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Multiple Myeloma Summit 2020

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In this review:

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ABOUT EXPERT FORUMS
Expert Forum publications are designed to encapsulate the essence of a local meeting of health professionals who have a keen interest in a condition or disease state.

In November, myeloma experts convened in person and online in Queenstown for the Myeloma New Zealand 2020 Myeloma Summit. This year's meeting included presentations from local and international experts in myeloma, including the keynote speakers Professor Graham Jackson from England and Associate Professor Peter Mollee from Australia. Highlights of the meeting have been summarised with unconditional funding from Celgene and Janssen.

MAINTENANCE APPROACHES IN MULTIPLE MYELOMA

Presented by Graham Jackson, Professor of Haematology at Newcastle University, UK

The goals of maintenance treatment in MM patients are to:

- Significantly prolong PFS, PFS2 and OS without a negative effect on treatment at relapse
- Be safe and well tolerated with minimal adverse effects
- Have minimal or no negative impact on QoL, particularly at first remission

Maintenance treatment in TEMM

The benefit of lenalidomide maintenance treatment following ASCT was demonstrated in a meta-analysis of 3 studies that showed an approximate 30 month improvement in PFS (HR, 0.48; 95% CI, 0.41 to 0.55).[1] Maintenance with lenalidomide also shows an approximate 2.5 year improvement in median survival.[1] It was uncertain, however, if patients with adverse cytogenetic factors would benefit to the same extent.

The Myeloma XI trial showed that lenalidomide maintenance treatment was associated with a 27 month improvement in PFS in all patients (HR=0.48).[2] It was also demonstrated that both MRD positive and MRD negative and patients with high risk cytogenetics benefited from lenalidomide maintenance.[2]

The STaMINA trial showed that discontinuation of lenalidomide maintenance was associated with inferior PFS (79.5% vs. 61% at 5yr; HR = 1.91, p = 0.0004) but similar OS.[3] The effectiveness of lenalidomide maintenance treatment has also been demonstrated in "real-world" population studies.[4]

Maintenance treatment with ixazomib is a new treatment option following ASCT. The TOURMALINE-MM3 study showed a significant 39% improvement in PFS from time to randomisation for patients receiving ixazomib versus placebo (HR: 0.72; 95% CI: 0.582–0.890, p=0.002), although improvements in OS are yet to be established.[5]

There is some early evidence that daratumumab may be effective in maintenance treatment. The CASSIOPEIA trial demonstrated that daratumumab before and after ASCT was associated with improved PFS.[6]

TAKE-HOME MESSAGES FOR TEMM

- In newly diagnosed TEMM both lenalidomide and ixazomib have been shown to prolong PFS in placebo-controlled trials
- Lenalidomide maintenance has been clearly shown to prolong overall survival.
- In TEMM bortezomib has been shown to be superior to thalidomide particularly in high risk patients
- Ixazomib and lenalidomide maintenance benefits patients who are both MRD negative and MRD positive

Abbreviations used in this review

ADL = activities of daily living
ALT = alanine aminotransferase
ASCT = autologous stem cell transplant
AST = aspartate aminotransferase
ATTRwt = wild type transthyretin
AL = immunoglobulin light chain
BCMA = B-cell maturation antigen
CAR = chimeric antigen receptor
CCI = Charlson co-morbidity index
CR = complete response
CRES = CAR T-cell encephalopathy syndrome
CRS = cytokine-release syndrome
DLCO = diffusion capacity of carbon monoxide
FEV1 = forced expiratory volume in 1 second
FISH = fluorescence *in situ* hybridisation
IADL = instrumental ADL
ISS/R-ISS = (Revised) International Staging System
LVEF = left ventricular ejection fraction
MM = multiple myeloma
MRD = minimal residual disease
MGUS = monoclonal gammopathy of unknown significance
ORR = overall response rate
OS = overall survival
PFS = progression-free survival
PI = proteasome inhibitor
RRMM = relapsed/refractory multiple myeloma
SCT = stem-cell transplantation
TEMM = transplant-eligible multiple myeloma
TNEMM = transplant-non-eligible multiple

Drug regimens

Dara-Rd = daratumumab, lenalidomide, dexamethasone
Dara-VMP = daratumumab, bortezomib, melphalan, prednisone
BP = bisphosphonate
CyBorD = cyclophosphamide, bortezomib, dexamethasone
KCD = carfilzomib, cyclophosphamide, dexamethasone
KIWI = kyprolis (carfilzomib) based induction in untreated myeloma with kyprolis post-transplant consolidation
MEL = Melphalan
RANKL = receptor activator of nuclear factor kappa-B ligand
Rd = lenalidomide, dexamethasone
Rd-R = Rd followed by lenalidomide maintenance
RVD = lenalidomide, bortezomib, dexamethasone
VCD = bortezomib, cyclophosphamide, dexamethasone
Vd = bortezomib, dexamethasone
VMP = bortezomib, melphalan, prednisone
VTD = bortezomib, thalidomide, dexamethasone
VRd = bortezomib, lenalidomide, dexamethasone

