Multiple Myeloma Research Review™

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In this issue:

Abbreviations used in this issue:

ASCT = autologous stem cell transplant; **CAR** = chimeric antigen receptor; **HR** = hazard ratio; **MM** = multiple myeloma; **MRD** = minimal residual disease; **ND** = newly diagnosed; **OS** = overall survival; **PFS** = progression-free survival; **RR** = relapsed/refractory.

Welcome to the latest issue of Multiple Myeloma Research Review.

This month we begin with the latest publication from the Myeloma XI trial, assessing the role of lenalidomide maintenance across a number of genetic subtypes. The clonal heterogeneity of multiple myeloma (MM) is the subject of two papers. One looks at a novel technique to detect multiple subclones, whilst the other assesses the impact of high-dose melphalan on the genetic composition of residual plasma cells following transplantation. Metronomic dosing with cyclophosphamide is the focus of one paper and we report the latest update from the IKEMA study. The perception of *t*(11;14) disease as prognostically favourable is challenged by a Spanish study and we look at the information needs of MM patients. Finally, we focus on the ethical challenges associated with equitable access to chimeric antigen receptor (CAR) T cell therapy as well as treatment sequencing after prior bispecific therapy.

Once again, I hope this month's selections prove to be of interest and useful to your practice. As always, I welcome any feedback or comment.

Kind Regards,

Professor Philip Campbell
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Optimizing the value of lenalidomide maintenance by extended genetic profiling

Authors: Panopoulou A et al.

Summary: An analysis of 556 patients in the Myeloma XI trial was conducted to clarify which patients are likely to derive optimal clinical outcomes from lenalidomide maintenance. Myeloma tumour cells from 556 patients (median age 59 years) with newly diagnosed (ND) disease who received lenalidomide maintenance or observation in MYELOMA XI following induction therapy and autologous stem cell transplant (ASCT) underwent molecular profiling to establish the presence/absence of six known adverse copy number aberrations or translocations. More than half of the study cohort had no adverse cytogenetic aberrations (no hit cohort), one-third had a single risk marker (high-risk cohort) and 17% had ultra high-risk disease with co-occurrence of two high-risk genetic lesions (double hit cohort). Kaplan-Meier estimations of progression-free survival (PFS) stratified by genetic profile revealed that while all subgroups derived a benefit with lenalidomide over observation, patients with single hit genetics derived the greatest magnitude of benefit with a hazard ratio (HR) of 0.38 on Cox proportional hazards regression analysis (no hit cohort, HR 0.46; double hit cohort, HR 0.55). Further granularity of efficacy according to genetic lesion found that in patients with copy number aberrations del(1p), del(17p) or adverse translocation *t*(4:14), lenalidomide elicited exceptional improvements in disease control with median PFS exceeding four years (vs 7.5-26.7 months with observation), as well as conferring a survival benefit (HR 0.41). In contrast, no benefit with lenalidomide over observation was found in single hit patients with the gain (1q) aberration. Finally, in the double hit cohort, lenalidomide was superior to observation (PFS, 22.5 vs 10.6 months, HR 0.55; OS, 47.3 vs 32.8 months, HR 0.88, p=0.7) but a median PFS of less than two-years was found across all double genetic abnormality combination subgroups, an unfavourable outcome compared to both standard-risk and high-risk populations.

Comment: Post-ASCT lenalidomide maintenance remains the standard of care in transplant-eligible newly diagnosed NDMM patients. However, improvements in our understanding of interpatient heterogeneity, better access to minimal residual disease (MRD) assessment and the increasing availability of highly active cellular and immunotherapies at the time of relapse, is prompting a re-evaluation as to which patients benefit the most. The UK Myeloma group in particular, have been leading the way with recent data from the Myeloma XI trial suggesting standard risk patients derive the most benefit from approximately three years of maintenance treatment. In this publication, Myeloma XI trial investigators examine the role of lenalidomide maintenance versus observation alone according to genetic profiling and the presence or absence of high-risk lesions. Double-hit and isolated gain (1q) patients would appear to gain little from lenalidomide maintenance therapy and clearly need more novel treatment approaches. Emerging data from both the FORTE and OPTIMUM/MUKnine trials supports a more intensive maintenance approach in high-risk patients rather than our current practice of lenalidomide alone.

Reference: Blood. 2023;141(14):1666-74
Abstract

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Mass cytometry reveals unique phenotypic patterns associated with subclonal diversity and outcomes in multiple myeloma

Authors: Baughn L et al.

