LETTER TO THE EDITOR

Health-related quality of life in Waldenström Macroglobulinemia and IgM-related disorders: A single institution experience

Waldenström macroglobulinemia (WM) is a rare disorder characterized by a serum IgM paraprotein and bone-marrow (BM) infiltration by lymphoplasmacytic lymphoma (LPL).1

Its clinical course is extremely heterogeneous. Observation is indicated for asymptomatic patients while treatment should be considered for symptomatic disease.2

WM may be preceded by previous IgM monoclonal gammopathy of undetermined significance (IgM-MGUS) consisting of the presence of IgM monoclonal component (MC) without LPL. In patients with IgM-MGUS, the risk of developing any lymphoid neoplasm is 16-fold higher than in the general population. The probability of progression is estimated at 1.5%/year with increased risk even 20 years after diagnosis.3

“Immunoglobulin-related disorders” (IgM-RD) identifies symptoms attributable to IgM MC in patients without lymphoma,1 above all IgM-associated neuropathy (30-50%).4

Significant symptoms or risk of organ damage, require treatment directed to the malignant clone. For minimally symptomatic patients, supportive care may be sufficient.5

Assessment of health-related QuoL (HRQuoL) is becoming a critical component of disease outcome evaluation, predicting in some cases patient survival. The concept of HRQuoL in fact, encompasses several aspects of a patients’ well-being, ranging from physical health to functional, psychological, and social features.

In the last decade, specific questionnaires were introduced for patients with different hematological malignancies to supplement the EORTC QLQ-C30.6,7 Considering WM and IgM-MGUS/IgM-RD clinical heterogeneity, their chronicity and advanced median age at presentation, HRQuoL assumes even greater importance in this setting. Despite this, there are no studies addressing the impact of Eastern Cooperative Oncology Group (ECOG) performance status and comorbidities on patients’ outcome. Furthermore, HRQuoL has never been evaluated in this category.

In this study, we analyzed the impact of diagnosis and patients’ characteristics on QuoL.

From October 2017 to January 2019, HRQuoL was assessed in 143 subjects with WM or IgM-MGUS/IgM-RD in our Institute through the administration of EORTC QLQ-C30.6 HADS.8 FACT-GOG neurotoxicity,9 and EQ-5D-5 L questionnaires.10 Patients with IgM MC and BM infiltration by a lymphoproliferative disorder apart from LPL were excluded. Demographic anamnestic and disease-related data were collected. The same questionnaires continue to be administered every 6 months for 3 years to capture changes in HRQuoL over time.

All participants signed an informed consent according to ethical guidelines and principles of the International Declaration of Helsinki.

Here, we present results from the baseline evaluation.

Among the 143 patients, 47 were treated WM (t-WM): 30 previously treated; 17 in treatment with BCR inhibitors. Forty-three patients had untreated disease (ut-WM). Despite none of them having received WM-specific therapy, in nine cases, supportive treatment with low-dose pregabalin was effectively administered for mild neuropathy. Among the 53 patients with IgM-MGUS/IgM-RD, six were defined IgM-RD due to peripheral neuropathy.

Patients’ characteristics are reported in Table 1. No differences were noted among the three groups.

Twelve patients showed ECOG ≥3:6 t-WM; 5 ut-WM, and 1 IgM-MGUS/IgM-RD. Cumulative Illness Rating Scale (CIRS) score > 6 was recorded in 18; 21 and 17 tWM, utWM and IgM-MGUS/IgM-RD, respectively. Vascular and genitourinary were the main systems involved. Genitourinary, vascular, musculoskeletal, and respiratory were the systems most commonly presenting CIRS score of 3-4.

No statistical differences were found among the three groups when analyzing EORTC QLQ-C30 global health status, functional scales (physical, role, emotional, cognitive, and social functioning) and symptoms scale, HADS anxiety and depression scores or FACT-GOG neurotoxicity score.

Notably, EQ-5D VAS score resulted significantly worse in tWM compared to both utWM and IgM-MGUS/IgM-RD, but did not differ when comparing utWM vs IgM-MGUS/IgM-RD.

