly diagnosed MM. There is also research reporting on the prognostic value of p53 protein isoforms for patients with MM. Long-term outcomes have been reported for a phase 2 trial of combination anti-BCMA and anti-CD19 CAR T-cell therapy in relapsed or refractory MM. The issue concludes with a subgroup analysis of the IKEMA trial, reporting that the benefits of adding isatuximab to carfilzomib and dexamethasone in patients with relapsed/refractory myeloma persisted in participants with renal impairment.

We hope you find the selected research interesting, and we look forward to comments and feedback.

Kind regards,

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Triplet therapy, transplantation, and maintenance until progression in myeloma

Authors: Richardson PG et al., for the DETERMINATION Investigators

Summary: This phase 3 trial randomised 722 adults aged <65 years with symptomatic myeloma to receive eight cycles of RVD followed by single-agent lenalidomide maintenance (n=357) or early autologous SCT after a single RVD induction cycle, followed by two consolidation RVD cycles plus continuous lenalidomide maintenance (n=365). With >21-month prolongation of median PFS in the early transplant versus triplet therapy-alone treatment arm, the trial well exceeded the prespecified efficacy superiority threshold of 9 months (46.2 vs. 67.5 months). This benefit did not translate into a survival benefit with comparable 5-year OS rates of 79.2% and 80.7% (HR 1.10 [95% CI 0.73, 1.65]). A greater than PR was achieved by 95% of the triplet-therapy arm and 97.5% of the early transplant arm (p=0.55). The grade ≥3 treatment-related adverse event rate was lower in the RVD-only arm (78.2% vs. 94.2%).

Comment (NC): This study was highly anticipated and generated much discussion at ASCO 2022 this year. Unlike IFM2009, it does not include preplanned delayed transplant at relapse for the RVD-only arm and maintenance lenalidomide was given until progression/intolerance. Therapy at relapse was chosen at patient's/treating physician's discretion. In the RVD-alone group patients who received subsequent therapy only, 35% had salvage autologous SCT. Overall, autologous SCT still offers additional PFS benefit even with this effective triplet combination. The rate of conventional response did not differ between the two arms; however, there was a trend towards higher MRD-negative rates in the autologous SCT group. There was no difference in PFS for those with MRD negativity regardless of the treatment arm. This again highlights the importance of reaching MRD negativity. The other noteworthy point is the benefit of autologous SCT in patients with high-risk cytogenetics, where PFS was 55 vs. 17 months in the autologous SCT group versus RVD-alone group. Like many other recent studies, there was no OS benefit shown with autologous SCT despite median follow-up of 76 months. This is likely due to the effectiveness of salvage therapies at relapse and the relatively short follow-up in the context of median OS of 8–10 years for myeloma patients treated in recent years. The remaining questions include whether autologous SCT is still required in standard-risk patients who achieve MRD-negative status. However, the answer is likely to remain 'yes' in NZ with the lack of effective salvage options. Secondly, the benefit of autologous SCT in patients receiving upfront quadruplet induction with doublet maintenance remains to be seen.

Reference: N Engl J Med 2022;387:132–47
Abstract

Expression of p53 protein isoforms predicts survival in patients with multiple myeloma

Authors: Rojas EA et al.

Summary: These researchers assessed the prognostic impact of p53 protein isoforms in CD138-purified samples obtained from 156 participants with newly diagnosed MM from the PETHEMA/GEM2012 clinical trial. A capillary nanoimmunoassay was used to quantify p53 protein isoform expression, and quantitative real-time PCR was used to corroborate the results at RNA levels. Prognosis was found to be worse for patients expressing low and high levels of short and TAp53β/γ isoforms, respectively; on multivariate Cox analysis, independent prognostic factors associated with shorter time to progression were high levels of TAp53β/γ and high-risk cytogenetics (respective HRs 4.49 and 2.69 [both p<0.001]). Adding expression levels of p53 protein isoforms to the current cytogenetic-risk classification resulted in a notable improvement.

Comment (HG): The interpretation of *TP53* abnormalities gets ever more complex. The clinical haematologist might be up to speed with deletions or monosomy of 17(p) in conditions like chronic lymphocytic leukaemia, acute myeloid leukaemia and myeloma, and understand that *TP53* mutations can exist and be important in the same conditions. There are evolving data (Jonathan Keats, personal communication, Myeloma NZ Summit, August 2022) that in myeloma, the negative prognosis of *TP53* loss is perhaps only markedly impactful in those with a concurrent *TP53* mutation on the other allele. If that complexity weren't enough, this paper informs the reader about the nature and impact of various p53 isoforms; i.e. variations in size and expression of the p53 protein based on alternative promoters and splicing. Suffice to say that these make a big difference to prognosis, and in fact the favourable isoforms abrogated the poor outcome of poor-risk cytogenetics. However, while interesting, this approach to p53 – proteomics rather than genomics – is far from clinical primetime.