Summary: In this study researchers at the Mayo Clinic employed single cell mass cytometry to characterise the proteomic landscape of primary MM tumours and evaluate the correlations with clinical outcomes. Analysis of 34 MM cell surface or intracellular signalling proteins in tumour samples from 49 patients with newly diagnosed or relapsed/refractory (RR) disease revealed 13 unique subclonal protein profiles. An association between the relative abundance of each subclonal protein profile and clinical disease behaviour was found and subsequently confirmed in an unrelated gene expression dataset.

Comment: MM is recognized as a genetically complex disease characterized by the presence of multiple subclones. These genetically distinct clones evolve during the natural history of the disease into chemotherapy-resistant populations of cells that lead to disease progression. Much of our understanding to date is reliant on RNA sequencing studies at a single cell level. This elegant study from the Mayo Clinic provides clonal evaluation at a protein level using single cell mass cytometry, the contention being that an improved understanding of proteomic heterogeneity may lead to novel protein-targeted therapies. They detected a number of subclonal protein profiles (phenotypic meta-clusters) with distinct clinical behaviour that are shared among patients and potential therapeutic targets for future studies.

Reference: Blood Cancer J. 2023;13(1):84
Abstract

Ixazomib, oral metronomic cyclophosphamide, and dexamethasone for first-line treatment of multiple myeloma

Authors: Pelcovits A et al.

Summary: A phase 2 Brown University Oncology Group study (BrUOG 299) assessed a front-line all oral triplet regimen for MM comprised of the protease inhibitor ixazomib plus metronomic cyclophosphamide and dexamethasone in an attempt to develop a more tolerable treatment and reduce the incidence of peripheral neuropathy associated with bortezomib-based therapies. Due to slow recruitment, only 12 adult patients with treatment-naïve disease were enrolled prior to premature study termination. Patients received six cycles of ixazomib and dexamethasone (4 mg/day and 20 mg/day on days 1, 4, 8, 11, 15 and 18, respectively) plus 50 mg/day continuous cyclophosphamide followed by 18 months of single-agent ixazomib maintenance. Analysis revealed an overall response rate (ORR) of 58.3%, comprised entirely of partial/very good partial responses. Median PFS and overall survival (OS) were 16 and 43 months, respectively. Half of the study population experienced severe (≥ grade 3) dermatologic toxicity but there were no severe cases of peripheral neuropathy. The study authors concluded that further evaluation of this regimen in newly diagnosed disease is not justified but that it may hold merit in the RR setting.

Comment: The concept of metronomic cyclophosphamide dosing has been explored previously. Low-dose oral cyclophosphamide is thought to exert its anti-myeloma effects through targeting of the tumour's microvasculature. In this US study, a novel oral triplet combination alternative to bortezomib/cyclophosphamide/dexamethasone is evaluated unsuccessfully due to poor recruitment and disappointing rates of response. Whilst the use of low dose oral cyclophosphamide may be mechanistically appealing, evidence to date do not support its use in NDMM patients, although there may be a role in frail and palliative patients.

Reference: Oncologist. 2023;28(5):462-e303
Abstract

High-dose melphalan treatment significantly increases mutational burden at relapse in multiple myeloma

Authors: Samur M et al.

Summary: Samur et al report an analysis of data from the French multicentre IFM/DFCI2009 trial that evaluated whether high-dose melphalan induces genomic changes in MM cells. A total of 68 paired diagnosis/relapse samples from patients treated with bortezomib- lenalidomide-dexamethasone (VRd) ± high-dose melphalan underwent deep whole-genome sequencing. Results showed that at diagnosis patients had approximately 71-72 thousand mutations and that number increased in both patient cohorts at relapse - by 29% in patients treated without melphalan and by 85% in patients who received high-dose melphalan (9,242 vs 13,383; p=0.005). Novel mutations acquired after treatment were predominantly located on the transcribed DNA strand and were mostly in DNA damage repair or double-strand break genes. The study found no significant changes in the frequency of copy number alterations or structural variants. Further analysis determined that clonal selection drove mutation evolution in melphalan-treated patients, while in contrast, patients who received VRd demonstrated a static mutational progression. Finally, the study reported that patients who attained a complete response with either treatment strategy had comparable survival, regardless of differing mutational burdens, a finding that the authors speculated may be attributable to variable neoantigens.