Maintenance therapy for TNEMM

The FIRST trial showed continuous treatment with lenalidomide and low-dose dexamethasone improved survival outcomes versus melphalan, prednisone, and thalidomide in patients with transplant-ineligible NDMM.[7]

The SWOG study was not specifically conducted in older patients (median age 63 years), but it did demonstrate that the addition of bortezomib to lenalidomide and dexamethasone resulted in significantly improved PFS and OS.[8]

The TOURMALINE-MM4 trial showed that maintenance treatment with the proteasome inhibitor ixazomib in older patients was associated with an 8 month increase in PFS.[9]

Daratumumab for induction and maintenance treatment may be important for older patients. The ALCYONE study showed that daratumumab in combination with bortezomib, melphalan, and prednisone prolonged OS in NDMM, compared to bortezomib, melphalan and prednisone alone.[10] The MAIA study demonstrated that continuous treatment with daratumumab was associated with a 44% reduction in the risk of progression or death after 30 months, compared to lenalidomide and dexamethasone alone.[7] The MAIA regimen may be the treatment of choice for older patients, where it is available.

TAKE-HOME MESSAGES FOR TNEMM

- In newly diagnosed TNEMM both lenalidomide and ixazomib have been shown to prolong PFS in controlled trials
- Maintenance has NOT yet been clearly shown to prolong overall survival.
- Daratumumab based induction with daratumumab based maintenance strategies are achieving very impressive responses, PFS and OS data

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BONE DISEASE IN MYELOMA

Presented by Nicole Chien, Haematologist from Auckland

Bone disease causes a significant impact in QoL for patients with MM. Current pharmacological treatments are 2nd generation BP or RANKL inhibitors, however, both classes are associated with ONJ and renal toxicity.

2nd Generation BP appear equally effective

A meta-analysis (24 RCTs, 7293 participants) found that ZA was not superior to other 2nd generation BP for MM treatment.[1]

Survival is improved with 2nd generation BP

Myeloma IX found that compared to the 1st generation BP clodronate, ZA significantly reduced SRE (35% vs 27%) in all patients with MM, not only those with bone lesions.[2] Survival increased by 5.5. months with ZA, compared to clodronate.[2]

The frequency and duration of treatment requires further study

Later, Dr Chien highlighted that current evidence on duration and frequency of treatment is limited and guidelines suggest using baseline bone disease burden and patient response to determine BP treatment duration and frequency.[3,4,5]

One-month versus three-month ZA dosing was investigated in 1822 patients (metastatic breast or prostate cancer or MM) and ≥ 1 bone lesion over two years.[6] The SRE rate was 29.5% with monthly infusions, versus 28.6% for 3-monthly infusions, with no differences in pain scores, ONJ or renal dysfunction.[6] Dr Chien noted the shortcoming of this trial including short follow up time and high drop out rate of around 30%.

ZMARK showed BP treatment can potentially be individualised using bone turnover biomarkers such as uNTX. Patients with high bone turnover received monthly ZA and those with low turnover three-monthly ZA. Overall, incidence of SRE was low at 5.8% and 4.8% after year 1 and 2 respectively.[7]

Denosumab is not inferior to zoledronic acid

The safety and effectiveness of the RANKL inhibitor denosumab (4-weekly, SC) compared to ZA (4-weekly, IV) was investigated in 1,702 patients. There was no difference in time to first SRE or survival.[8] Dr Chien reported, however, that post hoc analysis at 15 months showed denosumab was slightly superior. Denosumab caused less renal toxicity than ZA (10% vs 17%), but more hypocalcemia (17% vs 12%).[8] The rate of ONJ was similar (4% vs 3%).[8]

The role of vertebral cement augmentation

There is no evidence that vertebroplasty or kyphoplasty is superior for patients with symptomatic bone disease,[9] although Dr Chien noted that kyphoplasty may be less expensive. Guidelines recommend vertebral cement augmentation for patients with pain that has not resolved after 4-8 weeks of treatment.[10] Dr Chien noted that it is important to ensure the pain is related to vertebral fracture on imaging.

TAKE-HOME MESSAGES

- Bone disease is an important issue in MM
- BP and RANKL inhibitors reduce SRE but are associated with ONJ and renal toxicity
- There is no difference between 2nd generation BPs
- Frequency and duration of BP treatment requires further investigation
- Denosumab is non-inferior to ZA
- There is a possible improved survival benefit associated with BP or RANKL inhibitors

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MANAGING ELDERLY MYELOMA

Presented Dr Huib Buyck, Haematologist from Wellington

MM predominately occurs in older people. New Zealand has an ageing population therefore the burden of MM will continue to increase over time.

Survival outcomes in older patients with MM

Survival rates in MM patients aged < 75 years have improved, however, the same improvements have not occurred in patients aged > 75 years.[1] This is mainly due to increased treatment toxicity, use of fewer novel therapies and higher rates of treatment discontinuation. Adapting treatments to older patients to maximise the benefit is a challenge for haematologists.