Reference: Am J Hematol 2022;97:700–10
Abstract

Minimal residual disease and imaging-guided consolidation strategies in newly diagnosed and relapsed refractory multiple myeloma

Authors: Böckle D et al.

Summary: These researchers reported on combining next-generation flow cytometry with functional imaging (PET or diffusion-weighted MRI) with respect to its role for MRD-based consolidation strategies in patients with newly diagnosed (n=57) or relapsed or refractory (n=45) MM. MRD negativity was achieved in 45% of patients on both next-generation flow cytometry and imaging, with 8% and 40% negative on next-generation flow cytometry only and imaging only, respectively. Compared with patients with newly diagnosed MM, those with heavily pretreated disease were more likely to be MRD-positive on imaging while being negative on next-generation flow cytometry (p<0.01). Among patients who received MRD-triggered consolidation (n=29), 51% responded with MRD conversion and 21% experienced an improved serological response. Compared with standard treatment, MRD-triggered consolidation was associated with improved PFS (p=0.04).

Comment (NC): This is a single-centre, proof-of-concept study. There are many limitations, including the small patient number and short follow-up time. The importance of MRD negativity has been repeatedly shown in clinical trials. There is now increasing focus on concurrent use of imaging to detect focal lesions, as this has been shown to impact outcomes both at diagnosis and after treatment. Patients who are MRD-negative by next-generation flow cytometry but positive by functional imaging (8%) had similar PFS to those with double positivity. This occurred mostly in patients who were heavily pretreated (≥4 lines of therapy) with numbers needed to screen being three as opposed to 40 in newly diagnosed patients. As noted in the abstract, the use of consolidation therapy (mostly chemotherapy with a proteasome inhibitor and an immunomodulatory drug with or without anti-CD38 antibodies) for those with MRD/imaging-positive disease led to MRD conversion in half of the patients, and was associated with improved PFS. However, it is important to note that the number of patients included in the analysis is small. Currently, there is no consensus regarding the best imaging modality for monitoring response to therapy, and this will require ongoing investigation. PET-CT and diffusion-weighted MRI used in this study are both available in NZ, although with variable accessibility. The study also shows the feasibility and possible benefit of response-adapted therapy, which is being investigated by many ongoing trials.

Reference: Br J Haematol 2022;198:515–22
Abstract

Bortezomib and high-dose melphalan conditioning regimen in frontline multiple myeloma

Authors: Roussel M et al., for the Intergroupe Francophone du Myélome (IFM)

Summary: The phase 3 IFM 2014-02 study randomised 300 patients with symptomatic newly diagnosed MM to pretransplant bortezomib plus high-dose melphalan conditioning (200 mg/m^2; n=154) or high-dose melphalan conditioning alone (n=146). The trial did not meet the primary endpoint measure to show improved 60-day post-transplant CR with the addition of bortezomib versus high-dose melphalan alone (22.1% vs. 20.5% [p=0.844]). For secondary outcomes, there was a numerically longer median PFS duration with the combination conditioning regimen (34 vs. 29.6 months; HR 0.82 [95% CI 0.61–1.13]) and comparable undetectable MRD rates (41.3% vs. 39.4% [p=0.864]). Higher rates of serious adverse events and grade 3–4 painful peripheral neuropathy were reported with the addition of bortezomib (18.7% vs. 13.1% and 4% vs. 1.5%, respectively).

Comment (HG): High-dose melphalan, supported by autologous stem-cell rescue, has been a vital part of the myeloma armamentarium for 30 years. The principal question in 2022 is whether this toxic, blunt approach is still required if one has free access to newer therapies – as discussed elsewhere in this issue. Another question, of particular relevance to those of us with constrained myeloma drug options, is whether high-dose melphalan can be improved. Many attempts have failed and this paper adds to that list. In it, the IFM group report a simple phase 3 RCT of a bortezomib-enhanced (four doses) high-dose melphalan autologous SCT conditioning protocol. Importantly, all patients received bortezomib-containing induction, and it is likely to be this that underpins the absence of any differences in response rate or survival when also used peritransplant. Toxicity was not enhanced by peritransplant bortezomib. Other groups' attempts to improve on high-dose melphalan continue, and positive results have been reported for the addition of busulfan or bendamustine, to name but two.

