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

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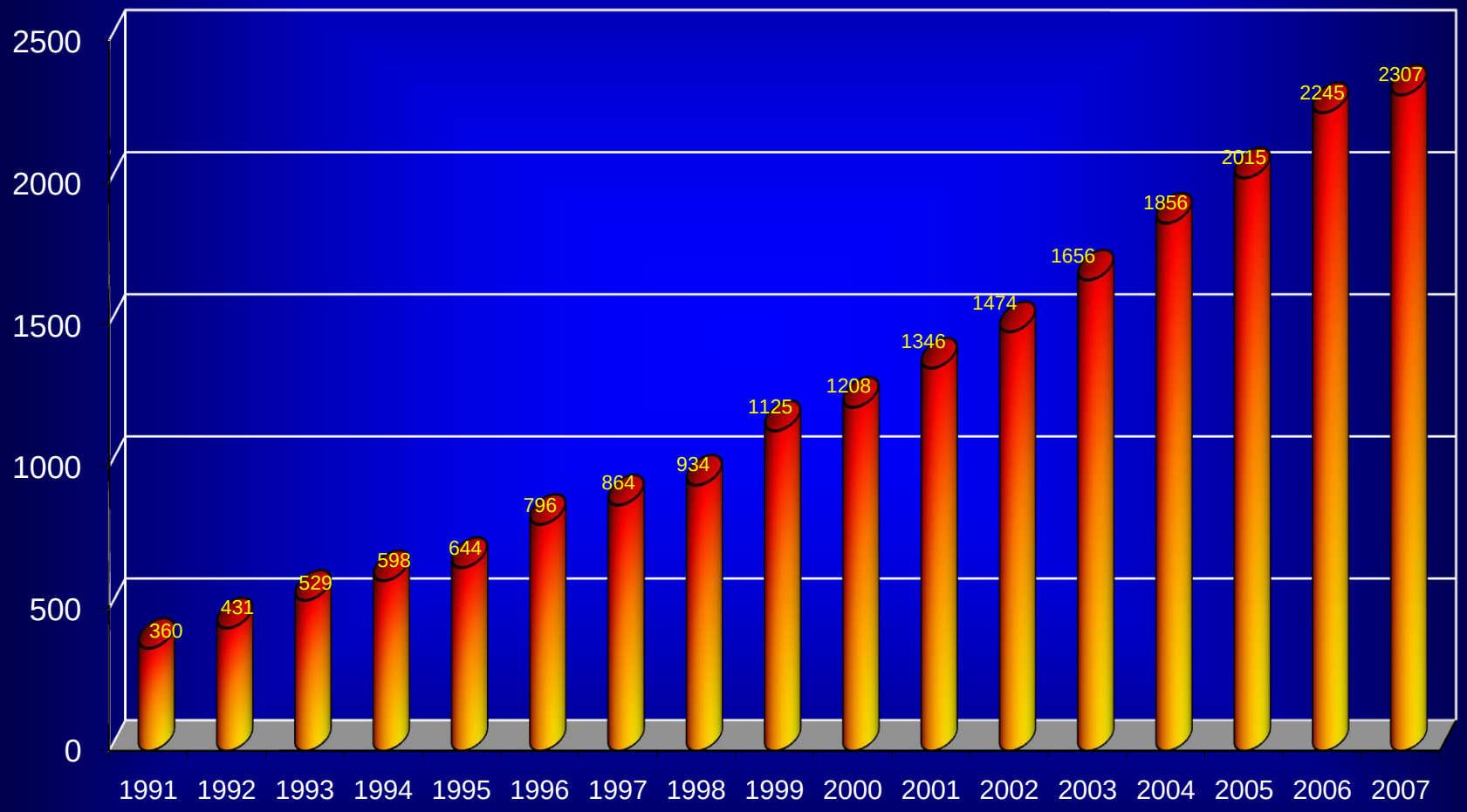
European Leukemia Net (ELN), February, 2010

Conflict of interest: none

Number of Publications about Quality of Life (QoL) in Oncology 1991- 2007



Data extracted from PubMed

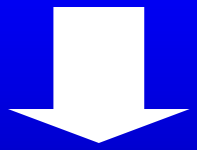
GIMEMA
Gruppo Italiano Malattie EMatologiche dell'Adulto

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!