"Stage the ageing"

Neither functional dependence nor co-morbidity number alone are necessarily a good measure of frailty. Guidelines recommend that older patients receiving chemotherapy receive a thorough assessment including function, co-morbidity, falls, depression, cognition and nutrition.[2]

The IMWG assessment score (**Figure 1**) was created from a prospective evaluation of pooled data including (median age 74 years and 46% over age 75 years).[3] Patients were classified as fit, intermediate-frail or frail.[3]

The R-MCI is based on a German registry with 801 patients (1997-2012). This patient cohort has a median age of 63 years and 13% > age 75 years.[4] 13 co-morbidities were assessed and patients stratified onto fit, intermediate or frail.

Online calculators are available for assessing older patients with MM and other versions are available. Dr Buyck reported that the IMWG online tool was cumbersome and the R-CMI was easier to use.

Start low and go slow

In older patients, start with a low dose and increase this depending on patient tolerability. Strategies to prevent complications include prophylactic antibiotics, e.g. co-trimoxazole, quinolones, prophylactic immunoglobulins (expensive), vaccinations and VTE prophylaxis.

Treatment modifications in older patients

EMN guidelines recommend assessing older MM patients with IMWG or R-CMI:[5]

- For fit elderly patients full-dose triplet therapy should be the goal, i.e. the same < 65 years
- Intermediate fit full-dose doublet or reduced dose triplet
- Frail reduced dose doublet or other appropriate treatment

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Selecting treatment options

Lenalidomide plus low-dose dexamethasone (Rd) improves PFS compared to melphalan and prednisone and is an oral treatment that can be taken at home.[7] Rd is also associated with improved QoL compared to melphalan.

In transplant-ineligble MM patients with median age of 72 years lenalidomide-bortezomib-dexamethasone (RVD lite) was associated with relatively good PFS and low rates of discontinuation and neuropathy.[8]

ASCT in older patients

There is real-life data showing the safety and efficacy of ASCT in MM patients aged > 70 years.[9] Clinicians need to be aware, however, of the increased risk of complications in this patient group.

TAKE-HOME MESSAGES

- We are facing a tsunami of elderly MM patients
- Older patients do benefit from newer therapy
- Treatment discontinuation and reductions affect PFS and OS, therefore administration needs to ensure tolerability
- Consider using Frailty Calculators
- Start Low and Go Slow
- Do not discount autologous transplantation in the fit older patient
- Newer therapies may allow orally or more tolerable acceptable options for less fit older patients
- Clinical trials incorporating frailty scores required

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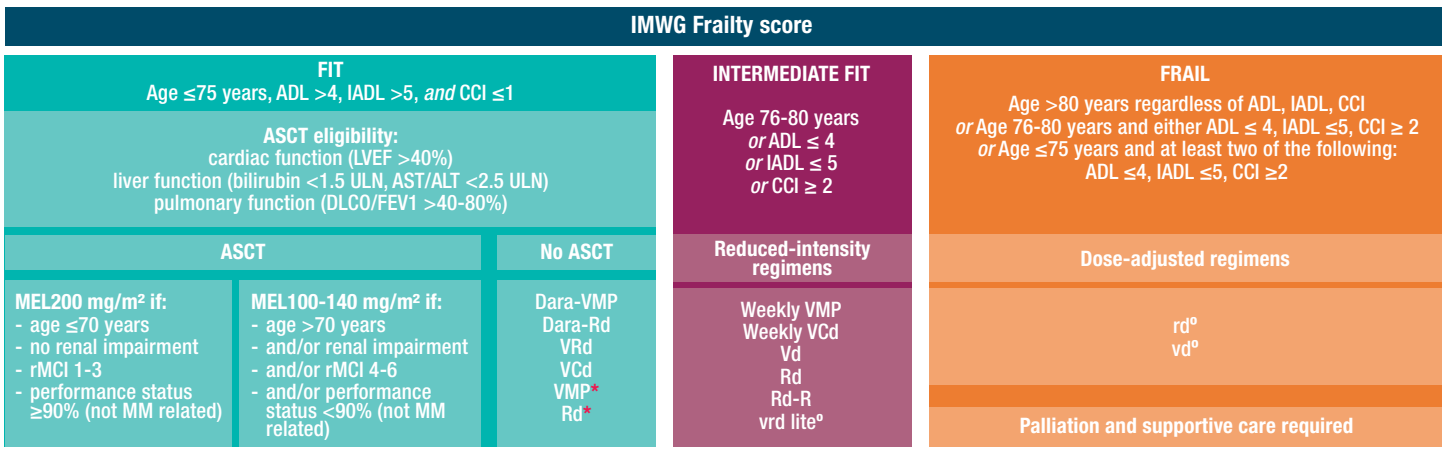

*If daratumumab-based combinations or VRd are unavailable; (o) Lower case indicates a reduced dose

Figure 1: Approach to the older patient with MM, adapted from Mina et al (2019)[6]

AMYLOIDOSIS

Presented by Peter Mollee, Associate Professor at Queensland University.