Reference: Blood 2022;139:2747–57
Abstract

Impact of autologous transplantation on survival in patients with newly diagnosed multiple myeloma who have high-risk cytogenetics

Authors: Chakraborty R et al.

Summary: This meta-analysis of data from six RCTs found that upfront transplant conferred a trend toward improved survival compared with standard-dose consolidation therapy in patients with standard-risk cytogenetics (HR 0.66 [95% CI 0.70, 1.17]) and a significant survival advantage in patients with high-risk cytogenetics (0.90 [0.45, 0.97]), a difference in magnitude of benefit that was statistically significant (p=0.03). Analysis of PFS benefit in pooled data from four trials found a similar trend, with upfront transplantation conferring 48% and 35% reduced risks of disease progression in patients with high- and standard-risk cytogenetics, respectively, although the differential efficacy did not reach statistical significance (p=0.25).

Comment (NC): Despite the advances in antimyeloma therapy in recent years, patients with high-risk cytogenetic abnormalities have not benefited as much as those with standard-risk cytogenetics. Studies mainly enrol patients according to their disease status rather than disease risk, and therefore most only have 10–15% of patients with high-risk cytogenetics included. The small numbers often make studies underpowered to specifically investigate the utility of the studied regimen and high-dose therapy in this group of patients. Furthermore, the definition of high-risk cytogenetics varies across trials. Despite all these caveats, the common themes remain that high-risk cytogenetic patients have worse PFS/OS compared with standard-risk patients, and achievement of MRD negativity is important. This meta-analysis has demonstrated the importance of high-dose therapy in high-risk cytogenetic patients, with statistically improved OS and PFS. On the contrary, for standard-risk patients, high-dose therapy offered improvement in PFS but not OS. The definition of high-risk cytogenetic abnormalities differed across trials, but all included t(4;14), t(14;16) and del17p. One trial included del13q as well, and was excluded from the OS analysis. It is worth noting that there was significant heterogeneity in the studies included, and different induction and maintenance therapies were used. Some patients also received tandem transplants. Nonetheless, it does affirm the importance of high-dose therapy for this group of patients; however, the definition of high-risk cytogenetics continues to evolve and may include heterogeneous disease biology. Questions remain regarding the best induction combination, single versus tandem high-dose therapy and if all high-risk cytogenetic patients will respond equally to therapy. Future studies recruiting specifically for high-risk cytogenetic patients with the use of novel combinations for induction, consolidation with or without transplantation and maintenance would be interesting, but this will require collaboration between research groups to achieve adequate numbers.

Reference: Cancer 2022;128:2288–97
Abstract

Risk of multiple myeloma and other malignancies among first- and second-degree relatives of patients with multiple myeloma

Authors: Langseth ØO et al.

Summary: This population-based study explored the risk of MM as well as other cancers for 24,845 first-degree and 41,008 second-degree relatives of 7847 patients with MM, with 86,984 first-degree relatives and 138,660 second-degree relatives of 26,511 matched controls used for comparative analysis. Pertinent findings were that: i) there was no significant increased risk of cancer for second-degree relatives of patients with MM (HR 1.99 [95% CI 0.86, 4.57]); ii) there was no significant difference in age of MM onset between parents and offspring of patients with MM compared with the patients themselves (1.28 [0.50, 3.28]); and iii) among parent-offspring pairs with MM, OS did not differ significantly between generations (0.74 [0.20, 2.69]).

Comment (HG): It is widely understood that there is a mild familial risk in myeloma, although the basis of that risk is yet to be clearly defined. This large Norwegian population study set out to confirm the risk in first-degree relatives, explore the risk in second-degree relatives and look for any evidence of anticipation (myeloma presenting at a younger age in later generations). The numbers are enormous – nearly 8000 myeloma patients with 65,000 first- and second-degree relatives, and around four times as many controls! The data show a two-fold risk for first-degree relatives, with no evidence of anticipation, and no increased risk of myeloma (or other cancers) in second-degree relatives. This addresses a common question from our patients and provides a clear answer.

Reference: Eur J Haematol 2022;108:486–92
Abstract

Long-term follow-up of combination of B-cell maturation antigen and CD19 chimeric antigen receptor T cells in multiple myeloma

Authors: Wang Y et al.

