

Development and validation of QOL-E© instrument for the assessment of health-related quality of life in myelodysplastic syndromes

Research Article

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Received 27 February 2013; Accepted 27 April 2013

Abstract: Objective. Supportive care and sustained health-related quality of life (HRQoL) are essential in the management of myelodysplastic syndromes (MDS), yet specific instruments for the measurement of HRQoL in MDS are lacking. We report on the development and validation of a psychometric questionnaire assessing HRQoL in MDS patients (QOL-E©). Methods. The questionnaire was developed in three stages. First, a Medline search and interviews in focus groups generated a list of concepts important to MDS patients. Second, pilot (derivation) study was performed in a cross-sectional sample of 52 MDS patients. Third, field (validation) testing in a clinical setting investigated psychometric properties in 147 MDS patients from six cohorts. Results. Forty-eight items were identified, and fine-tuned to a 37-item list, then a final 29-item questionnaire containing a general well-being dimension, four general health dimensions (physical, functional, social, and sexual), and disease-related dimensions (fatigue and MDS-related disturbances). Conclusion. Cognitive debriefing and psychometric analyses demonstrated good internal validity and patient acceptability. The QOL-E© is the first HRQoL instrument developed specifically for MDS patients.

Keywords: Myelodysplastic syndromes • Anaemia • QOL-E© questionnaire • Health-related quality of life

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1. Introduction

Myelodysplastic syndromes (MDS, ICD-10-CM D46) are a heterogeneous group of myeloid neoplasms characterized by ineffective haematopoiesis, peripheral blood cytopenias and abnormal cellular morphologies that typically occur in elderly individuals. According to the presence or absence of certain MDS features, which include severity of anaemia, transfusion-dependence, number of peripheral cytopenias, blast counts, cytogenetics, bone marrow fibrosis, and molecular biomarkers, patients are at a variable risk of progression to acute myeloid leukaemia [1,2]. Myelodysplastic syndromes may

be cured with allogeneic hematopoietic stem cell transplantation, but advanced age and patient comorbidities at diagnosis often preclude this therapeutic option [3]. Although treatments, such as erythropoiesis-stimulating agents, lenalidomide, decitabine, and azacytidine, have improved myelodysplastic syndromes management, treatment ultimately fails in most patients [4]. Thus, supportive care and sustained health-related quality of life (HRQoL) are essential in MDS management. The main treatment for myelodysplastic syndromes is red blood cell transfusion to attenuate the most important clinical features of chronic anaemia, which manifest as fatigue and frequent infections [5-7]. Disease burden

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and treatments affect HRQoL and highlight the potential of patient-reported outcomes in supporting clinical and therapeutic decisions [5-10].

Despite the clinical importance of HRQoL in MDS patients, data on the prevalence of MDS-specific disturbances and their correlation with symptoms and cytopenias have not been frequently reported. Historically, there is an absence of a validated instrument to specifically assess HRQoL in MDS patients [11]. Indeed, a review of the appropriateness of existing instruments for evaluating HRQoL in myelodysplastic syndromes found that no existing instrument fully evaluated HRQoL in this patient population [12]. The lack of a specific questionnaire for HRQoL evaluation in MDS patients prompted the development and introduction of a new specific psychometric tool, the QOL-E©, a reliable multi-dimensional self-administered questionnaire that assesses how MDS affects patients' lives. This paper describes the derivation and validation of the QOL-E©.

2. Patients and Methods

2.1. QOL-E© development

The creation of the QOL-E© was undertaken in three phases across several studies: 1) Questionnaire development, 2) Pilot testing (derivation), and 3) Field testing (validation) (Table 1). Informed consent was obtained from all subjects involved in the development of the QOL-E© tool.

Phase 1: Questionnaire development. A MEDLINE literature search was carried out in the year 2000 to identify HRQoL concepts of relevance in MDS patients. The following MeSH terms were searched and combined with "myelodysplastic syndromes": "quality of life", "performance status", and "well-being". All potentially relevant issues identified through the literature review were categorized and used to inform subsequent development stages.

