A RESEARCH REVIEW™
EXPERT FORUM

Multiple Myeloma Summit 2022

Making Education Easy

myeloma new zealand

Myeloma experts convened in person and online for the 2022 Multiple Myeloma Queenstown Summit, hosted by Myeloma New Zealand. This year's meeting included presentations from local and international experts, including the Chief Medical Officer of the International Myeloma Foundation, Professor Joseph Mikhael, Assistant Professor Jonathan Keats from Arizona, and Professor Simon Harrison and Dr Simon Gibbs from Melbourne. Highlights of the meeting have been summarised with unconditional funding from Novartis.

Abbreviations used in this review
AL = immunoglobulin light chain
ASCT = autologous stem cell transplant
ATTRwt = wild type transthyretin
BCMA = B-cell maturation antigen
BiTE = bispecific T cell engager
BMPC = bone marrow plasma cell
BSA = bi-specific antibody
CAR = chimeric antigen receptor
CR = complete response
CRES = CAR T-cell encephalopathy syndrome
CRS = cytokine-release syndrome
FISH = fluorescence *in situ* hybridisation
HFpEF = heart failure preserved ejection fraction
ICANS = immune effector cell-associated neurotoxicity syndrome
Ig = immunoglobulin
IMiD = immunomodulatory drugs
ISS/R-ISS = (Revised) International Staging System
MAb = monoclonal antibody
MGUS = monoclonal gammopathy of undetermined significance
MM = multiple myeloma
MRD = minimal residual disease
MRI = magnetic resonance imaging
NDMM = newly-diagnosed MM
ORR = overall response rate
OS = overall survival
PFS = progression-free survival
PI = proteasome inhibitor
RRMM = relapsed refractory MM
SCT = stem-cell transplantation
SFLCR = serum-free light chain ratio
SMM = smouldering myeloma
TEMM = transplant-eligible multiple myeloma
TNEMM = transplant-non-eligible multiple myeloma
(VG)PR = (very good) partial response

Drug regimens
D-KRD = daratumumab, carfilzomib, lenalidomide, dexamethasone
D-RVD = daratumumab, lenalidomide, bortezomib, dexamethasone
D-VRD = daratumumab, lenalidomide, bortezomib, dexamethasone
KCD = carfilzomib, cyclophosphamide, dexamethasone
KRD = carfilzomib, lenalidomide, dexamethasone
Isa-KD = Isatuximab, carfilzomib, dexamethasone
PD = pomalidomide, bortezomib
PVD = pomalidomide, bortezomib, dexamethasone
RVD = lenalidomide, bortezomib, dexamethasone
VCD = bortezomib, cyclophosphamide, dexamethasone
VD = bortezomib, dexamethasone
XVD = selinexor, bortezomib, dexamethasone

RECENT ADVANCES IN FRONTLINE MULTIPLE MYELOMA

Presented by Professor Joseph Mikhael
from the Translational Genomics Research Institute (TGen), Arizona (USA)

Treatment strategies for MM have historically been divided into either cure or control approaches. The cure approach involves a more aggressive therapy upfront to achieve MRD negativity, knowing it is prognostic for both PFS and OS.[1] Professor Mikhael believes treatment strategies are tipping towards cure but this needs to be balanced against toxicity and cost.

To transplant or not transplant?

The IFM 2009 study demonstrated an improved PFS in patients receiving transplant, however, there was no difference in OS and 79% of non-transplanted patients received a transplant at first relapse.[2]

The DETERMINATION study design was similar although <25% of patients underwent transplantation at first relapse.[3] After 76 months of follow-up, the study reported a 21.3-month PFS benefit in the transplant arm, but once again, no difference in OS.

Conclusions regarding transplantation

- ASCT remains very relevant and important in prolonging PFS in younger eligible patients
- BUT it may not be mandatory in all eligible patients upfront – as with other agents we need to INDIVIDUALISE the sequencing patterns
- ASCT does carry genuine toxicity, short-term and long-term
- Maintenance therapy remains an important part of treatment – but it is a blunt tool that must be carefully used as it is harder to give post-ASCT and dose adjustments are critical to minimise toxicity

Can we do better with a quadruplet?

The GRIFFIN trial compared D-RVD versus RVD in transplant-eligible NDMM patients.[4] At each treatment step there was a deepening of response (**Figure 1**). This suggests there may be sensitive disease that can be overcome following a transplant with consolidation and maintenance therapy.

A German study investigated isatuximab (Isa) + RVD versus RVD in NDMM transplant-eligible patients.[5] Isa-RVD is the first regimen to demonstrate MRD-negativity (50.1%) at the end of induction and to demonstrate superiority versus RVD in a Phase III trial.

Can we do better with longer induction without transplant?

The FORTE trial evaluated 8 cycles of KRD induction plus ASCT versus 12 cycles of KRD alone versus 8 cycles of KCD induction plus ASCT.[6] The results initially suggested that transplant maybe unnecessary due to a similar depth of response; however, PFS data demonstrated improved outcomes at a median follow-up of 51 months for KRD-ASCT vs KRD12. This finding demonstrated that the depth of response does not always correlate with duration of response and potentially justifies transplants in patients who have achieved CR or even MRD-negativity.

Can we be guided by MRD to STOP therapy?

The MASTER trial administered D-KRD, transplantation and D-KRD consolidation according to MRD status to NDMM patients.[7] Patients with two consecutive MRD-negative assessments began treatment-free surveillance. Patients with 1 high-risk cytogenetic abnormality had little difference in PFS and OS compared to patients without high-risk abnormalities. However, patients with ≥2 high-risk abnormalities did not do so well. This suggests there are subsets of patients who do not do well if treatment is withdrawn following MRD-negativity.

