Quality of Life in Myelodysplastic syndrome Patients: What have we learned so far?

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Conflict of interest: none
Number of Publications about Quality of Life (QoL) in Oncology 1991-2007

Data extracted from PubMed
A frequent and “implicit” assumptions about Quality of Life assessment in hematology

Evaluating Quality of Life in hematology...
...it is something “new”!

Is this entirely correct?

What has actually been changed over the last decade is the approach and the methodology.

THAT IS: From indirect measurements to patient-direct measures!
QUALITY AND QUANTITY OF SURVIVAL IN ACUTE MYELOID LEUKÆMIA

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Summary The quality of life in leukaemia is as important as its quantity. In fifty-one patients the quality and quantity of life were improved by less aggressive treatment than is usual. By not trying to induce complete remission at all costs, the morbidity and early mortality were reduced and at least an equivalence in survival was obtained.

and have specifically documented infections, which contribute to morbidity.

For convenience the survival-rates have been compared with the latest M.R.C. trial\(^1\) in which more aggressive treatment was used. It will be seen that, though our patients rarely entered complete remission, their survival is longer than that of the patients in the M.R.C. trial and we suspect their quality of life is better.

Patients and Methods

All previously untreated adult patients with acute non-lymphatic leukaemia presenting at University College Hospital between June, 1969, and June, 1975, are reviewed. Patients with blast transformations from chronic myeloid leukaemia and myeloid metaplasia are excluded. Private patients are also excluded because of the lack of follow-up. Fifty-one patients aged 13-88, are included. There is a high proportion of elderly patients in our series, and three patients had other malignan...
Patient-Reported Outcomes (PRO) Instruments:
For example:
- EORTC QLQ-C30
- FACIT-Fatigue
- SF-36
Guidance for Industry
Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
19003 New Hampshire Ave., Bldg. 8, Rm. 2201
Silver Spring, MD 20993-0002
Tel: 301-796-5400; Fax: 301-448-3714; E-mail: druginfo@fda.hhs.gov

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or
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(Tel) International Staff: 301-827-5993
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2009
Clinical/Medical

Draft agreed by the Efficacy Working Party
September 2004

Adoption by CHMP for Release for Consultation
November 2004

End of Consultation (Deadline for Comments)
February 2005

Agreed by the Efficacy Working Party
June 2005

Adoption by CHMP
July 2005

Date for Coming into Effect
January 2006

Committee for Medicinal Products for Human Use (CHMP)

Reflection Paper on the Regulatory Guidance for the Use of Health-Related Quality of Life (HRQOL) Measures in the Evaluation of Medicinal Products

London, 27 July 2005
SYSTEMATIC REVIEW ON QUALITY OF LIFE RESEARCH IN MDS PATIENTS

OBJECTIVES:

Based on...
- Efficace et al. EHA, Berlin, 2009 (Oral presentation)

1. How many prospective studies in patients with MDS have included Patient-Reported Outcomes (PROs) (e.g. quality of life and symptom burden) ?

2. What is the ‘quality’ of these studies and to what extent are these likely to support clinical decision-making?

Main criteria for considering studies:

- Only prospective studies (including RCTs)
- Any kind of MDS
- Any kind of PROs (e.g. Quality of Life)
- Selected from 1980 – 2009 (e.g. MedLine, SCOPUS...)
Main factors affecting patient’s quality of life (QoL) in patients with MDS (Thomas ML, 2006)

- Older Age
- Co-morbidity
- Transfusions
- Infections
- Symptom burden related to the disease/treatment (i.e. fatigue)
- Limited survival

While there is robust evidence on the value of QoL research in patients with solid tumors, no solid evidence exist in patients MDS.

Recent International Working Groups/guidelines in Hematology emphasize the role role of QoL and highlights the need of more research into this area (Tefferi et al, 2006; Rodeghiero et al. 2008; Cheson et al, 2006; Hallek et al, 2008).

Regulatory Agencies and Scientific Societies have been supporting the use of QoL as a key outcome measure in clinical trials for a number of years (FDA 1985, ASCO 1996...).

“...The FDA is encouraging the medical research community to use PROs in clinical trials to help tell whether a new drug or medical device is working and how well it is working” FDA Consumer Magazine, 40(6), Nov.-Dec, 2006
RESULTS 1980-2009
10 prospective studies enrolling 832 MDS patients

**Year of Publication**

- 2000-2004: 4
- 2004-2009: 6

**Sample Size** (No. of patients)

- Less than 100: 4
- More than 100: 6

**PRO measure used**

- FACT measures: 4
- EORTC QLQ-C30: 6

**RCTs versus non RCTs**

- No-RCTs: 5
- RCTs: 5

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10 prospective studies enrolling 832 MDS patients.
### 5 Prospective -non-RCTs- in patients with MDS