The Lancet · Saturday 4 October 1975

QUALITY AND QUANTITY OF SURVIVAL IN ACUTE MYELOID LEUKÆMIA

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D. S. THOMPSON
T. A. J. PRANKERD
M. SARE
P. WRIGHT

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Summary The quality of life in leukæmia 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.

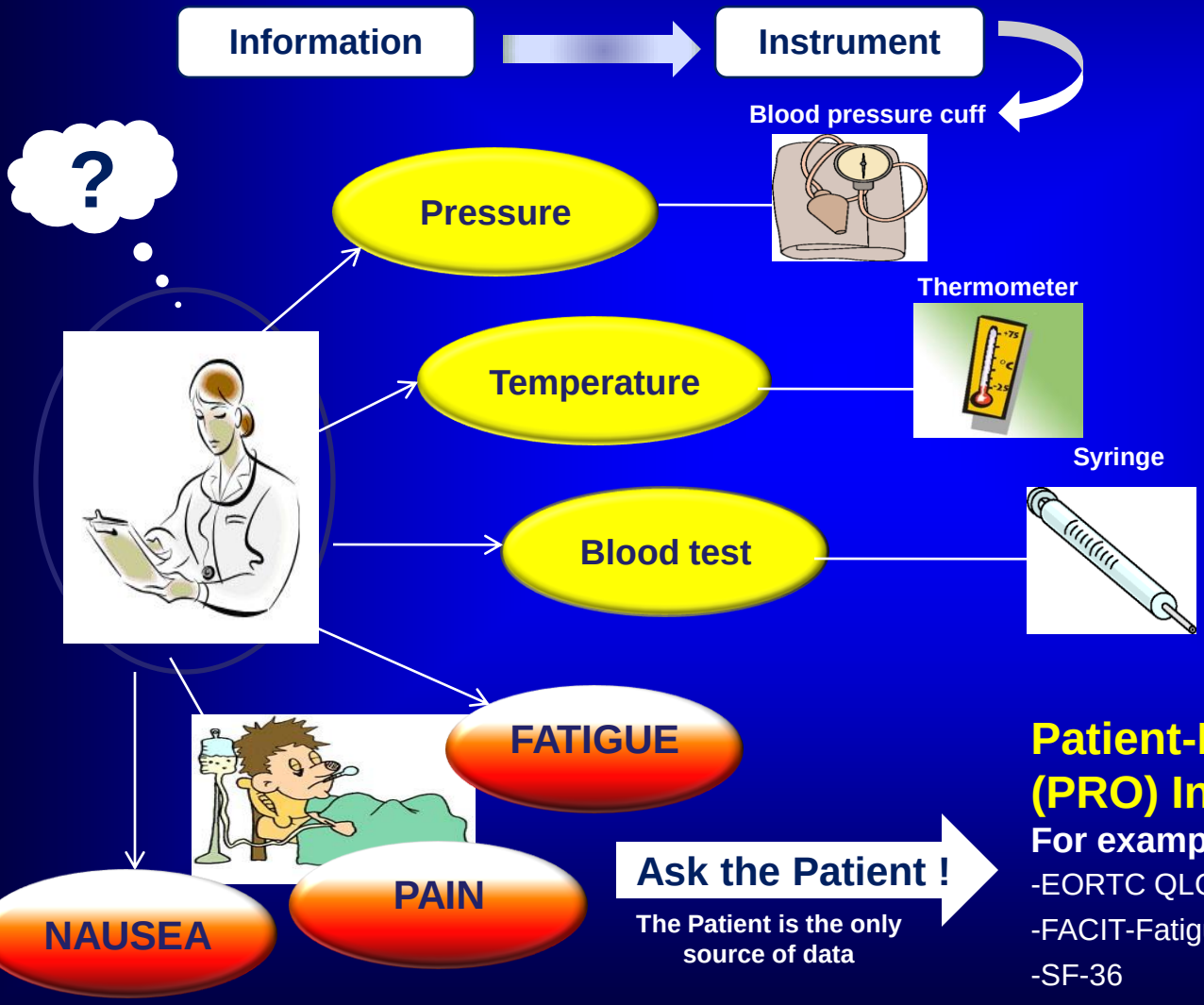
For convenience the survival-rates have been compared with the latest M.R.C. trial[1] in which more aggressive treatment was used. It will be seen that, though our patients rarely entered complete remission, their survival is longer than that of the patients in the M.R.C. trial and we suspect their quality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