Conclusions for frontline therapy and transplant

- We will likely be transitioning to quadruplets in frontline eligible patients in the near future – BUT the optimal length of a quadruplet is still to be determined!
- Transplant still has a role in MM, even with long-term use of novel agents
- MRD guided discontinuation may be possible in lower risk groups but not high-risk groups
- We can likely improve on current maintenance strategies of lenalidomide alone by adding daratumumab or carfilzomib

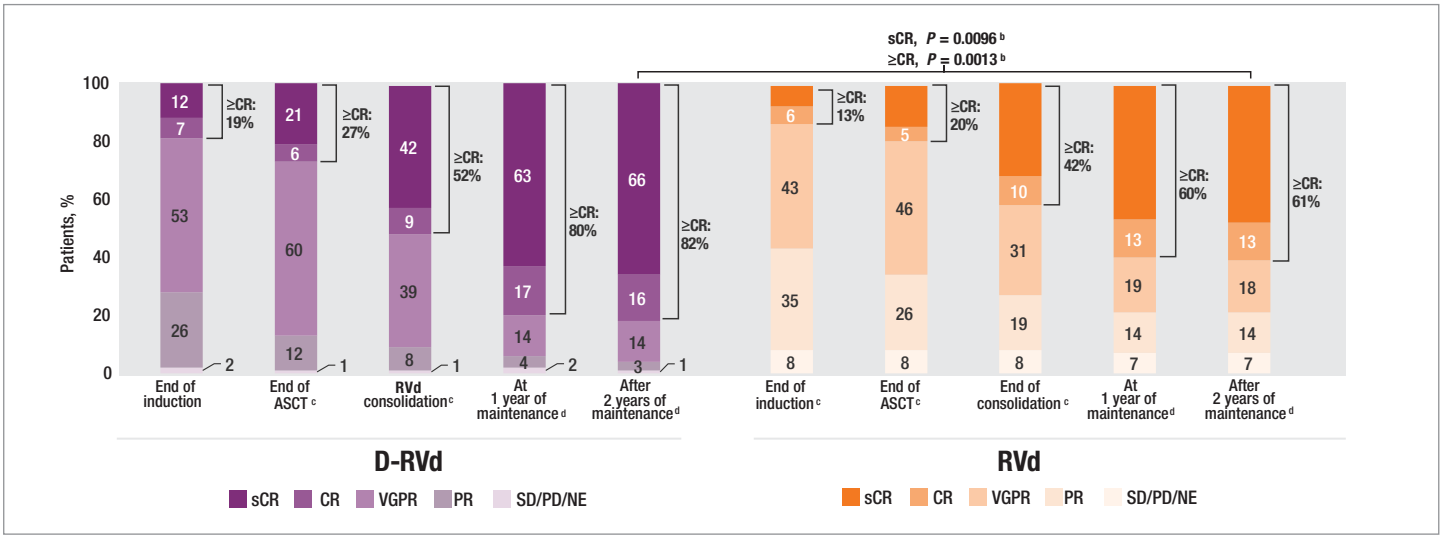


Figure 1: Depth of response in transplant-eligible MM from the GRIFFIN study. Adapted from Mikhael (2022).

What criteria are used to assess ASCT eligibility?

In the future, assessment for transplant eligibility may not need to be performed until after initial triplet therapy. Chronological age and renal function should also not be the sole criteria for determining transplantation eligibility.[8]

NDMM without transplantation

The MAIA trial compared D-RD versus RD in transplant-ineligible NDMM patients with a median age of 73 years.[9] D-RD continued to demonstrate a benefit with a median PFS for RD of 34.4 months and median PFS not reached for D-RD at 60 months. Over two-thirds of D-RD patients were alive at 5 years and over half are still in remission – there was both a PFS and OS advantage for D-RD over RD. These data provide a new PFS benchmark in transplant-ineligible NDMM patients.

Conclusions in transplant ineligible patients

- Although ASCT remains the standard of care, use is likely to decline in patients who are aged 65-75 years or with significant co-morbidities
- Continuous therapy has resulted in better outcomes
- The balance of toxicity and efficacy is particularly important in this population – ESPECIALLY with dexamethasone where dose reduction at the appropriate time is important
- Professor Mikhael's approach is to select 2 agents from 3 novel classes (PIs, IMiDs and MAbs) – he tends to favour D-RD in standard risk patients and V-RD in high-risk patients
- D-RD is more easily delivered and feasible
- D-VRD may well be a future standard of care even in these patients

REFERENCES

1. Lahuerta JJ, et al. Depth of Response in Multiple Myeloma: A Pooled Analysis of Three PETHEMA/GEM Clinical Trials. *J Clin Oncol.* 2017;35(25):2900-2910.
2. Attal M, et al. Drug Combinations with Transplantation for Myeloma. *N Engl J Med.* 2017;377(1):93-94.
3. Richardson P.G., et al. Lenalidomide, bortezomib, and dexamethasone ± autologous stem cell transplantation and lenalidomide maintenance to progression for nearly diagnosed multiple myeloma: The phase 3 DETERMINATION trial. In: *Abstract LBA4.* ; 2022.
4. Voorhees PM, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. *Blood.* 2020;136(8):936-945.
5. Goldschmidt H., et al. Addition of isatuximab to lenalidomide, bortezomib and dexamethasone as induction therapy for newly-diagnosed, transplant-eligible multiple myeloma: the phase III GMMG-HD7 trial. In: ; December 11-14.
6. Gay F., et al. Carfilzomib-Lenalidomide-Dexamethasone (KRd) Induction- Autologous Transplant (ASCT)-Krd Consolidation Vs KRd 12 Cycles Vs Carfilzomib-Cyclophosphamide-Dexamethasone (KCd) Induction-ASCT-KCd Consolidation: Analysis of the Randomized Forte Trial in Newly Diagnosed Multiple Myeloma (NDMM). *Blood.* 2018;132(Suppl 1):121.
7. Costa LJ, et al. Daratumumab, Carfilzomib, Lenalidomide, and Dexamethasone With Minimal Residual Disease Response-Adapted Therapy in Newly Diagnosed Multiple Myeloma. *J Clin Oncol.* Published online December 13, 2021:JCO2101935. doi:10.1200/JCO.21.01935
8. Mikhael J, et al. Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline. *J Clin Oncol.* 2019;37(14):1228-1263.
9. Kumar S., et al. Updated Analysis of Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) in Patients with Transplant-Ineligible Newly Diagnosed Multiple Myeloma (NDMM): The Phase 3 Maia Study. In: *2276.* ; 2020.

SMOULDERING MYELOMA: A TREATMENT INDICATION?

Presented by Dr Sarah Poplar, Haematologist (Northland)

SMM is a heterogenous disorder that includes patients with imminent progressive disease and potentially life-changing complications, as well as those that can be observed safely for many years. Two important questions are:

1. Can early treatment improve outcomes in SMM? And at what toxicity cost?
2. How do we identify patients that benefit from early treatment?