To evaluate the impact on HRQuoL, all patients, independently of diagnosis, were stratified according to clinical and disease characteristics. Patient-related conditions such as age, higher ECOG performance status and higher CIRS score negatively influenced HRQuoL. Importantly, even in cases of ut-WM and IgM-RD receiving only symptomatic pregabalin treatment with apparent satisfactory symptoms containment, IgM-related neuropathy was detrimental on QuoL. Time from diagnosis did not affect patients’ well-being. Results are summarized in Table 2.
A bivariate linear regression model analysis was performed to compare patients with WM (both ut-WM and t-WM) to those with IgM-MGUS/IgM-RD. Again, diagnosis itself did not impact on any scales. Only high ECOG instead, significantly affected EORTC QLQ-C30 global health status and physical, role, cognitive, and social functioning.

Patients with WM were more anxious than those with IgM-MGUS/IgM-RD, while diagnosis had no influence on HADS depression scale. As expected, both ECOG and neuropathy impacted FACT-GOG score.

Since new treatments tend to prolong overall survival of patients with IgM-related disorders, QuoL is becoming more important during treatment as well as in the observation phase. Our patients’ characteristics are reasonably representative of those commonly seen in daily clinical practice.

To the best of our knowledge, outside clinical studies, this is the first report on HRQuoL in IgM-related disorders. Noteworthy, this unselected population included patients with severe co-morbidity usually excluded from trials.

Our results show that age and clinical conditions, rather than diagnosis, strongly influence patients well-being. Since patients with comorbidity are growing steadily due to an ageing population and improved survival, future research should focus on the sustainability of treatments in this category and their effects on HRQuoL.

EQ-5D VAS score resulted considerably compromised in the group of treated patients although most of them were not receiving active treatment. Notably, the small number of patients enrolled is one of the main limitations of this study not allowing a comparison between therapies. Nevertheless, due to the rarity of these conditions, this would require a long inclusion period or an international approach.

Even though diagnosis per se did not seem to affect most of the questionnaires, patients with WM showed higher levels of anxiety. This could mean that, even for untreated patients, the impact of cancer diagnosis is greater than generally assumed.

In conclusion, the current study represents a real-life picture of patients’ health status useful in decision-making. Further information will come from a longer observation. Furthermore, as HRQuoL assessment is increasingly being recognized as a key component in judging the value of the health care provided, these results may also provide a starting point to measure value-incorporated therapeutic efficacy.

**TABLE 1**  Patients’ characteristics

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>M/F</th>
<th>Median age (years)</th>
<th>Median age at diagnosis (years)</th>
<th>Median time from diagnosis (months)</th>
<th>Median ECOG performance status</th>
<th>Median CIRS score</th>
<th>Median number of concomitant medications</th>
<th>Neuropathy (yes/no)</th>
</tr>
</thead>
<tbody>
<tr>
<td>t-WM (N = 47)</td>
<td>29/18</td>
<td>73.6</td>
<td>63.5</td>
<td>95.6</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>4/43</td>
</tr>
<tr>
<td>ut-WM (N = 43)</td>
<td>28/25</td>
<td>75.1</td>
<td>67.8</td>
<td>78.5</td>
<td>0</td>
<td>5</td>
<td>3</td>
<td>9/34</td>
</tr>
<tr>
<td>IgM MGUS/IgM-RD (N = 53)</td>
<td>28/15</td>
<td>72.4</td>
<td>63.4</td>
<td>98.5</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>6/47</td>
</tr>
</tbody>
</table>