Summary: After cyclophosphamide and fludarabine conditioning, 62 patients with relapsed or refractory MM received combination anti-BCMA CAR T-cells and anti-CD19 CAR T-cells 1×10^6 cells/kg in this phase 2 trial. After a median 21.3 months of follow-up, the overall response rate was 92% with a CR or better rate of 60%. Among 56 evaluable participants, 77% achieved MRD negativity. Participants responded for an estimated median 20.3 months. The median PFS duration was 18.3 months and the median OS duration was not reached. Survival was significantly worse for participants with extramedullary disease. Cytokine-release syndrome occurred in 95% of participants (10% grade ≥3) and neurotoxic events occurred in 11% (3% grade ≥3). With the exceptions of B-cell aplasia, hypogammaglobulinaemia and infections, late adverse events were infrequent.

Comment (NC): Anti-BCMA CAR T-cell therapy in myeloma has achieved impressive response rates in heavily pretreated patients and better PFS/OS outcomes than other novel therapies to date. However, the survival curve does not appear to reach a plateau for such a costly therapy. There are efforts looking into the reasons for relapse after anti-BCMA CAR T-cell therapy, which are likely to be multifactorial and include myeloma microenvironment, myeloma cell-related features and CAR T-cell manufacture/design/characteristics. One of the strategies is to use dual-targeting CAR T-cells. While myeloma cells only express a very low level of CD19, it is expressed on the myeloma stem cells, and targeting this fraction is thought to potentially improve therapeutic outcomes. This trial included patients who were heavily pretreated with a median of three prior lines of therapy. However, only 10% of patients had been exposed/refractory to anti CD38 antibodies, presumably due to limited access in China. The trial again showed an impressive response rate and PFS/OS with median follow-up of 20 months. However, it is too early to know if the response will be sustained long term. It is important to note that patients with extramedullary disease continue to do poorly with CAR T-cell therapy and other immunotherapies. Overall, CAR T-cell therapy is showing impressive efficacy in the heavily pretreated population with predictable and manageable toxicity. However, it is likely that it needs to be utilised in a different fashion and at an earlier disease timepoint to offer the possibility of cure.

Reference: J Clin Oncol 2022;40:2246–56
Abstract

Addition of elotuzumab to lenalidomide and dexamethasone for patients with newly diagnosed, transplantation ineligible multiple myeloma (ELOQUENT-1)

Authors: Dimopoulos MA et al., on behalf of the ELOQUENT-1 investigators

Summary: Adults with newly diagnosed, untreated, symptomatic myeloma were randomised to receive lenalidomide plus dexamethasone with (n=374) or without (n=374) elotuzumab in the phase 3 open-label ELOQUENT-1 trial. After follow-up of ≥65.3 months (median 70.6 months), there was no significant difference between the elotuzumab plus lenalidomide-dexamethasone and lenalidomide-dexamethasone-alone arms for median PFS (31.4 vs. 29.5 months [p=0.44]), with similar grade 3–4 treatment-related adverse event rates (17% vs. 21%) and toxicity-related mortality rates (1% in each arm).

Comment (HG): Elotuzumab is a monoclonal antibody against SLAMF7 that produced a statistically significant but clinically unimpressive benefit when added to lenalidomide-dexamethasone in the relapsed/refractory population – the ELOQUENT-2 study. This ELOQUENT-1 study moved the same combination into first-line therapy in the transplant-ineligible population. The result is convincingly negative with no improvements in response rates or prognosis. Discontinuations were higher in the elotuzumab group. It is difficult to avoid comparing – unfavourably – these data with daratumumab in the MAIA study, using the same lenalidomide-dexamethasone backbone in the same population, which showed large improvements in response rate, PFS and OS. NZ patients have been enrolled on the up-front isatuximab IMROZ study (with lenalidomide-bortezomib-dexamethasone), and it would be very surprising if this didn't repeat isatuximab's good results from second-line therapy (ICARIA, IKEMA).

Reference: Lancet Haematol 2022;9:e403–14
Abstract

Phase II trial of allogeneic transplantation plus novel drugs in multiple myeloma: effect of intensifying reduced-intensity conditioning with bortezomib and adding maintenance treatment

Authors: Reinoso-Segura M et al., on behalf of the European Myeloma Network, the European Society for Blood and Marrow Transplantation, and the Spanish Group of Transplantation

Summary: In this phase 2 trial, 24 patients with high-risk MM received reduced-intensity pretransplant conditioning with fludarabine, melphalan and bortezomib followed by postallogeneic SCT single-agent bortezomib or bortezomib, lenalidomide plus dexamethasone dependent on response; all participants also received lenalidomide maintenance. The 100-day disease control rate in 21 evaluable patients was 90%, including 12 CRs, four VGPRs and three PRs. At 2 years, the cumulative incidence of relapse was 28.5% and the NRM rate was 21.1%. At a median follow-up of 39 months, the event-free survival rate was 42.5% and OS was not reached.