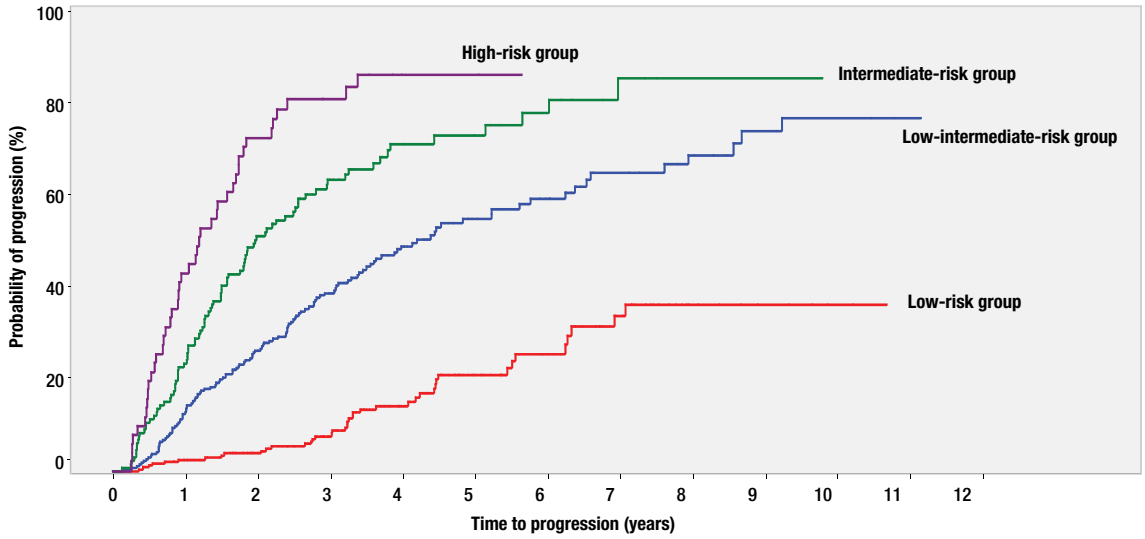
An ultra-high risk SMM cohort was identified with an >80% of progression in the first 2 years by stratifying bone marrow plasmacytosis, the SFLCR and focal lesions on MRI.[1] This upstaged approximately 15% of smouldering myeloma by previous definitions and are now regarded as having active myeloma requiring treatment (IMWG, 2014).

How to stratify risk in the remaining patients?

The 20-2-20 model (BMPC 20%, Mp 2g/dL, SFLCR 20) is widely-used for SMM risk stratification.[2] The incorporation of genetic abnormalities (del17p, t(4;14), +1q21, hyperdiploidy) and risk scoring has improved the model's predictive ability (**Figure 1**).[2]

There are many other models that can predict the risk of SMM progression, e.g.:

- The Czech Myeloma Group model uses only serum markers to predict an 80% risk of progression to symptomatic MM within 2 years.[3]
- Serological trends in the rate of M protein and anaemia progression.[4]
- Additional markers of interest include quantifying circulating tumour cells, abnormal plasma cell immunophenotype >95% + immunoparesis, BMPC proliferation index >1, and gene profiling.



Risk Stratification groups	Total risk score	Hazard Ratio (95% CI)	Risk of progression (2 years)	# of patients
Low	0-4	Reference	3.8%	241 (35%)
Low-intermediate	5-8	7.56 (3.77 – 15.2)	26.2%	264 (38.3%)
Intermediate	9-12	17.3 (8.63 – 34.8)	51.1%	133 (19.3%)
High	>12	31.9 (15.4 – 66.3)	72.5%	51 (7.4%)

Figure 1: Risk of progression after 2 years based on risk factors in SMM patients. Adapted from Mateos (2020).[2]

One step further: should MGUS be treated?

Can screening for MGUS help prevent MM complications? In New Zealand, this might involve targeting Māori aged > 50 years and people with a family history of MM.

The iSTOPMM study screened 75,000 people (2016–2020), finding an overall MGUS prevalence of 5% in Iceland.[5] People with MGUS were divided into three arms: not contacted (no SMM cases diagnosed); annual follow-up (56 SMM cases diagnosed); intensive follow-up (82 SMM cases diagnosed). Screening for MGUS also allows for the early detection of amyloidosis. The outcome of this study is eagerly awaited to determine if early detection improves outcomes.

Treatment of smouldering myeloma

Long-term follow-up is required to determine the effectiveness of SMM treatment. Examples of these trials include:

- QuiRedex, comparing lenalidomide plus dexamethasone versus observation.[6] However, this trial had methodological issues, although a survival benefit with early treatment was demonstrated.
- Lenalidomide monotherapy versus observation.[7] A substantial number of patients withdrew. The PFS benefit was greatest in patients meeting the 20-2-20 high-risk criteria. The rate of bone progression was higher in the observation group (11% vs 3%) supporting the theory that this reduces irreversible complications.
- CENTAURUS assessed daratumumab monotherapy of three intensities.[8] The primary endpoint of CR >15% was not met. Grade 3-4 adverse effects occurred in 44%, 27% and 15% in the highest to lowest intensity arms. PFS at 24 months was 89.9%, 82.0% and 75.3% respectively.
- There are many novel agents in phase II SMM clinical trials. KRD(8)-R is perhaps the most promising regimen with a MRD-negative CR rate of 70.4% after a median duration of 5.5 years and PFS at 96 months of 92%.[9] While several novel agents are efficacious in remitting SMM and improving PFS, many years of follow-up will be required to determine if OS can be improved.

TAKE-HOME MESSAGES

- Most important to accurately define high-risk patients
- Trial definitions of high-risk vary
- Continuous risk factors and arbitrary thresholds – when should treatment commence?
- Evidence for OS benefit with early treatment - But toxicity and tolerance issues
- Promising novel agents – is functional cure now possible?

REFERENCES

1. Kyle RA, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. *N Engl J Med*. 2007;356(25):2582-2590.
2. Mateos MV, et al. International Myeloma Working Group risk stratification model for smoldering multiple myeloma (SMM). *Blood Cancer J*. 2020;10(10):102.
3. Hájek R, et al. Identification of patients with smouldering multiple myeloma at ultra-high risk of progression using serum parameters: the Czech Myeloma Group model. *Br J Haematol*. 2020;190(2):189-197.
4. Atrash S, et al. Evolving changes in M-protein and hemoglobin as predictors for progression of smoldering multiple myeloma. *Blood Cancer J*. 2018;8(11):107.
5. Screening for monoclonal gammopathy of undetermined significance: a population-based randomized clinical trial. First results from the Iceland Screens, Treats, or Prevents Multiple Myeloma (iStopMM) study. In: *63rd American Society of Hematology Annual Meeting and Exposition*. ; 2021.
6. Mateos MV, et al. Lenalidomide plus dexamethasone versus observation in patients with high-risk smouldering multiple myeloma (QuiRedex): long-term follow-up of a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2016;17(8):1127-1136.
7. Lonial S, et al. Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma. *J Clin Oncol*. 2020;38(11):1126-1137.
8. Landgren CO. Daratumumab monotherapy for patients with intermediate-risk or high-risk smoldering multiple myeloma: a randomized, open-label, multicenter, phase 2 study (CENTAURUS). *Leukemia*. 2020;34(7):1840-1852.
9. Kazandjian D, et al. Carfilzomib, Lenalidomide, and Dexamethasone Followed by Lenalidomide Maintenance for Prevention of Symptomatic Multiple Myeloma in Patients With High-risk Smoldering Myeloma: A Phase 2 Nonrandomized Controlled Trial. *JAMA Oncol*. 2021;7(11):1678-1685.