**TABLE 2**  Impact of clinical and disease characteristics on patients’ HRQuoL

<table>
<thead>
<tr>
<th>Diagnosis (P value)</th>
<th>Sex</th>
<th>Med age</th>
<th>Med age at dx</th>
<th>Med time from dx</th>
<th>Med CIRS</th>
<th>Med ECOG</th>
<th>Med N conc med</th>
<th>Neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF2</td>
<td>.9588</td>
<td>.0175</td>
<td>&lt;.0001</td>
<td>0.0003</td>
<td>0.9262</td>
<td>&lt;.0001</td>
<td>0.0002</td>
<td>0.0069</td>
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<tr>
<td>QL2</td>
<td>.6722</td>
<td>0.0309</td>
<td>0.0223</td>
<td>0.0331</td>
<td>0.8774</td>
<td>0.0034</td>
<td>&lt;.0001</td>
<td>0.0819</td>
</tr>
<tr>
<td>RF2</td>
<td>.1146</td>
<td>0.3382</td>
<td>0.0366</td>
<td>0.0379</td>
<td>0.9750</td>
<td>0.0057</td>
<td>&lt;.0001</td>
<td>0.0883</td>
</tr>
<tr>
<td>EF</td>
<td>.4955</td>
<td>0.0688</td>
<td>0.8436</td>
<td>0.9053</td>
<td>0.4744</td>
<td>0.7965</td>
<td>0.1353</td>
<td>0.2783</td>
</tr>
<tr>
<td>CF</td>
<td>.7847</td>
<td>0.8179</td>
<td>0.0143</td>
<td>0.0119</td>
<td>0.8971</td>
<td>0.2115</td>
<td>&lt;.0001</td>
<td>0.2289</td>
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<tr>
<td>SF</td>
<td>.2254</td>
<td>0.7826</td>
<td>0.2872</td>
<td>0.4394</td>
<td>0.6097</td>
<td>0.8342</td>
<td>0.0245</td>
<td>0.8689</td>
</tr>
<tr>
<td>FA*</td>
<td>.4194</td>
<td>0.1222</td>
<td>0.1955</td>
<td>0.2255</td>
<td>0.9175</td>
<td>0.0225</td>
<td>0.0003</td>
<td>0.0483</td>
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<tr>
<td>EQ 5D VAS</td>
<td>.0001</td>
<td>0.5174</td>
<td>0.1588</td>
<td>0.0742</td>
<td>0.1278</td>
<td>0.0224</td>
<td>0.0013</td>
<td>0.0692</td>
</tr>
<tr>
<td>HADS (anxiety)</td>
<td>.6929</td>
<td>0.6102</td>
<td>0.1077</td>
<td>0.1304</td>
<td>0.8425</td>
<td>0.0485</td>
<td>0.0005</td>
<td>0.1023</td>
</tr>
<tr>
<td>HADS (depression)</td>
<td>.5320</td>
<td>0.8278</td>
<td>0.0816</td>
<td>0.0366</td>
<td>0.5206</td>
<td>0.2273</td>
<td>0.0261</td>
<td>0.4472</td>
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<tr>
<td>FACT-GOG</td>
<td>.3973</td>
<td>0.1160</td>
<td>0.0002</td>
<td>0.0018</td>
<td>0.1873</td>
<td>0.0078</td>
<td>&lt;.0001</td>
<td>0.1528</td>
</tr>
</tbody>
</table>

**Note:** Statistically significant values in bold. Abbreviations: CF, cognitive functioning; EF: emotional functioning; FA, fatigue; HADS, hospital anxiety and depression scale; QL2, Global health status; PF2, physical functioning; RF2, role functioning; SF, social functioning.

*aQLQ-C30 single items not reported (none was significant); among symptoms scale, only fatigue is reported (none of the others was significant).
Finally, these data should encourage the wide application of patient-reported outcome questionnaires in clinical practice.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS
A.M.F. and A.T. designed the work that led to the submission, acquired data, interpreted the results, and drafted the manuscript; moreover, A.T. revised the manuscript and approved the final version. M.N. statistically elaborated data, interpreted the results and revised the manuscript. M.D., G.Z., P.M., M.L.P., and R.C. acquired data and revised the manuscript.

Anna Maria Frustaci
Michele Nichelatti
Marina Deodato
Giulia Zamprogna
Periana Minga
Maria Luisa Pioltelli
Roberto Cairoli
Alessandra Tedeschi

ASST Grande Ospedale Metropolitano Niguarda, Department of Hematology, Niguarda Cancer Center, Milan, Italy

Correspondence
Anna Maria Frustaci, ASST Grande Ospedale Metropolitano Niguarda, Department of Hematology, Niguarda Cancer Center, Piazza Ospedale Maggiore 3, 20162, Milano, Italy.
Email: annamaria.frustaci@ospedaleniguarda.it

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ORCID
Anna Maria Frustaci https://orcid.org/0000-0003-2587-7901
Alessandra Tedeschi https://orcid.org/0000-0001-8724-2771

REFERENCES