ATTRwt and AL amyloidosis are the most common types of amyloidosis. Prior to the recent upsurge in diagnosis of ATTRwt amyloidosis, the incidence of amyloidosis in Australia was approximately 12.2 cases per million person years. Survival is generally poor, particularly for those with AL amyloidosis. ATTRwt amyloidosis, however, is much more common that AL amyloidosis. An autopsy study of 109 patients with heart failure with preserved ejection fraction found significant amyloidosis in 5% of cases suggesting that ATTRwt is under diagnosed[1]

Diagnostic modalities for cardiac amyloidosis

Serum troponin T (or I) and NT-proBNP (or BNP) are critical in the staging of AL amyloidosis and NT-proBNP is used, along with creatinine, to stage ATTRwt amyloidosis.

Strain imaging on echocardiography improves the sensitivity of echocardiography for detecting cardiac involvement. Cardiac MRI provides more accurate assessments than echocardiography. Cardiac MRI allows myocardial tissue to be characterised and can be used to monitor cardiac involvement. Bone scintigraphy is useful for diagnosing ATTR amyloidosis without the need for a biopsy (see below). Alzheimer's disease imaging agents can detect cardiac amyloidosis but may not be useful for whole-body assessments.

Diagnostic issues

Clinicians were reminded of the following pitfalls when diagnosing amyloidosis:

- Immunohistochemistry with commercial antibodies cannot reliably identify the type of amyloid present in biopsy samples
- A plasma cell dyscrasia in combination with amyloid on biopsy does not necessarily mean the patient has AL amyloidosis
- Positive cardiac uptake on bone scintigraphy does not necessarily equate to ATTR amyloidosis
- A lack of a family history does not exclude hereditary amyloidosis

Tandem mass spectrometry is an emerging diagnostic tool[2] Cardiac ATTRwt amyloidosis is always positive on bone scintigraphy, however, 20-25% of patients with AL amyloidosis will also be positive. Diagnostic criteria have been published for the non-biopsy diagnosis of ATTR amyloidosis using bone scintigraphy and a screen for monoclonal gammopathy.[3]

Treatment advances in AL amyloidosis

The principles of AL amyloidosis treatment are to:

- Reduce monoclonal protein production profoundly and quickly
- Tailor therapy to the individual patient
- Provide organ-specific supportive care

The addition of bortezomib to oral melphalan and dexamethasone resulted in a 28% absolute improvement in OS at 4 years in patients with AL amyloidosis.[4] In a retrospective study of 915 patients newly diagnosed with AL amyloidosis and treated with bortezomib, the median OS was 72 months, which compares favourably to other studies.[5]

Australian guidelines recommend bortezomib, cyclophosphamide, and dexamethasone for most (but not all) patients with AL amyloidosis.[6] Treatment should be assessed after 2 or 3 cycles to determine haematological response and assess whether to continue with the current therapy or to change to an alternate treatment. The general approach is referred to as response adapted therapy where treatment is delivered according to haematological and organ response.

Early data from the ANDROMEDA trial in AL amyloidosis patients indicates that the addition of daratumumab to cyclophosphamide, bortezomib and dexamethasone results in improved response rates (≥ VGPR improves from approximately 50% to 80%), with a faster time to response.[7] Cardiac and renal organ response is also significantly better.

Treatment advances in ATTR amyloidosis

The anti-sense oligonucleotide (Inotersen) and the RNA inhibitors (Patisiran and Revusiran) reduce ATTR production by 80-90%. Inotersen and Patisiran improved the manifestations and quality of life of patients with hereditary ATTR.[8,9] TTR stabilisers include diflunisal, tafamidis and AG10. Tafamidis has been shown to reduce all-cause mortality and CV-related hospitalisations in a clinical trial by slowing the course of the disease.[10]

TAKE-HOME MESSAGES

A new era in the treatment of amyloidosis has arrived due to:

- Increased awareness, especially regarding cardiac ATTRwt
- Diagnostic advances: tandem mass spectrometry, non-invasive bone scintigraphy and CMR imaging
- Many novel therapies to reduce amyloid protein production, however, it is important to distinguish between subtypes
- Antibody therapies to enhance amyloid clearance under investigation
- The high cost of medicines is a challenge

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MULTIPLE MYELOMA RESEARCH REVIEW

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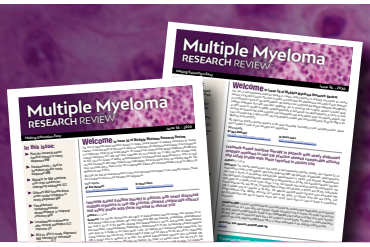

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MULTIPLE MYELOMA IN POLYNESIANS – INTERIM REPORT

Presented by Hilary Blacklock, Associate Professor at Auckland University

Unpublished data suggests that Polynesian people develop MM at a younger age than non-Māori or non-Polynesian people. It has also been reported that the annual, age-standardised incidence of MM per 100,000 people in NZ Māori (8.4 for males, 7.8 for females) is second only to the incidence in African Americans and substantially lower than in many Asian populations.[1] The median OS for MM patients in New Zealand over the past 20 years, however, has been 30.7 months for Europeans, 29.1 months for NZ Māori and 40.2 months for Polynesians.[2] It is known that Polynesian people in NZ have poorer health outcomes than people of other ethnicities in New Zealand.[3]

Data from the Australian and New Zealand Myeloma and Related Diseases Registry

This study aimed to assess whether Polynesians with MM also have poorer health outcomes than people of other ethnicities with MM in New Zealand.

