Qualità di Vita in Ematologia

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Chair Elect EORTC Quality of Life Group

The Lancet · Saturday 4 October 1975

QUALITY AND QUANTITY OF SURVIVAL IN ACUTE MYELOID LEUKÆMIA

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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.

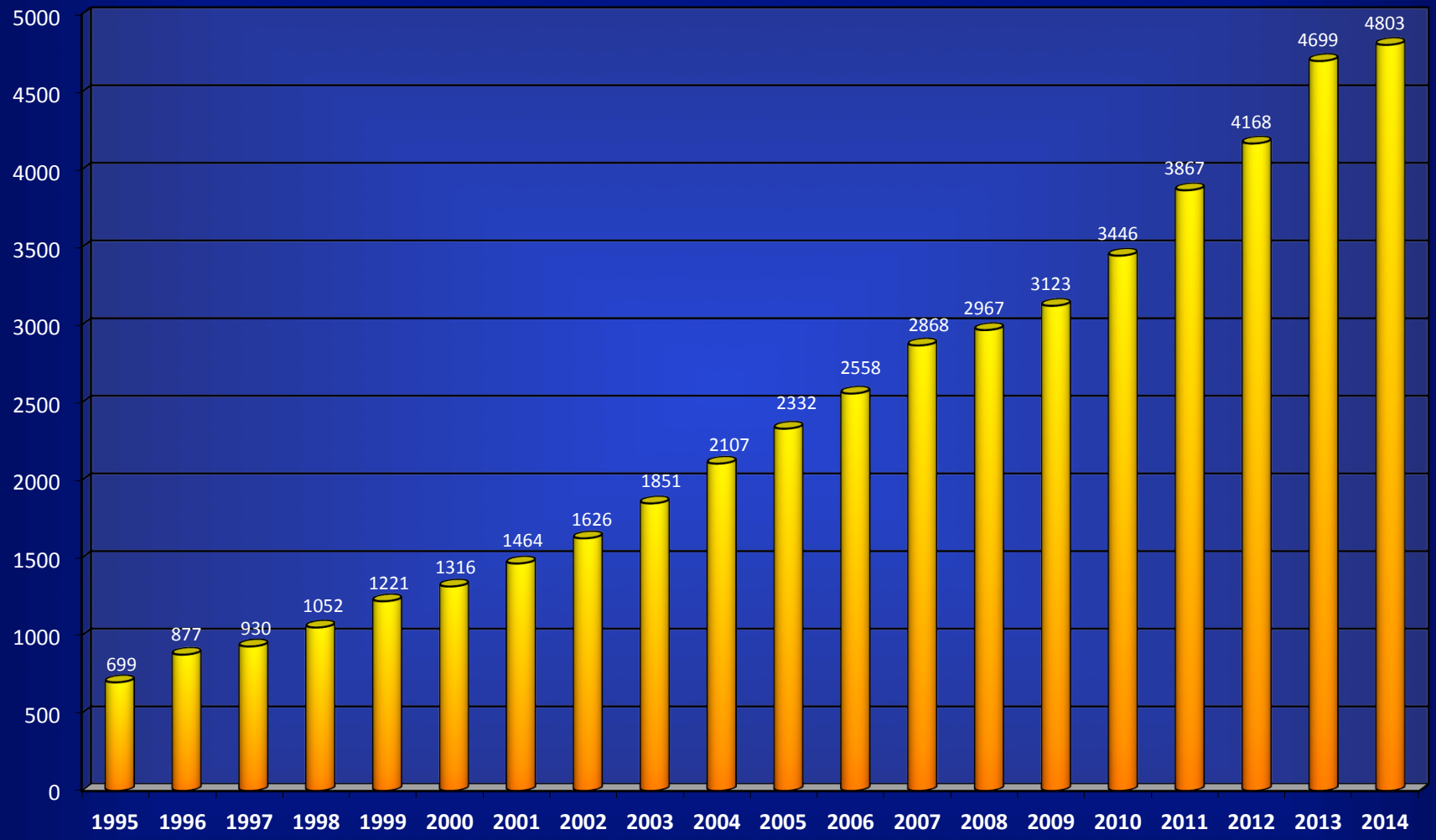
For convenience the survival-rates have been compared with the latest M.R.C. trial[1] in which more aggressive treatment was used. It will be seen that, though our patients rarely entered complete remission, their survival is longer than that of the patients in the M.R.C. trial and we suspect their quality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

Number of Publications including Quality of Life (QoL) Outcomes in Oncology
1995- 2014

