**Frailty Assessment in Multiple Myeloma**

**Findings from a recent inquiry**

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Fit and frail are terms increasingly used in consensus guidelines for the treatment of multiple myeloma (MM). An individual patients’ fitness often informs treatment choice, dose, schedule and duration, and a range of frailty assessment tools exist to help us measure for this construct. Furthermore, we know that treatment outcomes differ between frailty groups. But what do we mean by ‘FIT’ or ‘FRAIL’, which are the best tools to measure for it, and how do/can we put frailty assessment into practice? These were the questions recently put to members of the Myeloma Specialist Practice Network (M-SPN) and the findings are presented in this short summary article.

When asked if they undertook routine frailty assessment in their MM clinical practice it became clear a range of practices and assessment types were utilised. From ‘end of the bed clinical judgements’ to formal ‘comprehensive geriatric oncology assessment (CGA),’ with most, somewhere in between.

**Myeloma – the context**

Myeloma is predominantly a disease of older age, with a mean age at diagnosis of 70.2 years, 40% of patients > 75 years and 26% > 80 years of age (AIHW 2019). With improvements in overall survival (OS) for those with MM and an ageing of the population we expect to see more cases of MM being diagnosed each year. Myeloma commonly follows a multiply relapsing and remitting course with patients requiring successive lines of multi-drug therapy over increasing number of years. Recent approval of triplet therapy bortezomib, lenalidomide and dexamethasone (VRD) in the upfront setting for MM provides us with robust treatment approaches that aim to increase depth of response and further improve survival outcomes. The intensity of treatment needs to be balanced with ability to tolerate both predictable disease and treatment related toxicity. Incidence of toxicity may be similar between age groups, but capacity to tolerate toxicities decreases with increased age (Terpos et al 2015). Whilst transplant eligible and transplant ineligible pathways are established, optimising treatment choice should also be based on formal frailty assessment, tailoring treatment type, dose and schedule to frailty status.

**What do we mean by frailty?**

Frailty is a multidimensional state of diminished reserve (energy, physical ability, cognition and health) which gives rise to vulnerability and can result in reduced ability to resist stressors, including cancer and its treatment (Clegg 2013 & Rockwood 2005). Understanding the domains of vulnerability (frailty, comorbidity and disability) is essential in tailoring treatment that will optimise outcomes for individual patients.

**How can we measure for frailty?**

While there is no shortage of frailty tools, not all are formally validated and there appears a lack of consensus in how and when to use them. Whilst objective frailty assessment informs treatment choice, a range of other factors such as processes of care (number of hospital visits, travel, route of administration, financial concerns) and patient choice, are also taken into account.

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| **Frailty Assessment Tools in Multiple Myeloma** | | |
| **Tool** | **Factors reviewed** | **Comments** |
| IMWG Frailty Index  [www.myelomafrailtyscorecalculator.net](http://www.myelomafrailtyscorecalculator.net) | Age  Activities of Daily Living (ADL)  Instrumental Activities of Daily Living (IADL)  Charlson Comorbidity Index (CCI)  [www.mdcalc.com/charlson-comorbidity-index-cci](http://www.mdcalc.com/charlson-comorbidity-index-cci) | MM specific tool. Incorporating assessment of comorbidities alongside daily functioning. Widely reported in MM studies, online calculator available, relatively quick. |
| Revised Myeloma Comorbidity Index  (R-MCI)  [www.myelomacomorbidityindex.org](http://www.myelomacomorbidityindex.org) | Age  KPS  eGFR  PFT  Fragility  Cytogenetics | MM specific tool. Incorporating additional biological markers and performance measure. |
| Mayo Frailty Index | Age  ECOG PS  NT-Pro-BNP | MM specific tool. Simple, objective tool, predicts survival independent of age and performance status. |
| UK Myeloma Research Alliance Risk Profile (MRP) | WHO PS (ECOG)  ISS  Age  CRP | MM specific tool. Objective markers, quick to complete. |
| Comprehensive Geriatric Assessment (CGA) | Comorbidities, functional status, medications (including polypharmacy and inappropriate medication), cognition, psychological status, social support. | Generic tool, comprehensive but complex to undertake and time-consuming |

*ADL Activity of Daily Living, IADL Instrumental Activity of Daily Living, CCI Charlson Comorbidity Index, KPS Karnofsky Performance Status, eGFR estimated glomerular filtration rate, PFTs pulmonary function tests, ECOG-PS Eastern Cooperative Oncology Group performance status (also known as WHO PS) NT-proBNP N-terminal natriuretic peptide type B; ISS International Staging System; CRP C-reactive protein*

**Why should we measure for frailty?**

Frailty assessment aims to identify patients with increased care needs or vulnerability that allows clinicians to individualise treatment approaches (choice of drug combination, dose and scheduling) so as to improve outcomes. The most recent Clinical Practice Guideline: Multiple Myeloma (Quach & Prince 2019), Myeloma Scientific Advisory Group (MSAG)lists frailty separately from age, comorbidities and disability, with frailty “variously defined as poor endurance, weakness and low physical activity” (p24). The guidelines provide recommendations for the assessment of suitability of elderly patients for the intensity of therapy, suggesting clinicians determine patient ‘fitness’ (fit, intermediate, frail) so as to inform treatment choice.