Comment: High-dose melphalan followed by ASCT remains the standard of care in transplant-eligible patients and proved superior to VRD alone in the IFM 2009 study. Therapy-related neoplasms have always been a concern however, and recent data demonstrates an increased mutational burden in surviving MM cells, leading to accelerated growth at relapse and a negative impact on second PFS. In this laboratory sub-study of the randomised phase 3 IFM 2009 study, French and US investigators report the results of whole-genome sequencing performed on samples at diagnosis and relapse. These results confirm the mutagenic effects of high-dose melphalan on residual MM cells and the resultant increase in genetic complexity, although for patients in complete response, no compromise in survival was observed. The authors suggest a potential role for immunotherapy consolidation post-ASCT as means of overcoming the increased mutation burden, as well as exploiting the increased neoantigen repertoire seen in the residual tumour cells.

Reference: Blood. 2023;141(14):1724-36
Abstract

Sequencing T-cell redirection therapies leads to deep and durable responses in patients with relapsed/refractory myeloma

Authors: Mouhieddine T et al.

Summary: This retrospective analysis of salvage therapies for myeloma progression after bispecific antibody treatment from the Tisch Cancer Institute, Mount Sinai Hospital in New York indicates that sequential use of different T-cell redirection treatments is viable and potentially efficacious. Analysis included a heavily pre-treated cohort of 58 patients (median age, 57 years) who received a GPRC5D- or BCMA-directed bispecific antibody in a clinical trial between 2018 and 2021, with a median follow-up of just over 30 months from trial exit. The study cohort predominantly consisted of patients with adverse prognostic factors such as high-risk cytogenetics (78%), triple- or penta-class refractory disease and/or extramedullary disease. Two-thirds of patients received at least two lines of salvage therapy (range, 1-9) with T-cell redirection therapy (bispecific antibody or CAR T-cell therapy) employed as the first salvage treatment in 19 patients and second salvage therapy in a further 10 patients. Other first salvage treatments included conventional chemotherapy combinations; combination CD-38-, selinexor- or venetoclax-based regimens and more infrequently, antibody-drug conjugates. Overall response rates to first salvage T-cell redirection therapy were substantially higher than to other therapies (84% vs 49%) and included a high proportion of deep responses (≥ complete response, 63% vs 3%). Notably, deep responses were observed in patients treated sequentially with agents targeting the same antigen (i.e., anti-BCMA bispecific after an anti-BCMA CAR T-cell therapy or vice versa). Kaplan-Meier estimates of PFS to the first and second salvage were 28.9 and 30.9 months, respectively, in patients treated with a first or second-line salvage T-cell redirection therapy. Two-year overall survival in this cohort was 62%.

Comment: T-cell redirection therapies using either CAR T-cells or bispecific antibodies continue to produce unprecedented responses in RRMM patients. Efficacy very much depends on T cell numbers and fitness and it remains to be determined if these patients can be successfully salvaged with subsequent CAR T-cell or bispecific antibody therapy. This retrospective review from New York of 115 patients progressing after receiving bispecific antibodies on clinical trials, suggests that more than 80% of patients will respond, in contrast to just 50% receiving other forms of salvage treatment. There is a suggestion that when sequencing, CAR T-cells should precede bispecifics but this was not borne out in this study. Within an Australian treatment context where bispecifics are more likely to be used earlier than CAR T-cells, this data is relevant to local practice. Increasingly however, improved understanding of the immune microenvironment alongside real-time monitoring of the immunological compartment, will inform treatment sequencing decisions.

Reference: Blood Adv. 2023;7(6):1056-64
Abstract

Ethical challenges with multiple myeloma BCMA chimeric antigen receptor T cell slot allocation: A multi-institution experience

Authors: Kourelis T et al.

Summary: This survey-based study investigates how US CAR T-cell therapy centres handle the moral conundrum of insufficient idecabtagene vicleucel therapy supply to meet patient needs in the absence of established guidelines. Physician leaders at most US CAR-T treatment centres (17/20) agreed to participate in the study and completed surveys regarding the magnitude of supply issues and the criteria used to prioritise access to therapy. A substantial deficit between CAR T-cell therapy production slot allocation to centres and the quantity of patients was found, with a median of one production slot allocated per centre each month and up to 100 patients on each centre's waitlist (median, 20). Consequently, significant delays in treatment initiation were observed with lags of two-eight months (median, six months) prior to leukapheresis and more than one-quarter of patients never receiving CAR T-cell treatment. Universally, a committee of expert specialist physicians are responsible for triage of patients, although the framework to determine priority and rank are not consistent and generally only transparent to CAR T-cell providers but not patients. The criterion most influencing patient rank in 60% of centres was the likelihood of deriving a clinical benefit. Other factors considered in the process included time spent on the wait list, lack of alternative therapeutic options, disease burden, high comorbidity index, and younger age.