THE GENOMICS OF MULTIPLE MYELOMA

Presented by Assistant Professor Jonathan Keats, Translational Genomics Research Institute (TGen), Arizona (USA)

Technology is allowing aggressive disease MM subclones to be detected early and clonal analysis can help select treatments following progression.[1]

MM genetics can be divided into hyperdiploid and non-hyperdiploid, with approximately half of patients in each. Immunoglobulin translocations are common in non-hyperdiploid MM. Assistant Professor Keats recommended using the ISCN pathology report when interpreting translocations.

Important genetic events

The known important genetic events in MM are shown in **Table 1** and the frequency of common events is shown in **Figure 1**.

While hyperdiploid MM is generally thought to be good prognostically, patients with deletions on chromosome 13 and 1q gains have the worst PFS of hyperdiploid MM patients. Therefore, not all hyperdiploid MM is low-risk.

Table 1: Genetics events believed to be important in MM

Copy number	
Hyperdiploid	Two trisomies on chromosomes 3, 5, 7, 9, 11, 15, 19, and 21
Deletions	17p/17p13 - TP53 13q14, 1p31 – CDKN2C
Gains	1q21 – CKS1B
Translocations	
t(4;14)	NSD2/WHSC1/MMSET, t(14;16) – MAF, t(14;20) – MAFB, t(8;14) – MAFA
t(11;14)	CCND1 (therapeutic link – venetoclax?)
t(8;14)	MYC, t(6;14) – CCND3, t(12;14) – CCND2

TP53 mutations and deletions

The loss of both p53 copies is associated with survival reductions (median 29 months). In contrast, patients with one functional copy do not have high-risk disease and this accounts for most patients with p53 mutations. Therefore, in MM with p53 abnormalities 75% of patients have standard risk disease.

One-third of MM patients have gains on 1q21 and generally, patients with amplification of 1q21 are considered high-risk, although their median survival is 6-7 years. However, patients with two copy gains of 1q21 who are aged <75 years and are ISS stage III are categorically high-risk.

Translocations in MM

Regarding common MM translocations:

- Multiple loci are rearranged with MYC
- Ig lambda translocations are common, even in Ig kappa expressing patients
- Events targeting MAP3K14 are common

Data was presented showing no significant difference in time to second line therapy between t(4;14) patients and those with t(14;16). In the same patients, a small decrease in OS in t(4;14) occurred, compared to t(14;16) and others, although this may become less clinically significant with newer treatments.

Transitioning to high-risk phenotypes

Multiple genes can lead to dysregulation of WHSC1, i.e. the target gene of t(4;14) translocation. Often a translocation will bring an Ig enhancer in close proximity, however, highly expressed plasma cell genes can lead to WHSC1 expression levels similar to a translocation. FISH will not detect t(4;14) biology in these situations.

Gene expression profiling can identify high-risk subtypes of MM. PR patients have small amounts of many translocations and this subgroup does poorly. MM patients can acquire this phenotype and 28% transition to PR at progression.

Additional points

- TNFRSF17/BCMA is a good therapeutic target because expression is essential for plasma cell survival and it is located on the cell surface. Targeted treatment may be curative for some patients with high levels of BCMA expression.
- Sequential FISH provides additional data that can sometimes provide oncologists with therapeutic options that they may not have considered otherwise.
- Caution is required when interpreting cellular markers. For example, a BRAF V600E positive patient underwent cellular analysis showing 20% of tumour cells were positive. Would a clinically significant response occur if all these positive malignant cells were eliminated? It is possible that medicines have been discarded because methodology has not adequately assessed their potential benefits.

TAKE-HOME MESSAGES

- Not all hyperdiploid patients are low risk – consider other factors
- Deletion 17p13 is a good predictor of poor outcomes BUT the true signal is bi-allelic loss, so are you INCORRECTLY giving a patient bad news
- Features beyond the standard measures can more accurately predict patient outcome

REFERENCES

1. Keats JJ, Chesi M, Egan JB, et al. Clonal competition with alternating dominance in multiple myeloma. *Blood.* 2012;120(5):1067-1076. doi:10.1182/blood-2012-01-405985

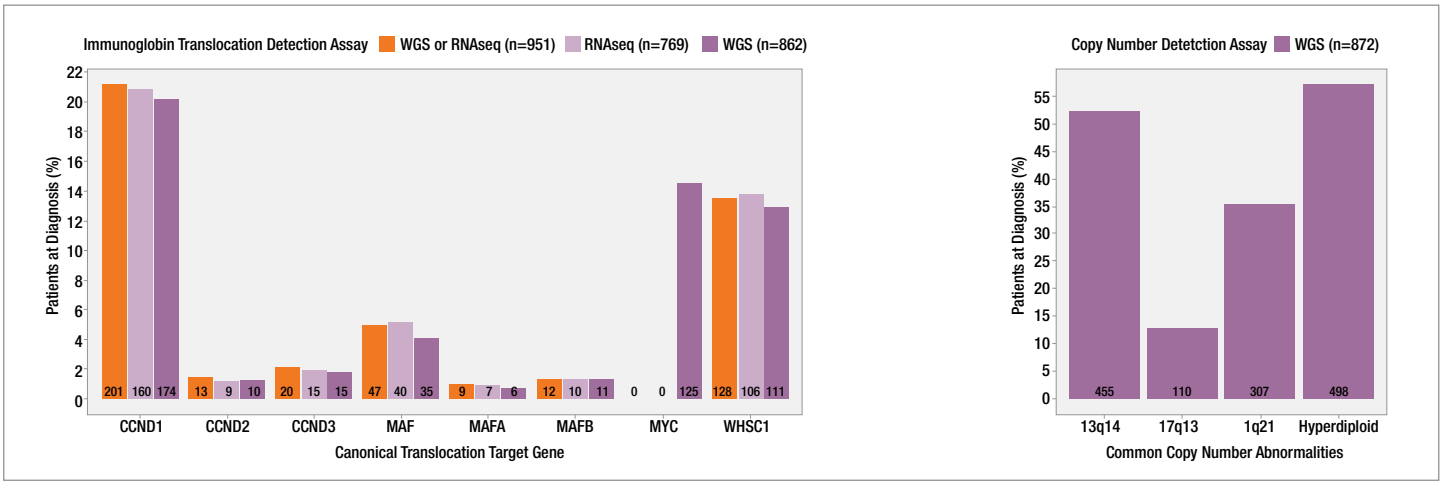


Figure 1: Frequency of common genetic events in MM patients. Adapted from Keats (2022).