Interviews were performed in a focus group of consecutive MDS patients (n=10) from Reggio Calabria, Italy, who referred to the clinic, to explore issues of importance. Patients described how their disease affected their lives and the issues that impeded their HRQoL. All information was registered for each patient and combined with issues identified from the literature to generate an initial list of concepts. Item phrasing and response options were graded. Recall periods of seven days were considered appropriate, based on transfusion dependence (*i.e.* patients referring weekly to the clinic). The list of concepts was reviewed by two haematologists (E. N. Oliva and F. Nobile) involved in interpreting the findings from each phase of the process. An additional patient also participated in the review (Table 1). The relevance and importance of each concept was rated, based on frequency and on clinical experience. Items associated with personal or unrelated problems were discarded. The list of generated items of the resulting instrument was applied in pilot testing.

Phase 2: Pilot testing. The draft item list was derived in a cross-sectional study of 52 MDS patients from

Table 1. Development of the QOL-E© instrument and study descriptions

Stage of development	Components	Procedure and study	N	Instrument
1. Development of draft questionnaire	Literature review Focus groups Physician input Concept elicitation Acceptability	Pilot interviews	10 + 1 patients 2 HCPs	-
2. Pilot testing and refinement draft questionnaire (V1.0 and V2.0)	Acceptability and feasibility Construct validity Concurrent validity Clinical validity Reliability Scoring	Pilot study Pilot study (re-analysis) Re-test of sub-group of pilot study population	52 52 39*	48-item draft QOL-E© FACT-G QOL-E© V1.0 (37-item) QOL-E© V1.0 (37-item)
3. Field testing and psychometric evaluation of QOL-E© V2.0	Reliability Construct validity Clinical validity Concurrent validity	Darb-MDS study [20] Catania study Heart-MDS study [19] QoL-ESC Rev-MDS study [21] US study Bulgaria study [22]	39 27 11 43 14 13	QOL-E© V2.0 (29-item)

Notes: *Same patient cohort as pilot study. Darb, darbepoetin; FACT-G, Functional Assessment of Cancer Therapy-General; HCPs, healthcare practitioners; Rev, Revlimid (lenalidomide)

Reggio Calabria, Italy. The same patients completed the Functional Assessment of Cancer Therapy-General (FACT-G) instrument for the purpose of comparison and validation. Acceptability and feasibility of the draft instrument was assessed, and item variability, severity, prevalence and inter-item correlation were tested. Subjects undertook the questionnaire in a clinic setting. After questionnaire completion, patients were asked questions concerning their interpretation of the items, the appropriateness of the response choices, the clarity of the instructions and the extent to which any important issues were not addressed. Based on statistical analyses, items were removed from the draft list and the QOL-E© V1.0 was produced and re-analysed using data from the original 52 patients. This version was also re-tested within two months in a sub-cohort of 39 patients of the original pilot study population to investigate its reliability (compared with the findings from the same items when completed by the same patients previously). Additional statistical analyses were performed to further evaluate the items, and a second 29-item version of the instrument was derived (QOL-E© V2.0).

Phase 3: Field testing. The QOL-E© V2.0 was investigated in a pooled validation database including 147 MDS patients from six cohorts from studies performed in Italy, the United States, and Bulgaria between 2002 and 2010 (Table 1). The psychometric properties of the instrument were explored in a clinical setting.

2.2. Statistical methods

Phase 1: Questionnaire development. Items were generated and placed in an order that reflected different domains, before further re-grouping them with applied statistical methods (factor analysis).

Phase 2: Pilot testing. Items from the completed questionnaires were scored, assessed and analysed for variability by descriptive statistics (mean, standard deviation [SD], and 95% confidence intervals [CI]), normality distribution tests (Kolmogorov-Smirnov or Shapiro-Wilk), and frequency distribution methods (chi-square). Statistical significance was assumed at $p < 0.05$, unless otherwise stated.