Comment: Managing demand versus availability continues to be a challenging issue for CAR T-cell providers, imposing significant ethical and practical responsibilities on treatment centres and the healthcare system in general. This interesting study highlights processes for CAR T-cell therapy selection across 17 US sites and how competing priorities are managed on a day-to-day basis. This is the first study of its kind, and it portrays a system beset by limited slot availability and administration delays. It highlights the importance of a national coordinated approach to cellular delivery to ensure appropriate allocation of this precious resource.

Reference: Transplant Cell Ther. 2023;29(4):255-58
Abstract

Patient confidence and information preferences during the treatment decision-making process

Authors: Mellqvist U-H et al.

Summary: Results from a large multiple myeloma patient survey across 12 countries in Europe and Israel reports that most patients have confidence in their treatment decisions but require greater dissemination of information, especially regarding therapy effectiveness. Over one thousand adult patients undergoing treatment for symptomatic myeloma outside of a clinical trial participated in the study and at least partially completed a survey through the umbrella patient advocacy group Myeloma Patients Europe. The study population had an age range of 54-64 years, 60% were undergoing a second- or later-line therapy, most were receiving treatment through a haematology clinic and more than half had made their most recent treatment decision within the last 12 months. Almost all patients expressed confidence in their treatment decisions, with only 5% reporting feeling not confident and this finding was fairly consistent across the lines of treatment. Despite treatment effectiveness information such as how long until disease returns or the overall survival benefit considered to be one of the most meaningful pieces of information, less than 40% of patients reported receiving this information.

Comment: Understanding and responding to the information needs of MM patients is critical to the patient/physician relationship. In general, patients feel more comfortable and retain a sense of empowerment when the information they receive correlates with their subsequent experience on treatment, further strengthening the relationship between physician and patient. Whilst there are a number of studies into patient treatment preferences, not much is understood about information preferences when it comes to the treatment decision-making process. This European study addresses the confidence and information preferences of patients with MM through a once off, anonymous patient survey. It provides an overall assessment of their experience including the quality of the relationship with their physician and availability of appropriate psychosocial support. More than two thirds of patients responded to the survey, with just over half reporting confidence and satisfaction with their latest treatment decision and the majority confident in their physician. The important contribution of other members of the multidisciplinary team, such as nurses and allied health practitioners, should not be underestimated however.

Reference: Clin Lymphoma Myeloma Leuk. 2023;23(5):e240-51
Abstract

Isatuximab, carfilzomib, and dexamethasone in patients with relapsed multiple myeloma: updated results from IKEMA, a randomized phase 3 study

Authors: Martin T et al.

Summary: Data from the primary interim analysis from IKEMA demonstrated superior disease control with prolonged PFS and improved depth of response with the addition of isatuximab to a doublet of carfilzomib and dexamethasone, with a manageable safety profile. Now, the IKEMA researchers provide updated data from the trial at a prespecified follow-up analysis with a median follow-up exceeding three-and-a-half years. Briefly, a total of 302 adult patients with previously treated RRMM who had received no more than three prior lines of therapy and had measurable M protein were accrued to the trial and randomised to undergo continuous carfilzomib and dexamethasone ± isatuximab therapy until disease progression or intolerable toxicity. The significant PFS benefit reported in the primary interim analysis with the addition of isatuximab was maintained at longer-term follow-up, eliciting an approximate doubling of median PFS duration and conferring a 42% reduced risk of disease progression or death compared to the control regimen (35.7 vs 19.2 months; HR 0.58). Other outcome measures consistently demonstrated the superior efficacy with the addition of isatuximab with improved likelihood of achieving a complete response or stringent complete response (44.1% vs 28.5%; odds ratio 2.09) and an almost three-fold improved odds of attaining MRD negativity (33.5% vs 15.4%; odds ratio 2.78). No new safety concerns were noted.

Comment: In this prespecified analysis of the IKEMA study, investigators report updated results. Along with daratumumab, istatuximab is an anti-CD38 monoclonal antibody with similar anti-myeloma activity and a subtle difference in antigen specificity. The overall efficacy and safety results are in-line with the previously reported interim analysis confirming the superiority of isatuximab-carfilzomib-dexamethasone over carfilzomib-dexamethasone. The safety profile was particularly impressive after an additional two years of follow-up, when one considers the elevated risk associated with the COVID-19 pandemic in MM patients receiving monoclonal antibody therapy. Despite 61% of carfilzomib-dexamethasone patients receiving subsequent monoclonal antibody therapy, second PFS was longer with isatuximab-carfilzomib-dexamethasone, indicating greater benefit with earlier antibody use. The inconvenience of intravenous administration is perhaps the only downside of isatuximab-carfilzomib-dexamethasone in this context.