RECENT ADVANCES IN RELAPSED MULTIPLE MYELOMA

Presented by Professor Joseph Mikhael, Chief Medical Officer, International Myeloma Foundation

Treatment of relapsed MM is not a simple algorithm. Four principles that guide management regardless of treatment availability are:

1. Depth of response matters
2. Tailoring to risk status is important (high risk versus standard risk)
3. Balance efficacy and toxicity, with communication being critical and the 'art' of treatment
4. Overcome drug resistance by changing mechanisms of action

Treatment guidelines for RRMM were published by the IMWG in 2021.[1] Following the first relapse, patients are categorised as lenalidomide sensitive or lenalidomide refractory. The preferred options for lenalidomide sensitive patients are DRD or KRD, where available. The preferred options for lenalidomide refractory patients are PVD, DaraKD or IsaKD, where available.

Professor Mikhael's principles for early relapse MM are:

- Use mechanisms of action not previously used
- Do not continue lenalidomide if the patient is progressing on lenalidomide maintenance
- Triplets are preferred over doublets, where available

Four phase 3 studies have been published involving anti-CD38 triplet therapy, with all displaying significant patient benefit:

AOLLO – daratumumab + PD versus PD after ≥ 1 prior lines with lenalidomide and a proteasome inhibitor.[2] The latest results report a median PFS of 12 versus 7 months (HR = 0.63).

CANDOR - daratumumab + KD versus KD after 1-3 prior lines.[3] The latest results report a median PFS of 29 months versus 16 months (HR=0.59).

ICARIA-MM – isatuximab + PD versus PD after ≥ 2 prior lines with lenalidomide and a proteasome inhibitor.[4] The latest results report a median PFS2 of 18 months versus 13 months (HR=0.76)

IKEMA– isatuximab + KD versus KD after 1-3 prior lines with no prior carfilzomib.[5] The latest results report a median PFS NR vs 19 months (HR=0.53).

Selinexor and the BOSTON study

The BOSTON study compared selinexor + bortezomib and dexamethasone (XVD) to VD in patients with 1-3 prior lines.[6] This was the first study to administer selinexor once weekly. The bortezomib in the XVD arm was given weekly via subcutaneous injection, resulting in 40% less bortezomib and 37% fewer clinic visits in the first 6 months. There was an increase in median PFS of 4.47 months in the intervention arm, equating to a 30% reduction in the risk of disease progression or death.

Selinexor is an effective medicine in early disease, however, it requires care to avoid toxicity, particularly in the first month.[7,8]

Conclusions on early relapse:

- Do not continue to use maintenance agents
- Introduce a new mechanism of action
- Use a triplet combination
- Select best combination based on patient, disease and treatment characteristics
- There is no perfect sequence

Newer approaches to triple class refractory MM

When a MM patient becomes triple class refractory treatment options are selinexor (+/- bortezomib or other), belantamab mafodotin or CAR T-cell therapy.

Belantamab mafodotin is the first FDA approved BCMA targeted therapy for MM. The DREAMM-2 study of patients with ≥ 3 prior lines reported an ORR of 31% with 60% of patients achieving VGPR or better.[10] Belantamab mafodotin is generally well tolerated, however, reversible keratopathy is an issue for approximately 75% of patients that requires very careful attention.

Principles for treating resistant MM

Professor Mikhael's guiding principles for treating resistant MM are:

- As much as possible use combination therapy
- Patients with resistant disease need continuous therapy
- Introduce a new mechanism of action
- Possibly re-introduce agents if not "fully" resistant
- Beware of discordant disease, especially in late-stage, e.g. extramedullary disease divergent to serum markers may suggest the presence of separate clones
- Respect the biology of evolving disease as it may grow very rapidly
- Multi-modality monitoring of disease activity to detect discordant disease
- Short-term versus long-term strategies and patient-centred decision making

REFERENCES

1. Moreau P, et al. Treatment of relapsed and refractory multiple myeloma: recommendations from the International Myeloma Working Group. *Lancet Oncol.* 2021;22(3):e105-e118.
2. Dimopoulos MA, et al. Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial. *Lancet Oncol.* 2021;22(6):801-812.
3. Dimopoulos M, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study. *Lancet.* 2020;396(10245):186-197.
4. Attal M, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. *Lancet.* 2019;394(10214):2096-2107.
5. Moreau P, et al. Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial. *Lancet.* 2021;397(10292):2361-2371.
6. Grosicki S, et al. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. *Lancet.* 2020;396(10262):1563-1573. doi:10.1016/S0140-6736(20)32292-3
7. Nooka AK, et al. Guidance for Use and dosing of Selinexor in Multiple Myeloma in 2021: Consensus From International Myeloma Foundation Expert Roundtable. *Clin Lymphoma Myeloma Leuk.* 2022;22(7):e526-e531.
8. Mikhael J, et al. Consensus Recommendations for the Clinical Management of Patients With Multiple Myeloma Treated With Selinexor. *Clin Lymphoma Myeloma Leuk.* 2020;20(6):351-357.
9. Tai YT, Anderson KC. Targeting B-cell maturation antigen in multiple myeloma. *Immunotherapy.* 2015;7(11):1187-1199.
10. Lonial S, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. *Lancet Oncol.* 2020;21(2):207-221.

TAKING A BITE FOR THE MM CAR T JOURNEY

Presented by Professor Simon Harrison (Melbourne, Australia)

CAR T cell therapy is ideal for strongly and consistently expressed extracellular surface antigens such as BCMA. CARs contain an external targeting domain, a transmembrane domain that may influence CAR expression, and a co-stimulatory domain providing the signal for T cell activation.