Factor and reliability analyses were performed to group items into domains and to identify redundant items for deletion. Principal component analysis with varimax rotation, and Kaiser normalisation was used with scree plots to establish item clusters (minimum 80% explained variance by the identified components). Factors were retained when the eigenvalue was > 1.0 . A threshold for factor loading of 0.45 was fixed for the principal component analysis: items that did not load well

(< 0.45) with their own factor and items that loaded ≤ 0.45 on more than one factor were considered for deletion.

Intra-class correlation coefficient and standardized Cronbach's alpha (SCA) coefficient were calculated to test the reliability of the dimensions and summary subscales, with alpha ≥ 0.70 assumed acceptable [13–15].

In order to further explore concurrent validity, the newly created dimensions of QOL-E© V1.0 were correlated with known similar dimensions of the validated FACT-G instrument in the 52 patients from the original cohort. Multiple regression analysis was performed with HRQoL domains as a dependent variable, and haemoglobin (Hb) level, age, number of transfusions and duration of myelodysplastic syndromes as independent variables.

Phase 3: Field testing. Reliability analysis (including correlation analysis and inter-item correlation) was performed. Construct validity was investigated using descriptive statistics (mean, SD, 95% CIs), normality of distribution tests (Kolmogorov-Smirnov or Shapiro-Wilk), and frequency distribution methods (chi-square).

2.3. Completion, scoring and standardization of QOL-E© V2.0

A standardized scoring algorithm was derived for the final instrument, based on the Head and Neck Quality of Life questionnaire scoring system [16]. The QOL-E© V2.0 is scored using a standardized scale, from 0 to 100. Item responses take the form of Likert-scale or dichotomous response options. A higher score indicates better HRQoL for that domain. Where items are temporal, the recall period for the instrument is one week, with the exception of one general health item (one month).

3. Results

Phase 1: Questionnaire development. The literature search identified 46 studies that reported HRQoL in MDS patients, none of which included myelodysplastic syndromes-specific HRQoL instruments. The following concepts important to patients were identified through the focus group: general well-being, ability to perform daily activities, difficulty in staying awake, physical well-being, sexual functioning, fatigue, perception of being a nuisance to family members, relationship with health-care practitioners, myelodysplastic syndromes-related disturbances (frequent hospital visits, transfusions, inability to travel, dyspnoea when climbing stairs, worry and stress). The first draft questionnaire, generated in Italian, consisted of 48 items across six domains (Table 1).

Phase 2: Pilot testing. Fifty-two MDS patients participated in the cross-sectional pilot study (Table 2). At the time of the assessment, patients were diagnosed according to the French-American-British (FAB) classification: 48 had refractory anaemia, two had refractory anaemia with excess blasts, one had refractory anaemia with excess blasts in transformation, and one had chronic myelomonocytic leukaemia. Gender distribution was equal. Forty-one patients (79%) had anaemia. Eleven transfusion-free (TF) patients were on recombinant human erythropoietin alpha treatment. Thirteen patients (25%) were receiving supportive care (1–4 red blood cell transfusions per month), of which five were also receiving rHuEpo alpha at the time of the evaluation.

Following initial assessment of all 48 items in these patients, the factor analysis identified 15 main components that explained at least 80% of the variance (Figure 1). After applying the pre-specified exclusion criteria, the number of items was reduced from 48 to 37 (Table 1), because they did not fit, were not comprehensible or were misunderstood by participants. After cognitive debriefing with respondents, some items were rephrased in order to improve clarity. This did not affect the test-retest comparison [12]. The first applicable version of QOL-E® V1.0 contained 37 items in six dimensions: physical (six items), functional (four items), social (five items), sexual (three items), fatigue (eight items) and MDS-specific (11 items) [17].

Results from re-testing within two months in a cohort of 39 of the original 52 patients were compared with those obtained at initial evaluation. SCA coefficients for the six domains of QOL-E® V1.0 were (test; retest): physical (0.83; 0.75), functional (0.80; 0.73), social (0.77; 0.67), sexual (0.88; 0.92), fatigue (0.73; 0.75) and MDS-specific (0.78; 0.76). All QOL-E® V1.0 dimensions

demonstrated good internal validity on the two consecutive applications in MDS patients. Test-retest analysis of the stability of scores over time showed intra-class correlation coefficients between 0.65 and 0.80 for the six domains over a period of less than two months, during which an MDS patient's condition would not have been expected to change significantly.