Ethnicity was determined by asking participants to record the ethnicity of their 4 grandparents; patients with ≥ 1 Polynesian grandparent were classified as Polynesian. Data was collected from 442 MM patients on the MRDR (Sep, 2012 –Sep, 2019) with analysis identifying 90 Polynesians (84 still to be completed) and 268 non-Polynesians (89% European). **Table 1** presents the differences.

Table 1: Statistically significant differences in characteristics between non-Polynesian and Polynesian patients with MM from the MRDR

Clinical feature	Non-Polynesian (n=268)	Polynesian (n=90)	P value
Median age at diagnosis	70 years	63 years	0.001
ECOG (2 to 4)	17%	32%	0.006
Renal insufficiency*	6%	14.4%	0.010
Median BMI	27	32	0.001
Diabetes requiring medication	6.3%	22.2%	0.001
Median lambda free light chains (mg/L)	13	36	0.003

* Renal insufficiency = serum creatinine>177µmol/L or eGFR<40ml/min

Karyotype abnormalities at diagnosis were present in 22% of non-Polynesians (3.1% for deletion 13q) and 40% for Polynesians (9.6% for deletion 13q, p=0.037).

Treatment differences between Polynesians and non-Polynesians

Significantly fewer Polynesians (86%) commenced first-line chemotherapy because of significant co-morbidities or declining therapy, they were unable to or elected not to, compared to non-Polynesians (93%, p=0.024). The number of Polynesians aged under 70 years who were accepted for, or agreed to, ASCT was 55%, compared to 66% for non-Polynesians (p=0.71).

OS was lower in Polynesians after adjusting for age and treatment

The raw data showed a trend towards shorter OS for Polynesians (51 months) versus non-Polynesians (69 months, HR: 1.44, p=0.10). This trend became statistically significant after adjusting for age (HR: 1.94, p=0.001) and after adjusting for age and not receiving chemotherapy (HR: 1.64, p=0.03).

TAKE-HOME MESSAGES

Compared to non-Polynesians, Polynesians with MM in New Zealand:

- Are younger
- Have more co-morbidities
- Have more adverse MM karyotypes at diagnosis
- Have a significantly shorter OS after adjusting for age and receiving chemotherapy

Further investigation is required to improve outcomes for Polynesians with MM and to elucidate the reasons why Polynesians develop MM at a younger age, and to improve outcomes for NZ Māori and Polynesians with MM.

N.B. This data is an interim assessment of patients enrolled on the MMDR and will be updated.

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SMOULDERING MULTIPLE MYELOMA

Presented by Ken Romeril, Wellington Haematologist and Summit Convenor

In patients with MGUS, adverse markers can be used to assess risk of progression to MM, i.e. the presence of IgA, an M-spike concentration ≥ 1.5 g/dL, sFLC ratio > 10 and immunoparesis.[1] Genomics can also be used to predict progression via the detection of aneuploidy chromosomal abnormalities or an Myc translocation.[2] It is important, however, to realise that progression risk is not constant and patients can convert from low-risk to high-risk over time.[1]

Patients with a low-risk MGUS signature may progress

It was highlighted that approximately 10% of MGUS cases will show a low-risk immune marker signature prior to progression to MM, including within the year prior to progression.[1] Furthermore, only 20% of MGUS cases that did progress fulfilled the criteria for SMM in bloodwork prior to myeloma onset.[1] Evidence also suggests that the majority of patients with SMM will eventually progress to MM.[3]

Defining SMM

The definition of SMM was updated by the IMWG in 2014:[4]

- Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60%; AND
- Absence of myeloma defining events or amyloidosis

A new risk stratification method has been developed with the IMWG criteria for SMM. Multivariable analysis of 1996 patients identified three independent factors predicting progression risk at 2 years:[5]

- M protein> 20
- Plasma cells > 20%
- sFLC ratio > 20

The inclusion of cytogenetic abnormalities allowed patients to be separated into four tiers of progression risk.[5]

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Risk assessment determines SMM management

A proposed management algorithm based on international best practice is provided in **Figure 2**.[6] If MM is present, systemic treatment is indicated. If the patient is assessed as high-risk SMM, treatment is also indicated, while low-risk patients undergo close observation. Dr Romeril noted that access to funded lenalidomide in New Zealand was a problem and treatment options may be limited. Later in the presentation bortezomib and thalidomide were identified as treatment options, depending on the patient's transplant eligibility.

