Quality of Life Considerations in Myeloma

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Conflict of interest disclosure

• Research Funding: Celgene, Takeda, BMS, Merck, Novartis, Karyopharm, Signal genetics
Case presentation

- BJ is a 69 yo man diagnosed with DS IIIA, ISS 1 standard risk myeloma in 2014. He received RVD and high dose melphalan and stem cell transplant in 2015. He discontinued maintenance therapy after about 2 years while in CR because of diarrhea and fatigue which affected his quality of life.

- He started having biochemical progression and is asymptomatic except for grade 1 occasionally painful neuropathy.

- He lives about 2 hours from the cancer center and he is currently retired. He would prefer an oral regimen if possible although doesn’t wish to compromise efficacy. He likes to travel and is particularly interested in preserving his quality of life.

1. Can we use quality of life data to determine when to start systemic therapy for patients with biochemical progression?
2. Can quality of life data help determine the optimal systemic therapy for this patient? Among the approved regimens in the US include retreatment with RVD, KRd, EloRd, Dara Rd, Ird, Dara VD, KD56
QoL: Everyone wants it, but what is it?

Defining Quality of Life: A Wild-Goose Chase?

Barbara Barcaccia*a, Giuseppe Esposito*b, Maria Matarrese*c, Marta Bertolaso*c, Marta Elvira*d, Maria Grazia De Marinis*c


“Quality of life (QoL) seems to be an obscure concept, or at least “a multi-level and amorphous concept” (Brown, Bowling, & Flynn, 2004, p. 6), to the extent researchers are said not to know what they are talking about when mentioning QoL. We may have a vague idea, but its definition is very complicated, inasmuch that in some scientific articles a definition of the concept is not even attempted, and QoL is only measured and meant as an indicator. The purpose of this article is to contribute to the scientific reflection on QoL, by analyzing how it is conceptualized and whether a definition is offered or not in various scientific articles which have been published in the last two decades. In addition, we shall provide an illustration of how widespread the use of QoL is in different fields, highlight the difficulties in reaching a shared understanding of this concept, as well as pinpoint which articles attempt to define the concept of QoL and which ones use it just as an indicator. As a matter of fact, only a minority of studies provide an original conceptualisation of QoL, while others rely on other authors’ formulations, some do not even attempt a theoretical conceptualisation, some are more concerned with measuring reliably QoL without defining it theoretically and many others consider QoL as a determinant or an indicator of something else.”
QoL: Definitions and limitations

• WHO: “individuals’ perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations and standards and concerns. It is a broad ranging concept affected in a complex way by the person’s physical health, psychological state, level of independence, social relationships, and their relationship to salient features of their environment” ¹

• “Scientists may use rating scales and visual analogue scales to measure pain, and they may even invent scoring systems quantifying types of handicaps, but when they talk about measuring quality of life, they have gone too far”²

• General agreement that it is subjective (the individual is the most suitable judge) & multi-dimentional / all-emcompassing

¹- WHOQOL Group. Social Science & Medicine, 1995, 41(10), 1403-1409
²- Wulff, H. Journal of the Royal Society of Medicine, 1999, 92, 549-552
HRQL

• HRQL is a one feature of QoL
• HRQL is a “concept that involves those aspects of quality of life or function, which is influenced by health status and is based on dimensions (i.e., physical, psychological, and social aspects), which can be measured”

• Relevance in MM:
  • Disease is not generally curable
  • Patient demographic most susceptible to toxicity from therapy (frail elderly)
  • Increasing costs of care
  • Access to specialists associated with socioeconomic burden

Defining More Acronyms

• PRO: patient’s self reported outcomes; without interpretation by caregiver
• GHS (Global health score): one of the EORTC QLQ-C30 measures
• MID (Minimal Important Differences): smallest clinical meaningful positive or negative change which can be perceived by a patient
• MMA (Mixed model analysis): statistical method to analyze HRQL longitudinally while preserving power and accounting for missing variables.
HRQL and Myeloma

Pubmed Search: quality of life[MeSH Terms]

