Elderly patients

**IMW 2019 | Management of elderly patients with multiple myeloma**

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During the *XVII International Myeloma Workshop* (IMW) meeting in Boston, US, Sonja Zweegman and Alessandra Larocca presented an educational session entitled: "Management of Elderly Patients with Multiple Myeloma (MM)".¹ The current treatment options for frail patients were discussed, along with classification systems, and potential future directions for therapies.¹

**Classification of frailty in MM**

- The International Myeloma Working Group (IMWG) classification:²
  - Includes evaluation of activities of daily living (ADL)
  - Indicates a higher incidence of functional, cognitive, mental and nutritional impairments in patients who are frail, compared to those who are unfit
  - Therefore, the IMWG score is considered to reflect biological frailty

- The revised Myeloma Comorbidity Index (R-MCI) quantifies comorbidities and adds disease characteristics:³
  - Includes assessment of age (≤ 60 vs 60–70 vs > 70 years), lung function, Karnofsky performance score (KPS), physician assessment of frailty, renal function by glomerular filtration rate (GFR) and cytogenetics³
  - May be more discriminative¹
  - However, the R-MCI was only evaluated in a population of German patients with MM¹,³

- Another method of assessing frailty is the Myeloma Risk Profile (MRP), which uses the World Health Organization (WHO) performance status, age, international staging system (ISS) and C-reactive protein (CRP) levels⁴
  - The MRP has been shown by Cook *et al.*, in the Myeloma IX trial to be associated with outcome⁴

Also, at the IMW meeting, Ho Sup Lee presented an analysis of the outcomes of patients treated with bortezomib (V)-based regimens, by frailty scoring systems. The group found that patients who were classified as frail by IMWG criteria, or high-risk by R-MCI criteria, had a shorter survival compared to patients who were not frail, or who were deemed low-risk. The R-MCI criteria was more accurately able to predict survival compared to IMWG, however R-MCI is less easy to implement, indicating a requirement for a more simplified and predictable frailty risk model to use in clinical practice. Read more about this study below.⁵

**Clinical questions**

Elderly and frail patients are often excluded from clinical trials, therefore clinical data on this population is lacking.⁵ When treating elderly patients, several factors should be considered;¹
- Are the patients fit, unfit or frail (depending upon classification system used)?
- What is the optimal drug regimen? Is it a doublet, triplet or quadruplet therapy?
- Is the patient eligible for autologous stem cell transplant (ASCT)?
- Duration of therapy; how many induction cycles should be used?
- Does the dose of the chosen medication(s) need to be modified? If so, how?
- Many elderly patients do not progress to later lines of treatment, and the treatment duration and treatment-free intervals decrease with each subsequent line of therapy. Therefore, response to first-line treatment is crucial.

**Treatment options**

The current treatment paradigm for elderly patients with MM is shown in Table 1.

**Table 1.** Frontline treatment of elderly patients with MM

<table>
<thead>
<tr>
<th>For fit elderly patients</th>
<th>Non-transplant eligible; without ASCT</th>
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<tbody>
<tr>
<td>Transplant eligible; ASCT</td>
<td>Non-transplant eligible; without ASCT</td>
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<tr>
<td>V-based induction therapy, followed by melphalan (M, 100mg/m²) and ASCT followed by lenalidomide (R) consolidation and maintenance</td>
<td>Outcomes of patients treated without transplant in the frontline setting are also promising</td>
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<tr>
<td>Promising progression-free survival (PFS) of 48 months was observed</td>
<td>Standard regimens such as VR + dexamethasone (d, VRd) have shown median PFS of 43 months, and a median overall survival (OS) of 75 months in the SWOG S0777 trial</td>
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<td>However, more adverse event (AE)-related deaths occurred in patients over the age of 70 (19%) compared to patients aged less than 70 (5%)</td>
<td></td>
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<td>Use of the hematopoietic cell transplantation specific comorbidity index (HCT-CI) to score comorbidities and demonstrated a treatment-related mortality rate of 0% at 100 days post-transplantation</td>
<td>The addition of daratumumab (dara) to frontline regimens for patients who are ineligible for transplant has further improved PFS</td>
</tr>
<tr>
<td>80% of patients had no, or only one other comorbidity at transplantation</td>
<td>ALCYONE trial (dara-VMP vs VMP): no impact of age on PFS; hazard ratio (HR) for progression or death of 0.53 in patients aged ≥75, and 0.49 in patients aged &lt;75</td>
</tr>
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<td>These results indicate ASCT is a viable first-line treatment approach for elderly patients, with age not being a defining factor of outcome</td>
<td>Whilst this indicates age should not be the defining factor for determining treatment, since IMWG frailty scoring was not assessed, it is not possible to draw conclusions based on frailty</td>
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</tbody>
</table>

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### Conclusion

Consider transplant, in combination with a monoclonal antibody containing regimen. For transplant ineligible patients, consider the approved regimens in the country, e.g., the European Medicines Agency (EMA) prefer VRd or dara-VMP. For patients with renal failure or high-risk cytogenetics, V-based regimens should be considered. Additional benefit may be seen by adding a monoclonal antibody to a proteasome inhibitor plus immunomodulatory drug regimen, e.g., elotuzumab-VRd or dara-VRd.