Concurrent validity was assessed for QOL-E® V1.0 against results obtained from administering the FACT-G questionnaire in the 52 patients (Table 1). Many items from the QOL-E® V1.0 mapped statistically significantly to the dimensions of FACT-G with a correlation coefficient ≥ 0.71 (considered as a strong relationship), particularly for the physical well-being, emotional well-being, functional well-being, overall, and treatment outcome index scores for the FACT-G. Construct validity was also supported by factor analysis, which showed that many domains between the two instruments formed clusters. The physical dimension of QOL-E® V1.0, for example,

Figure 1. Factor analysis of the 48-item draft QOL-E© instrument in the pilot (derivation) study (n=52 patients)

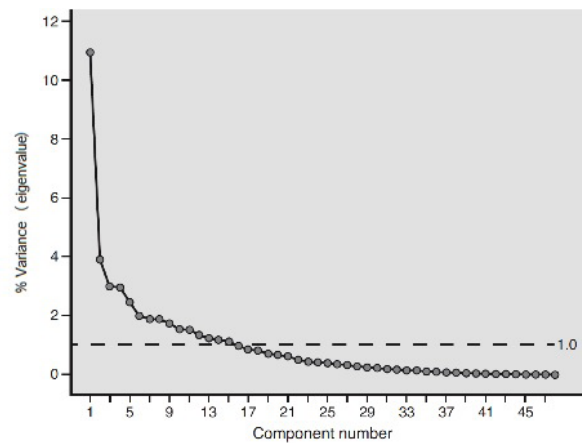


Table 2. Baseline characteristics from pilot study and validation database

Pilot study (derivation)				
Characteristics	N	Mean	SD	Median (range)
Age (years)	52	71.80	11.39	73.77 (40.86–88.48)
Hemoglobin (g/dL)	52	10.04	2.38	9.80 (6.80–16.40)
pRBC units transfused per month*	52	0.56	1.07	0.00 (0.00–4.00)
Time from diagnosis (months)	52	36.52	32.16	25.18 (1.17–139.73)
Validation database**				
Characteristics	N	Mean	SD	Median (range)
Age (years)	147	69.54	10.32	70.48 (35.63–88.07)
Hemoglobin (g/dL)	120	9.30	1.62	9.00 (7.00–16.00)
pRBC units transfused per month	103	0.64	1.31	0.00 (0.00–8.00)
Time from diagnosis (months)	133	32.36	41.44	18.20 (0.07–323.84)

Notes: *pRBC, packed red blood cells, **Baseline data were merged from all six validation studies, before any treatment was initiated.

clustered very well with functional well-being and physical well-being domains of the FACT-G (not shown).

Previously published data showed that QOL-E© V1.0 had good clinical validity in a stepwise regression analysis performed on cross-sectional data from the initial cohort of 52 patients. Hb level appeared as an independent predictor of physical well-being, fatigue, and general well-being, while associations with social, myelodysplastic syndromes-specific (MDSS), and treatment-outcome index (TOI) scores were not significant. Transfusion requirement maintained independent significant effects on social, MDSS, TOI, and total scores. At retest, Hb levels were not associated with QOL-E© measures, whereas the transfusion requirement was a significant independent marker of TOI and physical and MDSS well-being [12].

Based on these findings, eight further items were removed from the questionnaire and the final 29-item QOL-E© V2.0 was created (available from http://www.qol-e.com/Files/QOL-E_EN_v2.pdf). This version consists of two single items concerning general perception of well-being (not fitting into a multi-item scale), and four items addressing physical (QOL-FIS), three items in functional (QOL-FUN), four items in social (QOL-SOC), two in sexual (QOL-SEX) well-being, seven addressing HRQoL related to fatigue (QOL-FAT), and seven disease-specific items composing the QOL-MDSS domain (Table 3). The QOL-GEN is derived from the sum of all domains, except QOL-MDSS. The QOL-ALL score is the sum of QOL-GEN and QOL-MDSS. A treatment-outcome index (QOL-TOI), denoting the treatment-specific domain, is derived from the sum of QOL-FIS, QOL-FUN and QOL-MDSS [18].