Management of smoldering multiple myeloma

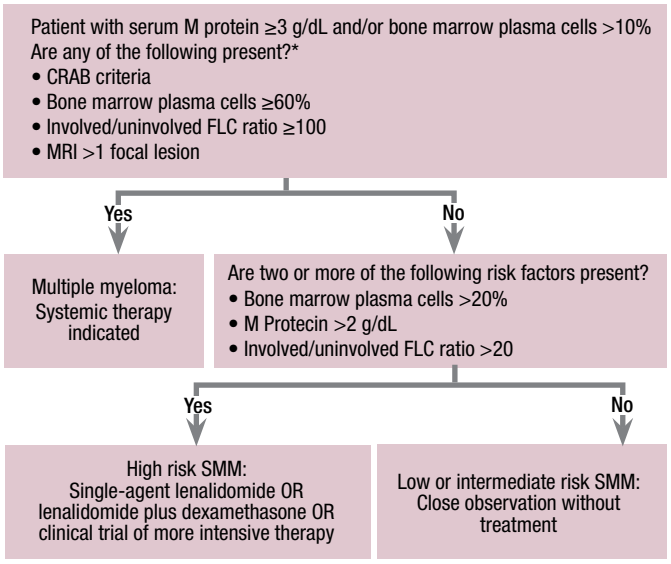

Figure 2: Smouldering myeloma risk stratification and management algorithm, adapted from Rajkumar S V, (2020)

TAKE-HOME MESSAGES FOR STAGING SMM

- An MRI is mandatory to assess for focal lesions
- Need to perform bone marrow plasma counts and FISH studies
- Assess sFLC to determine if the ratio of involved to uninvolved FLC ratio is > 20

The importance of FISH studies was emphasised as they provide important prognostic information. Comments from the audience confirmed that access to MRI was variable across the country, in which case a low-dose CT scan could be useful in staging SMM cases.

The case for early treatment

Landgren believes that the majority of patients with SMM should receive treatment because the majority of them will progress to MM. It is also likely that genetic tests will allow patients with ongoing processes who are acquiring driver mutations to be identified and treated earlier.

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CAR-T UPDATE IN MYELOMA

Presented by Rob Weinkove, Haematologist from Wellington

Plasma cells specifically express BCMA and expression is slightly higher in malignant plasma cells. In myeloma, BCMA promotes cell growth, chemotherapy resistance and immunosuppression. BCMA is now widely established as a target for myeloma immunotherapy and is the target antigen for the three leading 2nd generation CAR-T constructs (Idecabtagene Vicleucel, Ciltacabtagene Autoleucel and Ovacabtagene Autoleucel). All three anti-BCMA CAR-T therapies show very high (80-100%) overall response rates, with 40-80% complete response rates, frequently accompanied by MRD negativity, and toxicity appears acceptable. Patients who are chemorefractory and those with high-risk cytogenetics have responded equally well.

Durability of response to CAR T-cells is uncertain

The durability of response is a limiting factor for current CAR-T therapies for myeloma, alongside cost and the complex logistics of treatment. However, long-term follow-up is limited, and as positive dose-response relationships have been demonstrated, especially at higher dose levels, it is possible that some recipients will experience long-term PFS.

Improving durability of CAR-T cell response in myeloma

Two key issues being investigated to improve the durability of CAR-T cell responses are:

1. Would targeting other myeloma-associated antigens improve efficacy, i.e. is solely targeting BCMA the best approach?
2. Can other approaches enhance CAR T-cell activity, e.g. alternative costimulatory domains or cytokine-producing CAR T-cells?

We are already beginning to see results of early-phase trials of CAR T-cells that combine BCMA targeting with targeting of another antigen, e.g. CD19. This approach might help to eliminate a putative BCMA-negative myeloma stem cell population, and could help prevent relapse after CAR T-cell therapy. There are various approaches to combining CAR T-cell targets, e.g. tandem CARs, bicistronic CARs and dual CARs.[1]

3rd generation CAR-T cell therapies

Currently licensed CAR T-cell therapies are '2nd generation', and incorporate a single costimulatory domain inside the CAR. '3rd generation' CAR-T cells combining two co-stimulatory domains to improve the functionality of the CAR T cell. For example, a small trial in patients with relapsed or refractory non-Hodgkin's lymphoma found that after simultaneous infusion of 2nd and 3rd generation CAR-T cells, expansion of the 3rd generation cells was superior (**Figure 3**).[1] Expansion of CAR-T cells is considered important, because it is associated with increased response rates.[2]

A CAR-T clinical trial in New Zealand

Dr Weinkove's group initiated a phase 1 clinical trial of a new 3rd generation anti-CD19 CAR-T cell incorporating a TLR2 co-stimulatory domain in late 2019.[3*] These CAR-T cells, manufactured in a GMP facility at the Malaghan Institute, specifically kill CD19 positive targets *in vitro*. Patients remain on the ward for two weeks after administration followed by daily review for a week, to monitor for cytokine release syndrome and neurotoxicity. Preliminary data experience from five participants suggests that the CAR-T cells can expand well, and no dose limiting toxicities have been observed. It is too early to assess safety and efficacy.