<table>
<thead>
<tr>
<th>Time Period</th>
<th>MM &amp; QOL</th>
<th>MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990-95</td>
<td>7</td>
<td>4910</td>
</tr>
<tr>
<td>1995-2000</td>
<td>22</td>
<td>5153</td>
</tr>
<tr>
<td>2000-2005</td>
<td>45</td>
<td>6712</td>
</tr>
<tr>
<td>2005-2010</td>
<td>64</td>
<td>9629</td>
</tr>
<tr>
<td>2010-2015</td>
<td>112</td>
<td>13017</td>
</tr>
<tr>
<td>2015-2020</td>
<td>144</td>
<td>17000</td>
</tr>
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</table>
HRQL tools: FACT-MM

- Literature review identified 52 potential items to include
- 13 MM patients and 13 MM clinicians rated these items
- 14 items retained in FACT-MM
- Highest rated item by clinicians: pain, fatigue, easily tired, emotional ups and downs
- Highest rated items by patients: sexual function, uncertainty about health, fatigue and weight gain

Wagner Li et al. J Pain Symptom Manage 2012; 43: 1094–1104
HRQL tools: MDASI-MM

- Developed with clinician input, literature review and administered to 132 patients undergoing induction or transplant
- Validated against the EORTC QLQ-C30 and MY20
- Sensitive to measure the acute worsening of symptoms post transplant
- 26 questions rated from 0-10, recalled from the last 24 hours
- Little or no emotional, psychological or socioeconomic components although 6 questions address the impact of physical symptoms on activity, mood, work, relations, and employment

Jones D et al. Journal of Hematology & Oncology; 2013, 6:13
HRQL tools: EORTC QLQ-MY20

- Often co-administered with QLQ-C30
- 20 items focusing on 4 scales (disease symptoms, side effects, body image and future perspective)
- Validated in study with 240 patients
- One of the most common used PRO questionnaire in MM clinical trials
- Symptoms based also no / with little emotional, psychological or socioeconomic component

Myeloma Patient Outcome Scale (MyPOS)

- Module of the Palliative Care Outcome Scale (POS) enriched with myeloma-specific concerns
- Validated in UK practice; 238 patients recruited and completed the questionnaire every 2 months x 5
- 3 categories or scales: symptoms, emotional functioning and healthcare support subscale

Newly Diagnosed RCT with HRQL as an Endpoint

<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent(s)</th>
<th>HRQL instrument(s)</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOVON49¹</td>
<td>MP, MPT-T</td>
<td>QLQ-C30, MY20</td>
<td>Improved global health with therapy (MP or MPT) Improved physical function and constipation score with MP Worse neuropathy score with MPT Emotional / future perspective better with MPT</td>
</tr>
<tr>
<td>VISTA²</td>
<td>MP, VMP</td>
<td>QLQ-C30</td>
<td>Transient deterioration in QOL during early (1&lt;sup&gt;st&lt;/sup&gt; 4 cycles) therapy with VMP compared to MP but improvement after cycle 5 CR &amp; duration of response correlate with improved global health, pain and appetite Lower dose intensity of bortezomib associated with better HRQL</td>
</tr>
<tr>
<td>UPFRONT³</td>
<td>VD, VMP, VTD</td>
<td>QLQ-C30</td>
<td>Transient deterioration in global health status during induction followed by stabilization Findings were worst for VTD and notable for many of the symptoms and functioning</td>
</tr>
<tr>
<td>MM-015⁴</td>
<td>MP, MPR, MPR-R</td>
<td>QLQ-C30, MY20</td>
<td>Improvement from baseline in all scores except symptoms from treatment in all arms of therapy More frequent MID improvement in MPRR patients compared to MP and MPR All arms with similar side effects from treatment scores (highlights tolerability of R maintenance)</td>
</tr>
<tr>
<td>FIRST⁵</td>
<td>MPT, RD, RD18</td>
<td>QLQ-C30, MY20, EQ5D</td>
<td>Overall improved HRQL from baseline with all treatment arms in C30 and EQ5D Disease symptoms in MY20 improved with Rd more than with MPT Rd also resulted in better treatment side effect score in MY20 Cannot comment on maintenance R HRQL</td>
</tr>
</tbody>
</table>