Phase 3: Field testing. The QOL-E© V2.0 was validated in the pooled analysis of 147 patients from six clinical trials. The subjects enrolled (male/female ratio 64/83) represent a relatively diverse MDS patient group, with ages ranging from 36 to 90 years, and duration of disease of less than a month to over 10 years (Table 2). IPSS scores were available in 82 patients, 70% of which were low risk and the remaining Intermediate-1. According to FAB classification (missing=13) 95 cases had refractory anaemia with or without ringed sideroblasts, 10 had refractory anaemia with excess blasts, and 2 had chronic myelomonocytic leukaemia. Patients had been classified according to 2008 WHO classification (N=82): 34 were refractory anaemia with or without ringed sideroblasts, 32 had refractory cytopenia with multilineage dysplasia with or without ringed sideroblasts, 25 patients had myelodysplastic syndromes with del5q and 1 had MDS-unclassified. Thirty per cent of patients required regular transfusions. Of note, not all characteristics were available in all patients, due to the different data

sources that formed the pooled database. QOL-E© V2.0 data was collected cross-sectionally at baseline in all studies, alongside other measures of clinical effect and HRQoL, such as the EORTC QLQ-C30 questionnaire. Some cross-sectional and longitudinal data have been reported separately [19–22].

Feasibility and time to completion improved in the revised 29-item instrument. Descriptive analysis of the final instrument demonstrated a balanced distribution of the standardized scores within items and domains, with no observed floor or ceiling effects. Mean domain scores varied between 43.6 (Functional) and 68.1 (Fatigue) points across the nine sub-scales, within a range of values from 0 to 100 points (95% CI 39.3–71.34) (Figure 2A). Although it is difficult to completely exclude possible ceiling effects, these are very unlikely since the 95% CIs are well within the minimum and maximum of the middle 50 points (25–75) of the scale. Moreover, the summary scales, especially the treatment-outcome index, have minimal and maximal values well within the 0–100 limit. Reliability analysis showed good internal validity, with an SCA coefficient ≥ 0.70 in all domains (Figure 2B).

4. Discussion

Complications and symptoms of myelodysplastic syndromes and the most common forms of treatment are known to affect the lives and lifestyles of individuals with MDS [5–10]. Yet, formal assessment of HRQoL in this population has not routinely been undertaken in observational or clinical trials [10]. The lack of a reliable instrument specifically designed to elicit HRQoL information from MDS patients means that it is unclear whether HRQoL impact has been fully characterized in these patients. An initial evaluation of the HRQoL instrument, FACT-An, in MDS patients observed acceptable levels of internal consistency for the physical, functional, and fatigue components of the questionnaire, whereas the seven-item non-fatigue component of the anaemia subscale was not reliable [12]. In a systematic review evaluating the use of HRQoL instruments in MDS patients, QOL-E© was the only MDS-specific HRQoL instrument reported. The most frequently used HRQoL instruments in myelodysplastic syndromes research were FACT and EORTC QLQ-C30. Among the common problems identified in the published literature were a lack of power calculations to detect clinically relevant changes and small sample sizes, undermining the weight of study conclusions [10]. The QOL-E© is the first instrument developed to specifically assess HRQoL in MDS patients. To date, QOL-E© had not been

validated or widely evaluated in a large myelodysplastic syndromes cohort.

The impact of transfusions on daily living should be taken into account when evaluating the effects of supportive care. A recent report on the use of darbepoetin +/- G-CSF and transfusions to reach a target Hb level of 120 g/L showed that EORTC QLQ-C30 QoL scores improved significantly during the study, with similar results for transfused and untransfused patients, though the impact of transfusions on daily life was not evaluated [23]. Since there is no consensus on the optimal transfusion regimen to improve HRQoL in transfusion-dependent myelodysplastic syndromes, QOL-E[®] may help address this issue, by focusing on the domains most clinically important to MDS patients.