Patients and Methods

All previously untreated adult patients with acute non-lymphatic leukæmia presenting at University College Hospital between June, 1969, and June, 1975, are reviewed. Patients with blast transformations from chronic myeloid leukæmia 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

Burge et al., The Lancet, 7936:621-668,1975

CLINICAL DECISION-MAKING AND MEASUREMENT ISSUES



Patient-Reported Outcomes (PRO) Instruments:

For example:

-EORTC QLQ-C30

-FACIT-Fatigue

-SF-36

REGULTAORY AGENCY VIEWS ON QUALITY OF LIFE OUTCOMES

Food and Drug Administration (FDA)

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
10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
Tel: 301-796-3400; Fax: 301-847-8714; E-mail: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

or

Office of Communication, Outreach, and Development, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448
Tel: 800-835-4709 or 301-827-1800; E-mail: ocod@fda.hhs.gov
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm

or

Office of Communication, Education, and Radiation Programs
Division of Small Manufacturers, International, and Consumer Assistance, HFZ-220
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive, Rockville, MD 20850-4307
DSMICA E-mail: dsmica@cdrh.fda.gov
DSMICA Fax: 301-443-8818
(Tel) Manufacturers Assistance: 800-638-2041 or 301-443-6597
(Tel) International Staff: 301-827-3993
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

European Medicines Agency (EMEA)

emea

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 27 July 2005
Doc. Ref. EMEA/CHMP/EWP/139391/2004

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)

REFLECTION PAPER ON THE REGULATORY GUIDANCE FOR THE USE OF HEALTH-RELATED QUALITY OF LIFE (HRQL) MEASURES IN THE EVALUATION OF MEDICINAL PRODUCTS

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

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…)

RATIONALE : Quality of Life and MDS

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

Clinical-decision-making very challenging

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 higlights the need of more research into this area (Tefferi et al, 2006; Rodeghiero et al. 2008; Cheson et al, 2006; Hallek et al, 2008).

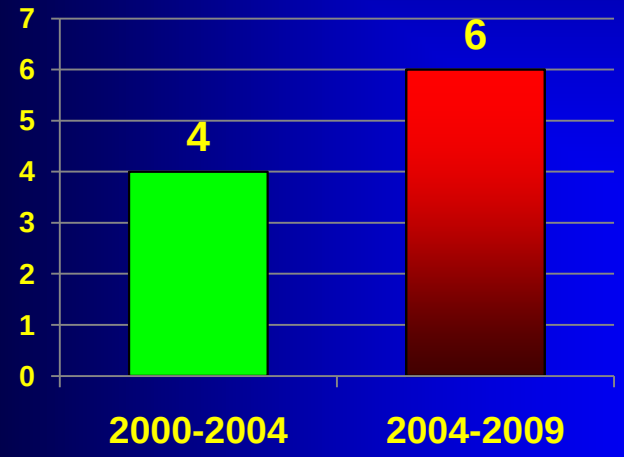
Regulatory Agencies and Scientific Societies have been supporting the use of QoL as a key outcome measure in clinical trials for a number of years (FDA 1985, ASCO 1996…).