### For the unfit and frail patients

- A phase IIb trial of upfront V-based regimens in 502 elderly patients with newly diagnosed MM (NDMM) compared Vd to V + thalidomide (T) + d (VTd) and VMP followed by five cycles of maintenance with V.
  - 42% of patients in the study were over the age of 75, with 18% being over the age of 80.
  - Median PFS (Vd vs VTd vs VMP): 14.7 vs 15.4 vs 17.3 months.
  - Median OS (Vd vs VTd vs VMP): 49.8 vs 51.5 vs 53.1 months.
  - Vd had the lowest response rate, but also the lowest rate of discontinuation due to AE indicating this is a viable option for transplant ineligible patients with MM.

- Dose-adapted therapy in unfit patients (intermediate-fit) with NDMM (n = 199).
  - Patients were randomized to either nine cycles of Rd induction and R-maintenance until disease progression (PD) or intolerance (Rd-R) or continuous Rd until PD or intolerance (Rd).
  - Median follow-up: 25 months.
  - PFS (Rd-R vs Rd) was 43% vs 42%.
  - OS (Rd-R vs Rd) was 84% vs 79%.
  - Therefore, treatment approaches should be adjusted to balance safety and efficacy.

Other trials: HOVON 143 (EudraCT 2016-002600-90): investigating the concept of non-toxic drugs for frail patients using ixazomib + dara + d.

Ongoing trials: UK-MRA FITNESS trial, Myeloma XIV (NCT03720041): frailty-adjusted dosing comparing standard reactive therapy to frailty adjusted adaptive therapy using ixazomib + Rd.

**IMWG frailty index, despite its limitations, is the best method of detecting frailty in MM. Treatment of these patients should include a shorter induction duration, a lower dosage and less dense therapy, whilst aiming to achieve a long duration of response. Drugs that are intended for ‘non-frail’ patients, like the monoclonal antibodies should be investigated further in this population.**

### Outcomes of patients treated with V-based regimens, by frailty scoring systems

Also during the XVII IMW meeting, Ho Sup Lee, Kosin University College of Medicine, Busan, KR, presented an evaluation of the clinical impact of frailty on outcomes in transplant ineligible MM patients treated with V-based chemotherapy as frontline treatment. Additionally, the authors compared the IMWG and R-MCI frailty scoring systems.

This retrospective study analyzed the outcomes of 366 patients (median age: 69 years) treated in South Korea between 2007 and 2017. Patients received VMP as frontline therapy, and were classified according to the IMWG (fit, unfit, frail) or R-MCI (low-, intermediate- or high-risk) criteria. For the IMWG criteria, ADL/instrumental ADL was substituted for Eastern Cooperative Oncology (ECOG) scores. More patients were classified as frail by IMWG criteria (43.4%) compared to high-risk by R-MCI criteria (13.7%).
The median PFS and OS for the total cohort, and for each frailty group, are shown in Table 2. When comparing frailty classification for PFS and OS by IMWG or R-MCI criteria, all were statistically significant ($p < 0.001$).

**Table 2. PFS and OS by frailty score**

<table>
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<tr>
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<th>N</th>
<th>Median PFS, months (range)</th>
<th>Median OS, months (range)</th>
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<tr>
<td>Total cohort</td>
<td>366</td>
<td>23.7 (18.62–28.84)</td>
<td>56.2 (46.36–66.04)</td>
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<tr>
<td>IMWG scoring</td>
<td></td>
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<tr>
<td>Fit</td>
<td>78</td>
<td>24.6 (15.8–33.4)</td>
<td>80.7 (54.3–107.2)</td>
</tr>
<tr>
<td>Unfit</td>
<td>129</td>
<td>38 (26.5–49.5)</td>
<td>118 (55.9–180.2)</td>
</tr>
<tr>
<td>Frail</td>
<td>159</td>
<td>16.7 (13.2–20.1)</td>
<td>38.5 (28.7–48.2)</td>
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<tr>
<td>R-MCI scoring</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Low risk</td>
<td>136</td>
<td>31.9 (24.1–39.8)</td>
<td>118 (57.1–178.9)</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>180</td>
<td>24.6 (17.5–31.6)</td>
<td>58.1 (47.8–68.4)</td>
</tr>
<tr>
<td>High-risk</td>
<td>50</td>
<td>12.8 (5.3–20.3)</td>
<td>26.9 (21.1–32.7)</td>
</tr>
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</table>

Using a cox proportional hazard model for PFS and OS, this analysis found that only classification system was significantly associated with PFS (for both IMWG and R-MCI), whilst for OS, age was significant for both classification systems, though classification system was only significant for R-MCI.

**Conclusion**

Patients who were classified as frail by IMWG criteria, or high-risk by R-MCI criteria, had a shorter survival compared to patients who were not frail, or who were deemed low-risk. The R-MCI criteria was more accurately able to predict survival compared to IMWG, however, due to the number of variables measured, R-MCI is less easy to implement. Therefore, there is a requirement for a more simplified and predictable frailty risk model to use in clinical practice.

**References**


5. Lee H.S. et al., The clinical impact of frailty in transplant ineligible patients with multiple myeloma treated with bortezomib-based chemotherapy as front line therapy. 2019 Sep 13. Oral Abstract #AB419. XVII International Myeloma Workshop (IMW), Boston, US