Comment (NC): The role of allogeneic SCT in myeloma has become increasingly challenging to define, especially in the era of effective and well-tolerated novel therapies. It is also tinted by earlier data that showed significant toxicity often with myeloablative conditioning. Despite the curative intent of allogeneic SCT, only a small fraction of patients achieve this. Toxicity was mitigated with the introduction of reduced-intensity conditioning and improvement in SCT techniques. This EMN study included high-risk patients in their first relapse. High risk in this study was defined as early relapse after autologous SCT (<24 months), high-risk cytogenetics or late relapse but failure to achieve CR after a second autologous SCT. The trial expanded on their phase 1 result with the use of bortezomib as part of conditioning and GVHD prophylaxis. This phase 2 trial also included post-transplant bortezomib and lenalidomide in an attempt to lower the relapse risk. However, it's worth noting that 70% of patients did not proceed with maintenance and the most common reason was the presence of GVHD. Therefore, it's difficult to believe that the lower relapse risk observed in the current study is attributed to the maintenance therapy as suggested by the authors. Overall, with a short follow-up, the event-free survival and OS data are encouraging for this group of high-risk patients. While a 2-year NRM rate of 21% is acceptable in the allogeneic SCT setting, it is extremely high compared with novel antimyeloma agents. Longer-term follow-up will be required to determine if there is a true survival benefit. The role of allogeneic SCT remains elusive given the NRM and GVHD risk with potential poorer quality of life when its comparison is a large selection of novel therapies with manageable toxicity, although efficacy can be limited in this group of high-risk patients.

Reference: Transplant Cell Ther 2022;28:258e1–8
Abstract

Isatuximab plus carfilzomib and dexamethasone versus carfilzomib and dexamethasone in relapsed multiple myeloma patients with renal impairment

Authors: Capra M et al.

Summary: This analysis of phase 3 IKEMA study data investigated carfilzomib and dexamethasone with versus without isatuximab in patients with relapsed MM for the subgroup with renal impairment. For this subgroup, the isatuximab-containing arm started a greater median number of cycles (20 vs. 9) and had a greater median duration of exposure (81.0 vs. 35.7 weeks) compared with the carfilzomib-dexamethasone arm. The addition of isatuximab (versus carfilzomib and dexamethasone alone) was associated with longer PFS duration after 20.8 months of follow-up (not reached vs. 13.4 months; HR 0.27 [95% CI 0.11, 0.66]) and a greater complete renal response rate (52.0% vs. 30.8%) with durability seen in a greater proportion of participants (32.0% vs. 7.7%); the grade ≥3 treatment-emergent adverse event incidence was similar (79.1% vs. 77.8%).

Comment (HG): IKEMA, an RCT adding isatuximab to carfilzomib-dexamethasone in relapsed/refractory myeloma, reported an interim analysis in 2021 showing a large response rate and PFS advantage to the triplet arm; OS data are not yet mature. The current study is another prespecified analysis of the ~20% of patients with an estimated glomerular filtration rate of <60 mL/min/1.73m^2. This renal impairment group seemed to obtain more benefit – response rate and PFS – from adding isatuximab than those without renal impairment. Presumably this reflects the importance of fast, deep responses in rolling back renal damage, as is the accepted principle in first-line therapy. Anti-CD38 antibodies are desperately needed for NZ myeloma patients.

Reference: Haematologica 2022;107:1397–409
Abstract

Independent commentary by Dr Hugh Goodman,
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Dr Hugh Goodman is a clinical haematologist at Waikato Hospital. After training in Auckland he undertook a Fellowship at the UK National Amyloidosis Centre. His main interests are myeloma, lymphoma and amyloidosis.

Independent commentary by Dr Nicole Chien,
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Dr Chien is a consultant haematologist at Auckland City Hospital. She completed her haematology training in Auckland and undertook a fellowship in bone marrow transplant and multiple myeloma at Vancouver General Hospital in Canada. Her main area of research interest is in therapy for plasma cell disorders.