Bi-specific antibody engagement

T cell activation occurs when a bi-specific antibody (BSA) binds the target and the CD3 domain of the T cell.[1,2] BSAs mediate synapse formation between the T cell and the tumour cell, upregulation of adhesion molecules, production of cytolytic proteins, cytokine release and proliferation of T cells.[3]

CAR T and BSAs can produce T cell-mediated toxicity, e.g. cytokine release syndrome (CRS), encephalopathy/immune effector cell-associated neurotoxicity syndrome (ICANS), haemophagocytosis, and rarely tumour lysis syndrome.[4] In general, CAR T cell therapy has a higher risk of toxicity due to T cell expansion, whereas BSAs wane over time.

Trial data

CARTITUDE-1 trialled CAR T cell therapy with two BCMA antibodies in RRMM with poor prognosis.[5] The results were unheard of with a 100% response rate and ciltacabtagene autoleucel was approved by the FDA in 2022. Almost all patients in CARTITUDE-1 (94.8%) experienced some degree of CRS. CARTITUDE-2 replicated this result in high risk MM with early relapse and reported a second response longer than the first, indicating that high-risk functional biology can be reversed.[6]

KarMMa also trialled BCMA-directed CAR T therapy in RRMM patients (idecabtagene vicleucel).[7] An MRD-negativity rate of 26% was reported and earlier treatment was associated with deeper responses. The FDA approved idecabtagene vicleucel as the first CAR T cell therapy in 2021.

A problem with CAR T cell therapy is the substantial delivery delays, therefore allogenic CAR T cell therapy is being trialled.[8]

Potential strategies to overcome mechanisms of CAR T cell therapy failure include:

- Poor T cell expansion - induce a stem cell memory-phenotype in the T cell.[9]
- Immunogenicity of CAR T cells - humanise the BCMA portion of the CAR.
- Toxicity - fractionated therapy with boosters, which may also induce good efficacy in extramedullary disease.[10]
- Tumour heterogeneity - dual targeting, e.g. anti-BCMA and either anti-CD19 or anti-CD38, with others in development
- Impaired T cell function - natural killer cells or macrophages for CAR therapy with BSA engagement.
- T cell infiltration -radiotherapy may make the tumour microenvironment more receptive.

N.B. The distribution of CAR T cells in MM is currently unknown and Professor Harrison's group is attempting to measure CAR T trafficking post-infusion in humans and its potential benefit in extramedullary disease.

Bi-specific antibodies

Harrison *et al* evaluated AMG 701, a bi-specific T cell engager binding BCMA on MM cells and CD3 on T cells.[11] The majority of CRS was Grade 1 or 2 and the ORR was 83% at the optimal dose with a substantial depth and durability of response. It appears patients with low levels of soluble BCMA respond well to this treatment. Multiple studies on other BSAs have reported consistently high response rates with CRS that is generally easy to control and relatively low neurotoxicity (**Table 1**).[12–15]

Non-BCMA MM targets

GPRC5D is a G protein receptor of unknown function and limited expression in healthy tissue, but high expression in myeloma cells and associated with poor prognostic factors.[16–18] MonumenTAL-1 is assessing this non-BCMA targeted therapy in highly refractory MM patients.[19] The Fc receptor-homolog 5 is targeted by the bi-specific antibody cevostamab.

Table 1: Safety and efficacy summary of BSAs in the RRMM patients. Adapted from Harrison (2022).

Drug	Target	Median prior lines, n	Dosing	ORR, %	Duration of response (months)	Prior BCMA, %	CRS, %	Neurotoxicity, %	Notes
Teclistamab[1] (n = 165)	BCMA	5 (2-14)	SC QW for RP2D	62 @ RP2D (n=150)	NR	Not allowed	71 .5 (0.6% grade 3/4)	12.7	SC dosing, Continue until PD
TNB-383B[2] (n = 118)	BCMA	5 (1-15)	Q3W	60 @ ≥40mg dose ESC and EXP cohort (n=60)	NR	Not allowed	54 (3% grade 3)	5	Q3W
REGN-5458[3] (n = 73)	BCMA	5 (2-17)	Q2W	51 among all enrolled 75 with higher doses	NR	Not allowed	38 (no grade 3)	4	Low rates of CRS
Pavurutamab/ AMG701[4] (n = 85)	BCMA	6 (2-25)	QW	83 @ most recent doses (n = 6)	3.8	Not allowed	65 (9% grade 3)	8	
Elranatamab[5] (n = 55)	BCMA	6 (2-15)	SC weekly	69 @ ≥1000 µg/kg dose	-	21.8	87.3 (no grade 3)	16	SC dosing
Talquetamab[6] (n = 55)	GPRC5D	6 (2-17)	RP2D 405 µg/kg SC QW or 800 µg/kg SC Q2W	70 at 450 µg/kg dose 66.7 at 800 µg/kg dose	NR	43	76.7 at 450 µg/kg dose (3% grade 3) 72 at 800 µg/kg dose (no grade 3)	-	SC dosing 43% of pts @RP2D had prior BCMA tx Some grade 3 skin and oral toxicity
Cevostamab[7] (n = 160)	FcRH5	6 (2-18)	Q3W	56.7 in higher target dose 36.1 in lower target dose	11.5	33.5	80.7 (1.2% grade 3)	14.3*	• 33.5% with prior BCMA tx • 17 cycles

NR – Not reached - Not reported

1. Moreau ASH 2021 Abstr 896 2. Kumar. ASH 2021. Abstr 900. 3. Zonder. ASH 2021. Abstr 160. 4. Harrison. ASH 2020. Abstr 181. 5. Sebag ASH 2021. Abstr 895 . 6. Krishnan ASH 2021. Abstr 158. 7. Trudel. ASH 2021. Abstr 157

N.B. Teclistamab has been approved by the EMA

TAKE-HOME MESSAGES:

- Car-T and BSA therapy for myeloma seems to be here to stay
- Managing toxicity will key to success given the population
- Atypical infections are an emerging problem, including reactivation of viruses[20]
- Studies now in earlier lines of therapy, novel combinations and CAR-T randomised against transplant
- Is there path to cure, at least in lower risk MM?