"…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" F DA Consumer Magazine, 40(6), Nov.-Dec, 2006

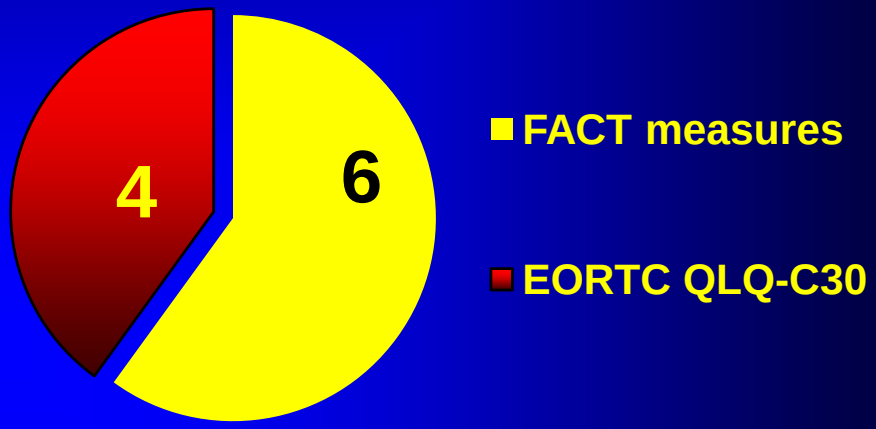
RESULTS 1980-2009

10 prospective studies enrolling 832 MDS patients

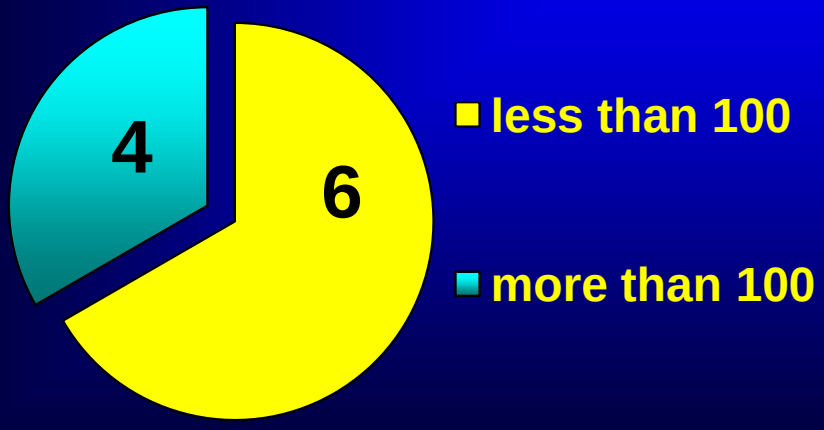
Year of Publication



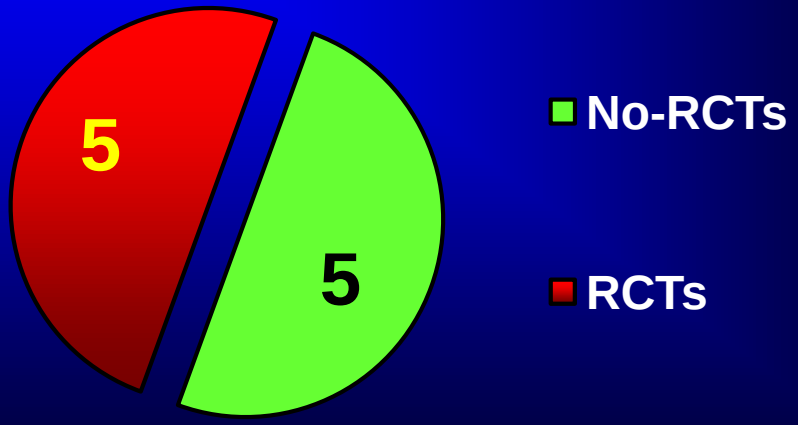
PRO measure used



Sample Size (No. of patients)