Several studies have reported a positive correlation between Hb levels and HRQoL [9,19,20,24–31], although this correlation is not consistent [6]. The current data reinforce the notion of a relationship between Hb levels and QOL-E[®] as specific patient-reported outcome in MDS patients. The independent impact of comorbidities on QOL-E[®] scores has been determined in a previous report, which also showed the lack of impact of other prognostic features on HRQoL in myelodysplastic syndromes [32].

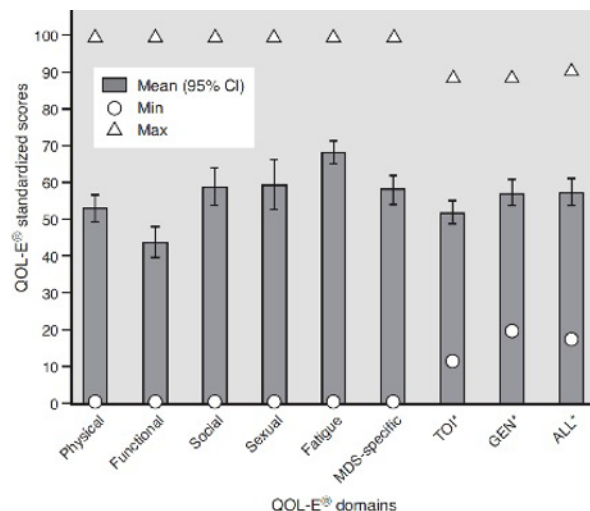
Content validity was established based on a robust derivation and conceptualization process involving physicians and patients, with over 300 participants, including individuals from different regions and with varying disease profiles. Construct validity was supported by the correlation observed between QOL-E[®] domains and relevant clinical measures of disease severity – such as Hb level and transfusion status – as well as with

established subjective measures of outcome in similar disease areas, such as the FACT-G instrument.

The reliability of QOL-E[®] was well established through extensive psychometric evaluation in both the pilot study and the pooled validation database of patients who completed the QOL-E[®] in the clinic. Internal consistency was shown to be good across all domains of the QOL-E[®] in both pilot and validation studies, with SCA coefficients ≥ 0.70 in all cases. Principal component analysis confirmed the structure of the QOL-E[®] as consisting of two single items and six domains incorporating 27 items (Table 3), which translate into a total of nine combined computed constructs.

Further prospective validation of the QOL-E[®] is underway, in particular with a view to exploring the sensitivity of the instrument to detect within-patient change in HRQoL over time in longitudinal cohorts. Examples include validation in low-risk MDS patients with severe thrombocytopenia to evaluate the sensitivity of QOL-E[®] to increases in platelet count. Importantly, QOL-E[®] has been also applied in elderly patients with such other diseases as acute myeloid leukaemia [33], and in several languages [34], and may become a widespread tool for the HRQoL evaluation in haemato-oncological diseases. For instance, the exploration of the dynamics of disease progression in myelofibrosis to acute myeloid leukaemia and, as it has also been recently shown, to acute lymphoblastic leukaemia [35], with its impact on HRQoL, may also be enriched by the reliable application of QOL-E[®] as shown previously [36]. Furthermore, linking the study of quality of life by QOL-E[®] with such novel independent prognostic indicators of outcomes in MDS patients as *TP53* mutations [37], while taking

Figure 2A. Distribution and reliability of QOL-E[®] V2.0 in 147 MDS patients Distribution of standardized QOL-E[®] scores



*Summary items. TOI, treatment outcome index; GEN: all domains except MDS-specific; ALL: GEN + MDS-specific

Figure 2B. Distribution and reliability of QOL-E[®] V2.0 in 147 MDS patients Standardized Cronbach's alpha coefficient