In the upfront setting, induction therapy followed by autologous stem cell transplant (auSCT) results in superior survival but can be hard to tolerate due to predictable treatment related toxicities, particularly in those > 70 years of age or with existing comorbidities. Furthermore, patients categorised as frail are more likely to experience grades 3-4 non-haematological toxicity of therapy, early discontinuation of treatment and a shorter OS (Palumbo et al 2015). Determining eligibility for transplant is arguably the most commonly utilised frailty assessment time point. In addition to informing transplant eligibility, frailty assessment can also inform treatment approaches, dose-attenuation and schedule changes with recommendations listed in the Clinical Practice Guideline Myeloma (Quach & Prince 2019 p24-27).

**Frailty assessment in clinical practice: M-SPN members experiences**

Myeloma Specialist nurses are well placed to screen for and implement frailty assessment in MM.The nurse-patient relationship can enable comprehensive patient assessment that can be hard to achieve during busy Specialist consultations. Frailty assessment and screening can provide additional information on functional or psychosocial status that may impact treatment tolerance.

The Myeloma Specialist Practice Network (M-SPN) identified variation in practice around frailty screening as a good opportunity for the group to review practices in our region. A brief email was sent out to members inquiring of their utility of frailty assessment in routine practice. Feedback was consistent across both public and private settings; while awareness of frailty measures existed, the utility of them was inconsistently applied. Approaches were admittedly ad-hoc, with medical prescriber discretion at its core. The exception was in speciality settings within MM, such as transplant centres wherethe **Haematopoeitic Cell Transplantation – Comorbidity Index (HCT-CI)** was commonly used by Transplant Nurse Coordinators pre-auSCT work-up. Other centres utilised the IMWG Frailty Index to assess newly diagnosed MM for transplant eligibility. Formal assessments using a recognised tool were also driven by study participation (e.g. ALLG/AMaRC study ‘Frail M’). The team at Barwon Health conducted a retrospective audit that looked at efficacy and safety of auSCT in elderly myeloma patients aged >65years (Er. J et al 2018). The study found the **Revised Myeloma Comorbidity Index (R-MCI**) tool to be useful in predicting survival in their patient population.

Other centres are incorporating systematic frailty assessment into standard MM care pathways. We identified a hospital who had embedded frailty assessment into the position description for a new MM Nurse Specialist role. They argued frailty assessment as a mechanism to identify patients at increased risk of poorer outcomes by measuring unfavourable frailty scores, optimising management of existing, undiagnosed or high risk co-morbidities, and assessing for psychosocial needs, amongst others. This is turn potentiates frailty reversibility, mitigates toxicity, prevents unplanned hospital admissions, improves therapy adherence, and enables continuation of therapy.

**What are some of the challenges for frailty assessment in routine practice?**

Formal assessment vs clinical judgment

Belotti and colleagues (2020) recently compared formal frailty assessment (IMWG frailty index) with clinical judgement in MM patients 65-75yrs being considered for auSCT and found similar outcomes between assessment type. This perhaps emphasises the role of clinical judgement within a multidisciplinary, patient-centred care environment as part of assessment of fitness for treatment.

Reproducibility & Reversibility

Completion of frailty assessment also involves clinical judgement, in part subjective, where assumptions can impact scoring. Robust assessment may also depend on the clinician’s experience in the care of the elderly. Factors assessed such as weakness, malnourishment, and physical endurance are modifiable especially with allied health input. Frailty scoring may therefore change over time. Furthermore, frailty scores in myeloma are commonly reported as they correlate with poor survival outcomes. Future studies could explore frailty assessment and its role in measuring ability to tolerate a treatment regimen not only for duration of therapy but its association with toxicities and impact on health-related quality of life.

Awareness

Traditionally, academic conversations on frailty that explore ‘*when is less more*?’ are found in Palliative Care or Geriatric Journals, which silos frailty away from academic reviews on optimal treatment found in mainstream myeloma literature. The Paper by Murillo and colleagues (2018) discussing the credentials of the **IMWG’s frailty score** is found in the Journal of Geriatric Oncology, not in a haematology journal.

Tools are tools.

Tools exist to guide, inform, qualify, and strategize. Perhaps the lack of widespread, routine frailty assessment we found in our brief review, indicates that clinical judgement has been working to date? Assessment of suitability of elderly MM patients for intensity of therapy is complex. Whilst frailty assessment is an important component of identifying appropriate therapy for an individual patient, treatment decisions are made within a complex patient-centred paradigm, that considers a broader range of issues, not restricted to those listed within frailty tools. Furthermore, frailty assessment is a process to be undertaken over time and not only at diagnosis. Formal frailty assessment can inform treatment choice but also guide referral for assistance with modifiable health and lifestyle factors which aim to improve health, reduce frailty and possibly re-inform treatment choice.

**Concluding comment**

Assessing frailty in myeloma is not a new concept, nor is there a lack of tools to do so. With an increasing number of therapies available to treat myeloma, and a treatment trajectory of successive lines of therapy over increasing number of years, continued improvements in survival will require patients to tolerate more therapies over longer periods of time~~.~~ Whilst formal frailty assessment has a role in optimising intensity of therapy it can occur alongside clinical judgment within a multidisciplinary framework of patient-centred care. Frailty evolves, and so must our approach to individual assessment.

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