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample</th>
<th>Treatment</th>
<th>PRO measure</th>
<th>Assessment schedule</th>
<th>PRO compliance over time</th>
<th>Summary of PRO results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stasi et al. 2005</td>
<td>53 low-int-1-risk MDS pts</td>
<td>Darbepoetin alfa for 24 weeks</td>
<td>FACT-An; LASA</td>
<td>Baseline and 24th week</td>
<td>baseline data missing; 90% after 24 weeks</td>
<td>Improvement of QoL in responders, especially on anemia and fatigue subscales</td>
</tr>
<tr>
<td>Giagounidis et al. 2005</td>
<td>29 isolated (5q) MDS pts</td>
<td>ATRA + Tocopherol-alfa for 180 days</td>
<td>EORTC QLQ-30</td>
<td>Baseline, 90 and 180 days</td>
<td>baseline and 90 days data missing; 69% after 180 days</td>
<td>No significant improvement of QoL in any pts</td>
</tr>
<tr>
<td>Aloe Spiriti et al. 2005</td>
<td>133 low-risk MDS pts</td>
<td>rHEPO alfa for 24 weeks</td>
<td>FACT-An</td>
<td>Baseline, 4th and 8th week</td>
<td>77% baseline; 73% after 4 weeks; 65% after 8 weeks</td>
<td>Improvement of QoL in responders, correlated to erythroid response</td>
</tr>
<tr>
<td>Clavio M et al. 2004</td>
<td>11 low-risk MDS pts</td>
<td>rHEPO alfa for 12-24 weeks</td>
<td>FACT-An</td>
<td>Baseline and 12-24th week</td>
<td>100% baseline; 73% after 12-24 weeks</td>
<td>Improvement of QoL in responders, correlated to erythroid response</td>
</tr>
<tr>
<td>Hellstrom-Lindberg et al. 2003</td>
<td>53 MDS pts</td>
<td>rHEPO beta+G-CSF for 12-20 weeks</td>
<td>EORTC QLQ-C30</td>
<td>Baseline and 12th week</td>
<td>68% baseline; 60% after 12 weeks</td>
<td>Improvement of QoL in responders</td>
</tr>
<tr>
<td>Authors</td>
<td>Overall no. of patients (patients with PRO data)</td>
<td>MDS Subtypes FAB or WHO (IPSS)</td>
<td>Treatment outline</td>
<td>PRO measure used</td>
<td>Summary of traditional clinical outcomes</td>
<td>Summary of PRO results</td>
</tr>
<tr>
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<tr>
<td>Greenberg et al, 2009</td>
<td>102</td>
<td>RA, RARS, REAB, CMML</td>
<td>EPO and support care versus supportive care alone</td>
<td>FACT-G</td>
<td>No difference in OS between treatment arms. Improved erythroid responses in EPO arm</td>
<td>No difference between treatment arms. However, patients with erythroid responses reported some QoL benefits over time</td>
</tr>
<tr>
<td>Kantarijan et al. 2006</td>
<td>170 (unknown)</td>
<td>FAB: RA, RARS, RAEB-t, CMML (int-1; int-2; high-risk)</td>
<td>Decitabine versus supportive care</td>
<td>EORTC QLQ-C30</td>
<td>Higher overall response rate and longer median time trend to AML in patients treated with decitabine compared to those on supportive care</td>
<td>Decitabine &gt; best supportive care</td>
</tr>
<tr>
<td>Balleari et al. 2006</td>
<td>30 (18)</td>
<td>WHO: RA, RARS, RCMD, RAEB-1  (low-risk)</td>
<td>rHEPO Beta versus rHEPO Beta + G-CSF Filgrastim</td>
<td>FACT-An</td>
<td>Better although not statistically significant erythroid response in the rHEPO Beta + G-CSF arm compared to the rHEPO arm</td>
<td>No difference</td>
</tr>
<tr>
<td>Casadevall et al. 2004</td>
<td>60 (57)</td>
<td>FAB: RA, RARS, RAEB (low; int-1; int-2; high-risk)</td>
<td>rHEPO alfa + G-CSF lenograstim versus supportive care</td>
<td>FACT-An</td>
<td>Better erythroid response in the rHEPO alfa + G-CSF lenograstim arm in comparison with supportive care</td>
<td>No difference</td>
</tr>
<tr>
<td>Kornblith et al. 2002 (Silverman et al)</td>
<td>191 (189)</td>
<td>FAB: RA, RARS, RAEB, RAEB-t; CMML (unknown)</td>
<td>Azacitidine versus Supportive care</td>
<td>EORTC QLQ-C30; Mental Health Inventory; Patient’s perception of improvement</td>
<td>Azacitidine treatment yielded a higher response rate, reduced risk of leukemic transformation and improved survival</td>
<td>Azacitidine &gt; supportive care</td>
</tr>
</tbody>
</table>
Conclusions

- There is **lack of data** regarding QoL in patients with MDS, although the number of studies has been increasing since 2000 and it is expected to grow...

- There is **robust evidence** that AZA can provide better QoL outcomes than supportive care alone.

- There is **preliminary evidence** suggesting that Decitabine could potentially provide better outcomes as compared with supportive care, but this **needs to be confirmed by additional data**.

- **Urgent efforts are needed to implement** methodologically sound studies in this area to understand what is the burden of the disease and treatment related effects from the patient’s perspective.

**GIVEN THE LACK OF RESEARCH....**
Prognostic significance and longitudinal assessment of patient-reported QoL and symptoms in high-risk MDS. 

An international prospective observational study

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**Participating Centers:**

Participating countries = **15** (including: Austria, Italy, Germany, Belgium, France, China, UK, USA)

Centers obtained IRB/ethics approval = more than 40

**General Scope**

To provide patient-reported evidence based data to further facilitate clinical decision-making process in higher-risk MDS patients (IPSS int-2 and high-risk).

**Some key research questions of the study**

- Is pretreatment patient’s self-reported *fatigue* an independent prognostic factor for survival beyond previously known key prognostic data?
- to prospectively evaluate short-term quality of life and symptoms.
- **CLINICAL DECISION-MAKING PROCESS:** for example...to extent patients prefer to be involved in treatment decision-making? Can we identify patients who might benefit most from a ‘*shared decision-making*’ approach?
- to establish international QoL and symptoms baseline reference data to be used as benchmarks for comparisons in future therapeutic trials.
- to investigate the prognostic value of early change of QoL and symptoms for overall survival and for disease progression (i.e. AML transformation).

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