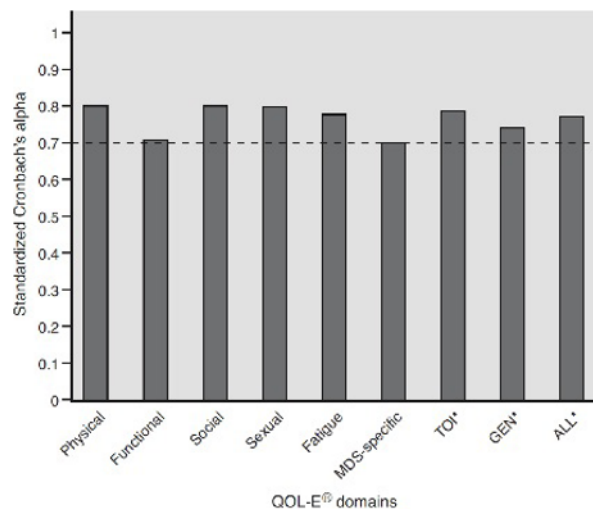


Table 3. QOL-E© V2.0 domains and items*

Domain	Item
General perception of well-being 1	In general, you would say that your health is
General perception of well-being 2	Compared to a month ago, your health is
Physical well-being (QOL-FIS)	Performing heavy activities
	Climbing stairs
	Lowering myself
	Taking care of myself
Functional well-being (QOL-FUN)	I got very little done
	I had more fatigue doing my work
	Difficult for you to stay awake during the daytime?
Social / family well-being (QOL-SOC)	My present condition interferes too much with my life
	I feel oppressed by my disease
	I feel that I am a burden for my family
	Your health would be an impediment for you to keep a paid job
Sexual well-being (QOL-SEX)	The effect on your sex life
Fatigue (QOL-FAT)	In the last week, was getting sexually excited a problem for you?
	How much did fatigue get in the way with your daily chores?
	How much fatigue did you have?
	How much did headache disturb you?
	How much did palpitations (i.e. heart pounding) disturb you?
	How much did the difficulty in taking care of yourself disturb you?
	How much did being bedridden disturb you?
	Did you get enough sleep?
	Did shortness of breath while climbing the stairs disturb you?
	Being dependent on transfusions
MDS-specific (QOL-MDSS)	Not being able to do house chores
	Not being able to travel
	Being dependent on the hospital, doctors and/or nurses
	Stress and worry because of the disease
	Side effects of treatment

*Note: The description is extracted from the original QOL-E questionnaire (www.qol-e.com/Files/QOL-E_EN_v2.pdf)

into account the conceived cytogenetic risk, will not only contribute to the improvement of the future MDS scoring systems, but will certainly further refine the classification of prognosis types in this heterogeneous group of haemato-oncological disorders.

5. Conclusion

The QOL-E© is the first reliable specific instrument for assessing the impact of myelodysplastic syndromes on patient HRQoL. The use of this questionnaire in observational and interventional studies will help to reveal better the burden of disease-associated complications and

symptoms in MDS patients, and improve understanding of how treatment affects patient well-being.

Acknowledgements

We are grateful to Dr Stefana Impera, MD (Haematology Unit, Presidio Ospedaliero Garibaldi-Nesima, Catania, Italy) for the recruitment and assessment of patients in the Catania Study; to Dr Donka Serbezova (Clinical Laboratory Division, Government Hospital, Ministry of Health, Sofia, Bulgaria) for the patients in the Bulgarian study; as well as to Mary Thomas (Veterans Affairs Palo Alto Health Care System, CA 94304, United States) for

the patients in the USA study. We also thank Dr Vanessa Gray-Schopfer, OmniScience SA and Adam Hutchings, Global Market Access Solutions, who provided medical writing assistance and technical services as facilitated and funded by Celgene International (Switzerland). BDD was sponsored by an unrestricted grant from Celgene International (Switzerland). The sponsor, however, did not have any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval and submission of the manuscript for publication. The authors take full responsibility for the final version.

Contributions

All authors were responsible for performing the research, data interpretation and drafting the manuscript.

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Conflicts of interest

The authors have received licensing fees for utilisation of the QOL-E© instrument.

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