Impact of transplant on HRQL

• Limited randomized data in the era of novel agents
• Several studies have noted a decrease in HRQL scores during transplants with improvement as early as 1-2 months \(^1, \, 2\)
• In addition, in one study comparing to MP therapy, the transplant arm had better HRQL (less fatigue) at 36 months \(^1\)
• Predictors of post transplant symptom burden were the pre-transplant MDASI score, female gender and prolonged time from diagnosis to transplant \(^3\)
• Outpatient versus Inpatient transplant resulted in better social well being but worse physical well being \(^4\)

What are the implications for maintenance therapy?

- MM-015 is the only RCT to address the impact of lenalidomide maintenance on HRQL

- Little HRQL data for post transplant maintenance
  - Thalidomide maintenance adversely impact HRQL

- Connect MM database analysis: 238 met the analysis criteria for Any maintenance, 167 for LEN-only, and 138 for No maintenance

- 84% of patient community based

- About 5 EQ-5D questionnaire completed / patients on each arm

- No significant differences in EQ5D, FACT MM or BPI score for any of the 3 groups

- Decline in FACT-MM score at the time of progression

2- Abonour R et al. ASH 2016 abstract 537
Relapsed Myeloma RCT with HRQL as an endpoint

<table>
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<th>HRQL instrument(s)</th>
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<tr>
<td>APEX(^1)</td>
<td>Bort vs. Hi Dex</td>
<td>QLQ-C30, FACT</td>
<td>Bort arm had better mean GHS over the study, significantly better Physical Health, Cognitive and Emotional Functioning scores, better FACT-Ntx. However, declining trend in GHS in both arms.</td>
</tr>
<tr>
<td>MM003(^2)</td>
<td>Pom LoDex vs. Hi Dex</td>
<td>QLQ-C30, MY20, EQ5D, FACT</td>
<td>Greater MID improvement on Pom arm in 7/8 domains (incl disease symptoms and side effects from treatment). Pom arm had a prolonged time to deterioration in most HRQL measured compared to HiDex.</td>
</tr>
<tr>
<td>ASPIRE (^3)</td>
<td>KRd vs. Rd</td>
<td>QLQ-C30, MY20</td>
<td>KRd arm had improved GHS at all time point but was significant at month 12-18 (proportion of patients with improvement in 5 or 15 points MID). Longer time to deterioration of HRQL with KRd. No worsening in symptoms with KRd vs. Rd.</td>
</tr>
<tr>
<td>TOURMALINE (^4)</td>
<td>IRd vs Rd</td>
<td>QLQ-C30, MY20</td>
<td>Similar GHS with IRd versus Rd, trends toward better physical / emotional functioning and fatigue with IRd versus Rd. Similar nausea but worse diarrhea.</td>
</tr>
<tr>
<td>ELOQUENT (^5)</td>
<td>EloRd vs Rd</td>
<td>QLQ-C30, MY20</td>
<td>No differences in HRQL noted between the two arms; pain and fatigue were highest baseline reported symptoms.</td>
</tr>
</tbody>
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Factors predicting HRQL (analysis of MM-015)

- Female gender, advanced age and progressive disease negatively affected HRQL
- Achieving VGPR or better (but not PR) associated with HRQL
- While grade ¾ anemia was associated with worse HRQL, grade ¾ neutropenia was not

What other factors impact HRQL in MM

- For each additional year with MM, GHS decreased by 1 point\(^1\)
- Receiving \textit{any} type of therapy within 30 days was associated with 9.5 point decrease in GHS compared to observation\(^1\)
- First treatment free interval (TFI) associated with better HRQL than other treatment phases\(^2\)
- Longer first TFI associated with better HRQL (future perspective, body image, physical functioning and role functioning)\(^2\)

Patients with moderate to severe symptoms had a decrease of 12 -19 points respectively in HRQL scale

How do we go beyond signs and symptoms?