RCTs *versus* non RCTs



5 Prospective -non-RCTs- in patients with MDS

Authors	Sample	Treatment	PRO masure	Assessment schedule	PRO compliance over time	Summary of PRO results
Stasi et al. 2005	53 low-int-1-risk MDS pts	Darbepoetin alfa for 24 weeks	FACT-An; LASA	Baseline and 24th week	baseline data missing; 90% after 24 weeks	Improvement of QoL in responders, especially on anemia and fatigue subscales
Giagounidis et al. 2005	29 isolated (5q) MDS pts	ATRA + Tocopherol-alfa for 180 days	EORTC QLQ- 30	Baseline, 90 and 180 days	baseline and 90 days data missing; 69% after 180 days	No significant improvement of QoL in any pts
Aloe Spiriti et al. 2005	133 low-risk MDS pts	rHEPO alfa for 24 weeks	FACT-An	Baseline, 4th and 8th week	77% baseline; 73% after 4 weeks; 65% after 8 weeks	Improvement of QoL in responders, correlated to erythroid response
Clavio M et al. 2004	11 low-risk MDS pts	rHEPO alfa for 12-24 weeks	FACT-An	Baseline and 12-24th week	100% baseline; 73% after 12-24 weeks	Improvement of QoL in responders, correlated to erythroid response
Hellstrom-Lindberg et al. 2003	53 MDS pts	rHEPO beta+G-CSF for 12-20 weeks	EORTC QLQ-C30	Baseline and 12th week	68% baseline; 60% after 12 weeks	Improvement of QoL in responders

5 Prospective RCTs in patients with MDS

Authors	Overall no. of patients (patients with PRO data)	MDS Subtypes FAB or WHO (IPSS)	Treatment outline	PRO measure used	Summary of traditional clinical outcomes	Summary of PRO results
Greenberg et al, 2009 ✓	102	RA RARS REAB CMML	EPO and supportive care versus supportive care alone	FACT-G	No difference in OS between treatment arms. Improved erythroied responses in EPO arm	No difference between treatment arms. However, patients with erythroid responses reported some QoL benefits over time
Kantarijan et al. 2006 ✓	170 (unknown)	FAB: RA; RARS; RAEB; RAEB-t; CMML (int-1; int-2; high-risk)	Decitabine versus supportive care	EORTC QLQ-C30	Higher overall response rate and longer median time trend to AML in patients treated with decitabine compared to those on supportive care	Decitabine > best supportive care
Balleari et al. 2006	30 (18)	WHO: RA; RARS; RCMD; RAEB-1 (low-risk)	rHEPO Beta versus rHEPO Beta + G-CSF Filgrastim	FACT-An	Better although not statistically significant erythroid response in the rHEPO Beta + G-CSF arm compared to the rHEPO arm	No difference
Casadevall et al. 2004	60 (57)	FAB: RA; RARS; RAEB (low; int-1; int-2; high-risk)	rHEPO alfa + G-CSF lenograstim versus supportive care	FACT-An	Better erythroid response in the rHEPO alfa + G-CSF lenograstim arm in comparison with supportive care	No difference
Kornblith et al. 2002 (Silverman et al) ✓	191 (189)	FAB: RA; RARS; RAEB; RAEB-t; CMML (unknown)	Azacitidine versus Supportive care	EORTC QLQ-C30; Mental Health Inventory; Patient's perception of improvement	Azacitidine treatment yielded a higher response rate, reduced risk of leukemic transformation and improved survival	Azacitidine > supportive care

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….

ONGOING STUDY… NCI number: NCT00809575

Prognostic significance and longitudinal assessment of patient-reported QoL and symptoms in high-risk MDS.

An international prospective observational study

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STUDY DETAILS AND OBJECTIVES

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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