REFERENCES

1. Frankel SR, Baeuerle PA. Targeting T cells to tumor cells using bispecific antibodies. *Curr Opin Chem Biol.* 2013;17(3):385-392. doi:10.1016/j.cbpa.2013.03.029
2. Klinger M, et al. Immunopharmacologic response of patients with B-lineage acute lymphoblastic leukemia to continuous infusion of T cell-engaging CD19/CD3-bispecific BiTE antibody blinatumomab. *Blood.* 2012;119(26):6226-6233. doi:10.1182/blood-2012-01-400515
3. Bargou R, et al. Tumor regression in cancer patients by very low doses of a T cell-engaging antibody. *Science.* 2008;321(5891):974-977.
4. Neelapu SS, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nat Rev Clin Oncol.* 2018;15(1):47-62. doi:10.1038/nrclinonc.2017.148
5. Berdeja JG, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. *Lancet.* 2021;398(10297):314-324.
6. Agha M, et al. CARTITUDE-2, Cohort B: Updated Clinical Data and Biological Correlative Analyses of Ciltacabtagene Autoleucel, a BCMA-Directed CAR-T Cell Therapy, in Patients With Multiple Myeloma and Early Relapse After Initial Therapy: Functional High Risk. In: *EHA.* ; 2022.
7. Munshi NC, et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. *N Engl J Med.* 2021;384(8):705-716.
8. Mailankody S, et al. Universal: An Allogeneic First-in-Human Study of the Anti-Bcma ALLO-715 and the Anti-CD52 ALLO-647 in Relapsed/Refractory Multiple Myeloma. *Blood.* 2020;136(S1):24-25.
9. Blaeschke F, et al. Induction of a central memory and stem cell memory phenotype in functionally active CD4+ and CD8+ CAR T cells produced in an automated good manufacturing practice system for the treatment of CD19+ acute lymphoblastic leukemia. *Cancer Immunol Immunother.* 2018;67(7):1053-1066.
10. Fernandez de Larrea C., et al. Efficacy and safety of ARI0002H, an academic BCMA-directed CAR-T cell therapy with fractitionated initial therapy and booster dose in patietns with relapsed/refractory multiple myeloma. In: *EHA.* ; 2022.
11. Harrison J, et al. A Phase 1 First in Human (FIH) Study of AMG 701, an Anti-B-Cell Maturation Antigen (BCMA) Half-Life Extended (HLE) BiTE® (bispecific T-cell engager) Molecule, in Relapsed/Refractory (RR) Multiple Myeloma (MM). *Blood.* 2020;136(S1):28-29.
12. Moreau P, et al. Teclistamab in Relapsed or Refractory Multiple Myeloma. *N Engl J Med.* 2022;387(6):495-505.
13. NCT04108195. A Study of Subcutaneous Daratumumab Regimens in Combination With Bispecific T Cell Redirection Antibodies for the Treatment of Participants With Multiple Myeloma. Published 2019. https://www.clinicaltrials.gov/ct2/show/NCT04108195
14. Costa L, et al. First Clinical Study of the B-Cell Maturation Antigen (BCMA) 2+1 T Cell Engager (TCE) CC-93269 in Patients (Pts) with Relapsed/Refractory Multiple Myeloma (RRMM): Interim Results of a Phase 1 Multicenter Trial. 2019;134(S1):143.
15. Li J, et al. Membrane-Proximal Epitope Facilitates Efficient T Cell Synapse Formation by Anti-FcRH5/CD3 and Is a Requirement for Myeloma Cell Killing. *Cancer Cell.* 2017;31(3):383-395.
16. Smith EL, et al. GPRC5D is a target for the immunotherapy of multiple myeloma with rationally designed CAR T cells. *Sci Transl Med.* 2019;11(485):eaau7746. doi:10.1126/scitranslmed.aau7746
17. Pillarisetti K, et al. A T-cell-redirecting bispecific G-protein-coupled receptor class 5 member D x CD3 antibody to treat multiple myeloma. *Blood.* 2020;135(15):1232-1243. doi:10.1182/blood.2019003342
18. Atamaniuk J, et al. Overexpression of G protein-coupled receptor 5D in the bone marrow is associated with poor prognosis in patients with multiple myeloma. *Eur J Clin Invest.* 2012;42(9):953-960.
19. Hasselbalch C., et al. S180: RG6234, a novel GPRC5D T-cell engaging bispecific antibody, induces rapid responses in patients with relapsed/refractory multiple myeloma: preliminary results from a first-in-human trial. *HemaSphere.* 2022;6(1):81-82.
20. Longhitano AP, et al. Bispecific antibody therapy, its use and risks for infection: Bridging the knowledge gap. *Blood Rev.* 2021;49:100810.

AMYLOIDOSIS IN 2022: WHERE ARE WE NOW AND WHERE ARE WE GOING?

Presented by Dr Simon Gibbs (Melbourne, Australia)

Systemic A L amyloidosis is a multi-organ disease of monoclonal light chain proteins misfolding and depositing into tissues and organs, leading to their eventual failure if effective therapy is not introduced in a timely manner. Amyloidosis is poorly understood and can be challenging to diagnose and manage.

Over 35 proteins have the potential to cause systemic amyloidosis. The AL and ATTR (Transthyretin) are the most common types, accounting for approximately 95% of all cases of systemic disease. Clinical Practice Guidelines to assist with the diagnosis and management of AL amyloidosis are available here. Early diagnosis and treatment is associated with improved survival, although survival overall remains poor in patients with advanced cardiac disease at diagnosis, despite gains.[1]

Treatment

The objectives of AL treatment are to:

1. Reduce monoclonal immunoglobulin protein production
2. Tailor therapies to individual patients, accounting for organ involvement
3. Provide optimal supportive care

Staging of AL involves measuring the cardiac biomarkers NT proBNP and Troponin T, and determining the difference between the involved and uninvolved monoclonal serum free light chains (the "dFLC").[2] Patients who obtain a reduction of their dFLC to <40mg/L are labelled as achieving a VGPR. A VGPR or better is associated with a relatively good survival compared to patients with <50% response.

ASCT results in excellent outcomes for eligible AL patients, although toxicity is a significant issue and thus, only 20% are eligible.[3]

There are now multiple options to reduce monoclonal immunoglobulin production. A management algorithm is shown in **Figure 1**. The criteria defining organ responses are in the AL Management Guidelines.[4]

Adding bortezomib to melphalan and dexamethasone resulted in a significant survival benefit for AL patients.[5] Melphalan and dexamethasone is, however, still a good treatment option where a significant neuropathy is present at diagnosis.

Daratumumab produces a deep and rapid haematological response and remains an effective treatment for relapsed disease, with a 2-year survival rate of 74% after a median 26 months of follow-up.[6] AL patients who respond to daratumumab are likely to do so in the first month of treatment.