- Cross-sectional qualitative study, literature review, phone interview with MM specialists in the US, Europe, Australia and China as well as phone interview with 20 patients in the US
- Fatigue and pain were the most common symptoms
- Impact of clinic visits: most visit ranged from very quick to up to 2 hours. Most patients did not find visits inconvenient however some noted a burden to get to appointments
- Impact of mode of administration of therapy: most noted no inconvenience with oral therapy; some noted that IV monthly bisphosphonate had a big impact on QoL

Table 5 Examples of patient-reported impact of MM treatment on HRQL

<table>
<thead>
<tr>
<th>Impact on HRQL</th>
<th>Example participant quotation</th>
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</thead>
<tbody>
<tr>
<td>Impact of clinic visits</td>
<td>“...the biggest thing is the fact that it’s a full two hour drive to get to the cancer center and back each way. So, today we left at 5:30, and luckily, the lab was on time and the pharmacy was on time, and we got back by noon. There’s been other days where we go over there and...we don’t get back until four or five in the afternoon.” [1 year since diagnosis; first-line therapy]</td>
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<tr>
<td>Mode of treatment administration</td>
<td>“I don’t think anybody likes getting an IV every month...time-wise... I don’t work or anything, so that doesn’t bother me so much. It’s more or less the actual IV, because they don’t always get it the first time, so it’s a couple of sticks. The process is not fun.” [4.5 years since diagnosis; first-line therapy]</td>
</tr>
<tr>
<td>Mode of treatment administration</td>
<td>“Well, if they miss the IV, number one, and number two, I always have these marks every time I leave there. I always have marks on my arms. Looks like I’m a drug user.” [4.5 years since diagnosis; first-line therapy]</td>
</tr>
<tr>
<td>Mode of treatment administration</td>
<td>“anything other than an infusion deal where you’ve got to run down there all the time, that’s great” [20 years since diagnosis; third-line therapy or more]</td>
</tr>
<tr>
<td>Impact of clinic visits</td>
<td>“The interruption to my lifestyle is the fact that I’ve got to go down there and get my new stuff... wherever I am. It wouldn’t matter what part of the country I’m in, I’ve got to go to find a lab and go over there and get my blood drawn; get them then to fax the results to [clinic name] and [clinic name] calls me and says, “Okay, your results are okay, you go ahead and take your dosage.”” [20 years since diagnosis; third-line therapy or more]</td>
</tr>
</tbody>
</table>

These were selected as typical responses that best illustrate the impact on each area of HRQL

Modeling the impact of MM on HRQL

Gaps in the literature

• Available data do not allow for cross treatment / trial comparison due to differences in study population, design and methodology of HRQL analysis (use of different HRQL tools and time points in measurements)

• Limited data of HRQL outside the context of clinical trials (possibility of selection bias)

• Data on the impact of socio-economic factors on QoL is lagging behind the impact of symptom reporting (for example: cost and affordability of therapy, impact of distance of from treatment center, mode of administration)

• Can anticipated changes in HRQL guide therapy choices (similar to the case presented)
  • When should you initiate therapy for biochemical progression?
  • Should a particular patient receive KRd versus IRd?
  • What is an acceptable copay for an oral agent (for example lenalidomide, pomalidomide or ixazomib)?
Summary

• Despite the fact that myeloma is considered generally incurable, there is a paucity of data on the impact of therapy on HRQL
• In general, HRQL often mirrors the course of the disease (worsening with disease progression and improving with effective therapy)
• Continued Incorporation of HRQL assessments in RCT (preferably blinded studies) is of importance
• HRQL refers to more than signs or symptoms of the disease and its therapy. Socioeconomic and psychological factors may not be well assessed in current HRQL measurement tools.
• Future studies should also evaluate the HRQL in the “real world” outside the context of RCT where the impact of financial toxicity and other social factors may be more marked
Thanks...

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**Our patients and families**