Reference: Blood Cancer J. 2023;13(1):72
Abstract

Multiple myeloma with t(11;14): impact of novel agents on outcome

Authors: Puertas B et al.

Summary: This retrospective study sought to elucidate the prognostic ramifications of the translocation of chromosomes 11 and 14 [*t*(11;14)] in patients with newly diagnosed myeloma. A chart review of 591 patients who received first-line treatment for ND disease over two decades (1998 to 2018) at two Spanish hospitals (the University Hospital of Salamanca and the University Hospital of Leon) was undertaken. Outcomes were compared between three cytogenetic groups – patients harbouring only the *t*(11:14) aberration (n=102); patients with high-risk chromosomal abnormalities including *t*(4;14), *t*(14;16) or del17p ± *t*(11:14); and patients with standard-risk disease. Results showed a similar prognosis in patients harbouring *t*(11:14) translocations versus patients with standard-risk cytogenetics (PFS: 35.3 vs 31.1 months, *p*=0.959; OS: 75.8 vs 87.2 months, *p*=0.438). Both these patient groups had a favourable prognosis compared to patients with high-risk cytogenetics. Analysis of response rates according to receipt of front-line novel agent (e.g., protease inhibitors, immunomodulatory drugs and anti-CD38 monoclonal antibodies) versus conventional agents such as chemotherapy or polychemotherapy showed that unlike the standard-risk cohort in which novel agents improved ORR, complete response rate as well as PFS and OS, patients with *t*(11:14) translocations did not derive a benefit that reached statistical significance by any measure.

Comment: *T*(11;14) is the most common translocation in NDMM, present in around 15%-20% of cases and more frequently observed in amyloidosis and primary plasma cell leukaemia. It is considered a distinct biological entity based on its lymphoplasmacytic morphology, CD20 expression and elevated BCL-2 levels. Previous studies suggested that *t*(11;14) patients had a favourable outcome, yet more recent clinical experience in an era of routine protease inhibitors and immunomodulatory drug use suggests the opposite. In this retrospective observational study of 591 patients from Spain, the authors observed an expected prevalence of 17% but suboptimal responses to protease inhibitor/immunomodulatory drug-based therapy. Clinically these patients are more likely to have heavier marrow involvement and oligo-secretory or non-secretory disease. Given the activity of BCL-2 inhibitors, the presence of this pattern of disease should prompt a thorough search for this biomarker.

Reference: Blood Cancer J. 2023;13(1):40
Abstract

Preclinical models for prediction of immunotherapy outcomes and immune evasion mechanisms in genetically heterogeneous multiple myeloma

Authors: Larrayoz M et al.

Summary: In a step towards preclinical immunotherapy research that would enable explication of the paradoxical efficacy of different immunotherapeutic approaches in myeloma, an international collaborative research effort has created 15 murine models of the disease, epitomising the heterogeneity in clinical, genetic and immunological characteristics and key steps in pathogenesis. Transgenic mice were engineered that had one, two or three genetic drivers of myeloma such as *KRAS* ^{G12D} mutation, antiapoptotic BCL2 expression, c-MYC expression or *TP53* deletion, introduced into immature pre-B lymphocytes or mature germinal centre B lymphocytes. Examination of 500 genetically heterogenous mice and over one thousand tumour samples from patients with myeloma by multiomic cellular and molecular technologies revealed mechanisms of genetic lesion accrual, primarily through the MYC oncogenic pathway, that drive progression from precursor states to active disease. The preclinical murine models have translational applicability for assessment of targeted therapeutics and immunotherapy combinations.

Comment: Chromosomal translocations of immunoglobulin-coding genes and hyperdiploidy are the most common early genetic events in MM, with abnormalities in the NF-κB, MAPK-RAS and apoptotic pathways following on, and contributing to the malignant phenotype. MYC rearrangements and *TP53* alterations are usually late progression events seen in the RRMM state when disease biology becomes more aggressive. Responses to novel immunotherapy and cellular therapy interventions are not consistent, and this Spanish pre-clinical study sets out to uncover the mechanisms responsible for such a diversity in outcomes. They deployed 15 genetically engineered mouse models to recapitulate the disease at different stages, and examining the role of the bone marrow microenvironment at transformation and its influence on outcomes to immunotherapy. These results point to MYC as a key regulator of tumour progression and the heterogeneity of clinical responses to immunotherapy. This is an important step in the design of precision approaches to immunotherapy in MM.

Reference: Nat Med. 2023;29(3):632-45
Abstract

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Independent commentary by Professor Philip Campbell

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