The ANDROMEDA trial was a game-changer. Patients were randomised to bortezomib, cyclophosphamide, and dexamethasone (VCD) either alone or with subcutaneous daratumumab followed by single-agent monthly daratumumab maintenance.[7] Daratumumab tripled and quickened the CR rate and doubled the cardiac and renal response rates compared to VCD alone.[7]

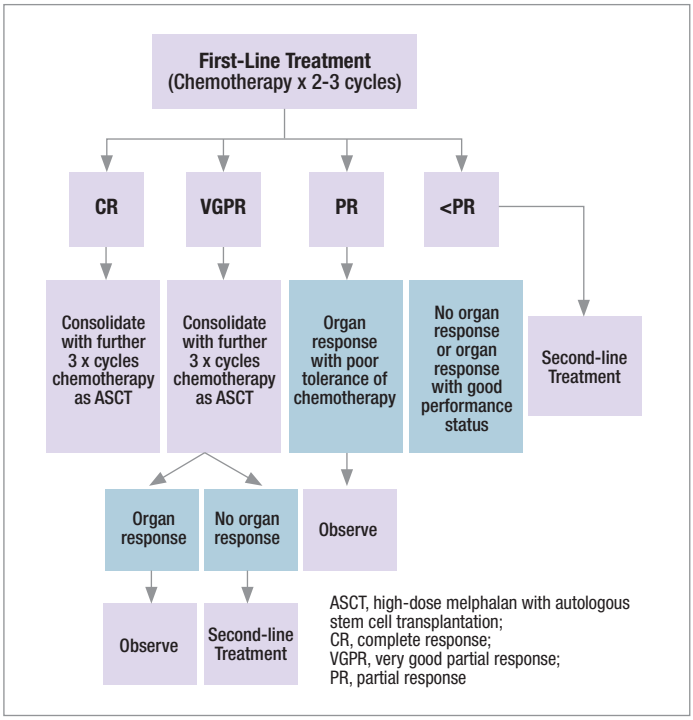


Figure 1: Treatment algorithm for AL amyloidosis. Adapted from Gibbs (2022).[4]

Additional AL amyloidosis treatment considerations:

- VRD is effective, however, toxicity is significant.[8] This regimen is not recommended due to poor tolerance of lenalidomide.
- Bortezomib-based regimens have slightly poorer outcomes in patients with t(11;14) and this translocation is present in up to 50% of AL patients.[9]
- Isatuximab, pomadlidomide and dexamethasone is a second line option for patients that have not achieved VGPR that is being assessed in the ALLG/IFM PISA MM24 study.
- Doxycycline 100 mg twice daily may disrupt fibril formation and can be added to chemotherapy regimens for AL amyloidosis. The impact of doxycycline on patient survival remains unclear.
- The VITAL study assessed VCD + birtamimab or placebo and was terminated due to futility. However, *post hoc* analysis detected a potential benefit for advanced cardiac AL patients and a trial testing this hypothesis is ongoing.
- CAEL-101 is a monoclonal antibody that has produced impressive and rapid cardiac biomarker responses in early phase trials and is now the subject of an upfront treatment trial with VCD +/- daratumumab (trial CAEL-301/302).[10]

Supportive care

Supportive care is essential and needs to improve for AL patients. Dr Gibbs recommends cutting dexamethasone by 50-75% in patients who have achieved a VGPR or better.

A 'low or no' salt diet with fluid restriction and gentle exercise is recommended for HF patients. Patient information is available here. Dr Gibbs recommends loop diuretics and notes that spironolactone appears to work well in synergy with these agents.

Albumin infusions are helpful for refractory nephrotic syndrome with severe oedema. Withdrawal of beta-blockers and ACE inhibitors/ ARBs should be considered if AF is absent and HFpEF has been diagnosed. Cardiac rehabilitation programmes are recommended.

Dr Gibbs strongly recommends domperidone to treat poor appetite and weight loss and he normally prescribes a PPI. Postural hypotension can be challenging. Beta-blocker withdrawal and prescribing maximum dose midodrine can be beneficial, alongside albumin infusions.

Practical resources are available from www.amyloidosis.net.au. This group holds monthly, multidisciplinary online clinical meetings, advocates for treatment funding and is a hub for clinical trials.

CONCLUSIONS AND FUTURE AIMS

- AL amyloidosis remains the poor cousin
  - Diagnosed late, poorly researched, no funded drugs – but it's improving
- VCD +/- dara upfront treatment for AL (not RVD)
- Monitor NT proBNP every 6 months to determine cardiac organ responses
- Early mortality remains significant in those with advanced cardiac disease
  - If no VGPR by end of cycle 3, change therapy
  - ASCT is used in 20% of patients
- Daratumumab is well tolerated, excellent rescue Rx
- Plenty of trials – MAbs, BCL-2 inhibitors, BITES
- Supportive care is vital and often neglected
- Always remember domperidone and midodrine - these are under-used and can be very beneficial

REFERENCES

1. Wisniowski B, et al. The epidemiology of amyloidosis in Queensland, Australia. *Br J Haematol.* 2019;186(6):829-836.
2. Kumar S, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. *J Clin Oncol.* 2012;30(9):989-995.
3. Sidiqi MH, et al. Stem Cell Transplantation for Light Chain Amyloidosis: Decreased Early Mortality Over Time. *J Clin Oncol.* 2018;36(13):1323-1329.
4. Gibbs S, Mollee P. Clinical Practice Guideline Systemic AL Amyloidosis. Published online 2019. https://myeloma.org.au/wp-content/uploads/2019/10/MSAG_ATG_oct19.pdf
5. Kastritis E, et al. Bortezomib, Melphalan, and Dexamethasone for Light-Chain Amyloidosis. *J Clin Oncol.* 2020;38(28):3252-3260.
6. Roussel M, et al. A prospective phase 2 trial of daratumumab in patients with previously treated systemic light-chain amyloidosis. *Blood.* 2020;135(18):1531-1540.
7. Kastritis E. Daratumumab-Based Treatment for Immunoglobulin Light-Chain Amyloidosis. *N Eng J Med.* 2021;385(1):46-58.
8. Kastritis E. Primary treatment of light-chain amyloidosis with bortezomib, lenalidomide, and dexamethasone. *Blood Adv.* 2019;3(20):3002-3009.
9. Bochtler T, et al. Translocation t(11;14) is associated with adverse outcome in patients with newly diagnosed AL amyloidosis when treated with bortezomib-based regimens. *J Clin Oncol.* 2015;33(12):1371-1378.
10. Edwards CV, et al. Phase 1a/b study of monoclonal antibody CAEL-101 (11-1F4) in patients with AL amyloidosis. *Blood.* 2021;138(25):2632-2641.