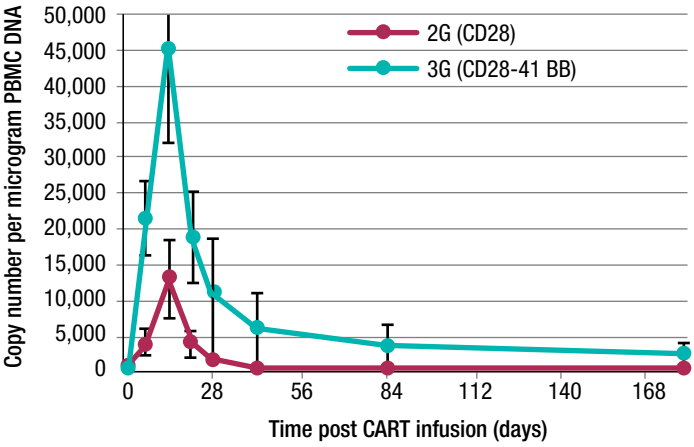

Figure 3: An additional co-stimulatory domain to enhance CAR T-cell expansion & activity, adapted from Mikkilineni and Kochenderfer (2020)[1]

FUTURE CHALLENGES AND OPPORTUNITIES

- Improved feasibility and reduced cost of manufacturing, e.g. through automation, and potentially through 'off-the-shelf' products
- Improve response rates and lower relapse rates, e.g. through dual-specificity constructs, via additional co-stimulatory domains, or other CAR modifications for enhanced
- Enhance safety, e.g. site preparation and training, infection prevention, developing new "off-switches"
- Early ENABLE trial experience indicates that it is feasible to deliver CAR T-cell therapies in New Zealand

*Not all the material included in Dr Weinkove's presentation is covered in this summary.

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CARFILZOMIB RELATED TOXICITIES

Presented by Dr Rajeev Rajagopal, Haematologist from Auckland

Carfilzomib is not funded in New Zealand, but it is registered for patients with RRMM who have received at least 1 prior treatment, in combination with lenalidomide/dexamethasone or dexamethasone. The optimal dose of carfilzomib is yet to be established.

Clinical trials of carfilzomib in patients with MM

The evidence supporting the use of carfilzomib is for RRMM patients only. ENDEVAOUR compared carfilzomib (56 mg/m2, twice weekly) + dexamethasone, versus bortezomib (1.3 mg/m2) + dexamethasone.[1] The median PSF in the carfilzomib group (n=464) was 18.7 months (95% CI 15.6-NE), compared to 9.4 months (8.4-10.4) in the bortezomib group (n=465).[1]

ASPIRE compared carfilzomib (27 mg/m2) and lenalidomide/dexamethasone to lenalidomide/dexamethasone alone.[2] The median PSF in the carfilzomib group (n=396) was 26.3 months, compared to 17.6 months in lenalidomide/dexamethasone alone (n=396).[2]

ARROW compared weekly (70 mg/m2) and twice-weekly (2x27 mg/m2) carfilzomib. Median PFS in the weekly group (n=240) was 11.2 months (95% CI 8.6-13.0), versus 7.6 (5.8-9.2) in the twice-weekly group.[3] Adverse effects were increased in the weekly group.

No evidence that carfilzomib is superior to bortezomib in NDMM

CLARION compared carfilzomib-melphalan-prednisone with bortezomib-melphalan-prednisone in transplant-ineligible NDMM.[4] There was no difference in median PFS and discontinuation rates were similar between the groups.[4]

Anaemia is the most important adverse effect associated with carfilzomib

Anaemia due to carfilzomib is caused by dose dependent oxidant haemolysis. This is the most common adverse effect associated with carfilzomib treatment and occurs in approximately 37% of patients.[4]

There is good evidence from two series of case studies (including published by Dr Rajagopal) that high dose carfilzomib proteasome inhibition induces anaemia by oxidative haemolysis.[5] A retrospective study of 24 patients treated with carfilzomib also identified haemolysis occurring in 16 patients by generally unclear mechanisms.[6]

Managing the adverse effects of carfilzomib

There is no literature guiding the management of anaemia related to carfilzomib treatment (unlike other cytopaenias) and most haematologists are unaware of the underlying mechanism of anaemia. If patients develop progressive anaemia with or without macrocytosis, haemolysis should be suspected and biochemical markers of haemolysis requested (LDH, haptoglobins, bilirubin and direct Coombs test) and the blood film examined specifically for bite cells. The presence of bite cells is diagnostic for oxidant haemolysis and if confirmed, the dose of carfilzomib (and/or infusion frequency) should be reduced if the patient has symptoms of anaemia or if haemoglobin is < 100 gm/L.

Carfilzomib (certainly high dose) should be avoided in patients who are G6PD deficient. Drugs which could cause oxidant haemolysis (e.g. dapsone) should be avoided in patients on carfilzomib. Severe cases of oxidant haemolysis can mimic thrombotic microangiopathy.

Dr Rajagopal presented a series of case studies showing that patients with underlying heart conditions are at increased risk of cardiotoxicity (as are older patients). Carfilzomib should be avoided in patients with cardiac amyloidosis.

TAKE-HOME MESSAGES

- Anaemia due to *dose dependent oxidant haemolysis* is the most common (and most important) side effect of carfilzomib
- Most cases of anaemia are mild and well compensated with haemoglobin of >100 gm/l, but many patients develop moderate to severe anaemia
- Not all cases of anaemia due to carfilzomib are due to haemolysis, but most cases are
- Consider dose reduction (and/or frequency) of carfilzomib if patients develop symptomatic anaemia due to oxidant haemolysis
- Haemolysis might be contributing to the vascular side effects of carfilzomib (heart failure, hypertension, dyspnoea, oedema)
- Check G6PD prior to commencing carfilzomib
- Avoid carfilzomib in G6PD deficient patients
- Avoid drugs capable of causing oxidant haemolysis with carfilzomib
- Weekly dosing most likely to most effective
- Higher doses more effective, but adverse effects increased

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CARFILZOMIB BASED INDUCTION IN UNTREATED MYELOMA WITH CARFILZOMIB POST-TRANSPLANT CONSOLIDATION (KIWI)

Presented by Liz Thatcher, Clinical Nurse Specialist at Waitemata DHB

The KIWI study is an ongoing, multicentre clinical trial designed to compare the treatment effectiveness in NDMM of KCd, versus the effectiveness of historical treatment with CyBorD. The induction phase of treatment was 5 x 28 cycles of carfilzomib (56 mg/m^2) combined with cyclophosphamide and dexamethasone. Patients then underwent stem cell mobilisation and autologous bone marrow transplant followed by carfilzomib, thalidomide and dexamethasone as consolidation.

The study hypothesis

It was hypothesised that a treatment regimen containing carfilzomib would be more effective because carfilzomib inhibits the β5 and β2 proteasome subunits, whereas bortezomib only inhibits β5.[1] Besse *et al* (2019) demonstrated that β5/β2 co-inhibition is the most effective pattern of proteasome inhibition in proteasome-sensitive and proteasome-resistant MM.[1] Carfilzomib treatment is also expected to be associated with less neuropathy and diarrhoea than bortezomib. Carfilzomib may, however, be associated with more cardiotoxicity than bortezomib, although cardiotoxicity is reversible and can be managed by reducing the dose or pausing treatment.

Treatment and results

The first patient in the KIWI study was enrolled in April, 2017. Further patients were recruited from the North Shore and Middlemore hospitals. The target for patient enrolments was 50 which was reached in October, 2020.

Approximately 40% of patients achieved MRD after the induction phase and by the end of treatment >80% of patients had achieved MRD. Eleven patients discontinued treatment, 5 of whom due to adverse effects, 3 patients withdrew, 2 patients died and there was 1 PD. The predominant grade 3 and 4 adverse effects were haematological (anaemia, neutropenia and thrombocytopenia). Most adverse effects were manageable and the majority of patients were able to complete treatment. Preliminary data shows that 24 patients have achieved PFS, 2 patients have died and there have been 5 with PD.

LEARNINGS FROM OUR FIRST INVESTIGATOR INITIATED STUDY

- Focus on what you really want to capture
- Ensure protocol and timelines are clear
- Have more study sites
- Have a monitor for sites

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MYELOMA GENOMICS

Presented by Ian Morison, Professor at Otago University

Somatic changes in MM

Somatic genetic changes driving MM are complicated and 63 driver genes have been identified.[1] In general, somatic changes tend to be scattered with relatively little association of mutations with any particular translocation.

Family pedigrees of MM are small

Family clusters of MM suggest disease heritability, although there are few common gene variants known to contribute to familial MM. Furthermore, the importance of genetic versus environmental risk in MM aetiology remains unclear due to the small size of the affected studies. Later in the presentation, Professor Morison provided examples of pedigrees with at best two generations and 4-6 affected individuals.

The heritability of MM was investigated by pooling case-control studies. MM risk was elevated in association with a first-degree relative with MM (OR = 1.90), particularly among men (OR = 4.13) and African Americans (OR = 5.52).[2]

Familial MM is likely to be polygenic

A Swedish study of 38 familial cases demonstrated an enrichment of common myeloma risk alleles in familial MM, compared to sporadic cases.[3] Familial cases are therefore likely to occur due to co-inheritance of multiple risk alleles, rather than inheritance of single genes. Family studies can also be complicated by the background incidence of MGUS occurring in individuals without mutations.[4]

TNFRSF13B is a strong genetic risk factor for MM

A large genome-wide study of 12.4 million autosomal SNPs in 7,319 cases and 234,385 controls identified 17 loci associated with the development of MM.[5] In total, 23 risk alleles have been identified for MM and ORs calculated, however, these risk scores are of little clinical value as they cannot provide a meaningful individual risk profile for a patient. The allele associated with the strongest risk for MM is TNFRSF13B (TACI), which is also the allele most strongly associated with serum globulin levels.[6]

Does TNFRSF13B explain why Pacific people are at high risk of MM?

The A allele confers increased risk of MM and the risk is synergistically increased in homozygous patients. The 1000 Genomes project shows the prevalence of the A allele in Europeans is 11%, compared to 42% in South Asia (the origin of Pacific peoples). It has been calculated that 1% of Europeans are homozygous for allele A, compared to 23% of Pacific people. Professor Morison predicts that 50% of Pacific people with MM will be homozygotes for the risk allele.

As well as increasing globulin levels, TNFRSF13B is involved in important cellular processes. The theory that TNFRSF13B may explain the elevated rates of MM among Pacific people is, however, not supported by the lower rates of MM seen in South Asia, compared to Pacific people. Professor Morison speculated that this could potentially be due to differing rates of obesity.

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