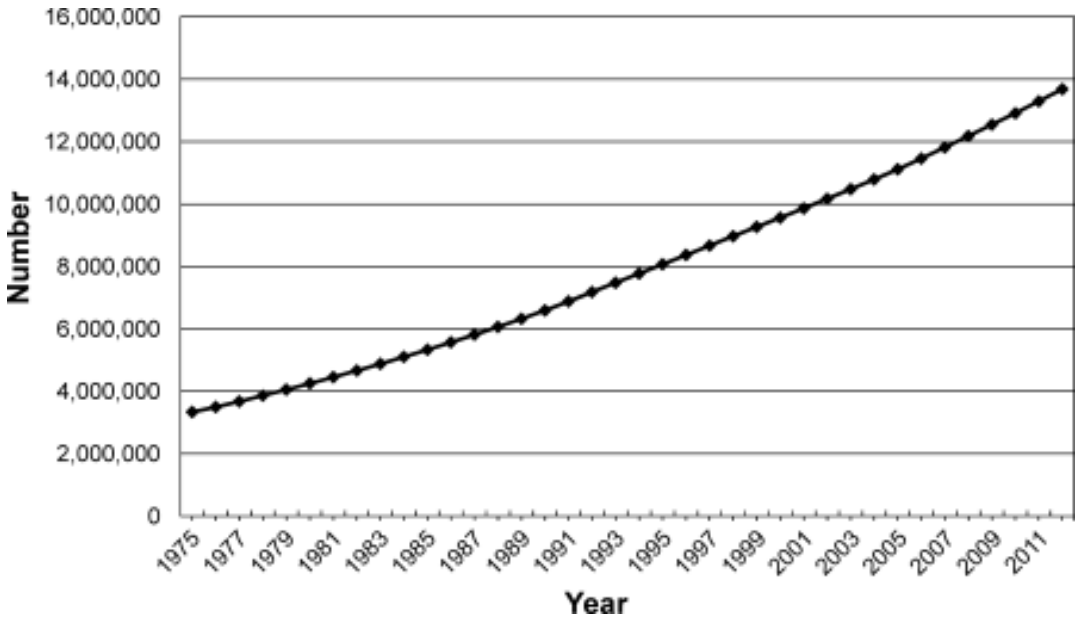


PubMed extracted data: ("quality of life" OR "health related quality of life" OR "health outcomes" OR "patient reported symptom" OR "patient reported outcomes" OR "patient reported outcome") AND cancer

An increased population of cancer survivors

Estimated number of cancer survivors in the United States from 1975 to 2012.

With continued improvements: 1) early detection; 2) effective therapies; 3) better supportive care, the number of cancer survivors has increased substantially worldwide



Rowland J, et al. Cancer, 2013, Jun 1;119 Suppl 11:2094-108

Common Terminology Criteria for Adverse Events (CTCAE)

The most widely used method for quantifying harm from treatment experienced by patients

Containing some 800 items documenting a wide range of toxicities

Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.0

Published: May 28, 2009 (v4.03: June 14, 2010)

U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute

How valuable are Toxicity Criteria to get insights on Patient burden of therapy?

…they cannot capture patient's Quality of Life

Common Terminology Criteria for Adverse Events (CTCAE)

The most widely used method for quantifying harm from treatment experienced by patients

Laboratory - based information

- Anemia
- Neutropenia
- QT prolongation

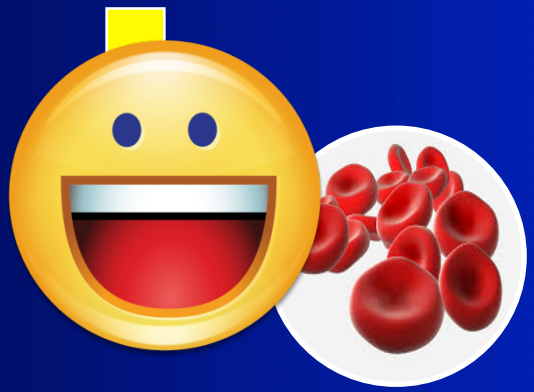
Direct Clinician observation or Physician judgment

-Rash
-Purpura
-Pain
-Fatigue

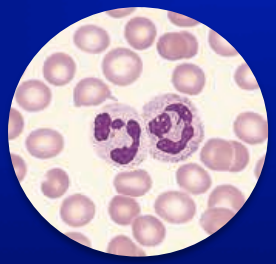
Di Maio M et al. Nat Rev Clin Oncol 13: 319-325, 2016; Fromme E, et al, J Clin Oncol 22:3485-90, 2004; Dueck AC et al, JAMA Oncol. 1:1051-9, 2015

Physician judgment of Patients toxicities

Laboratory measures



NEUTROPENIA

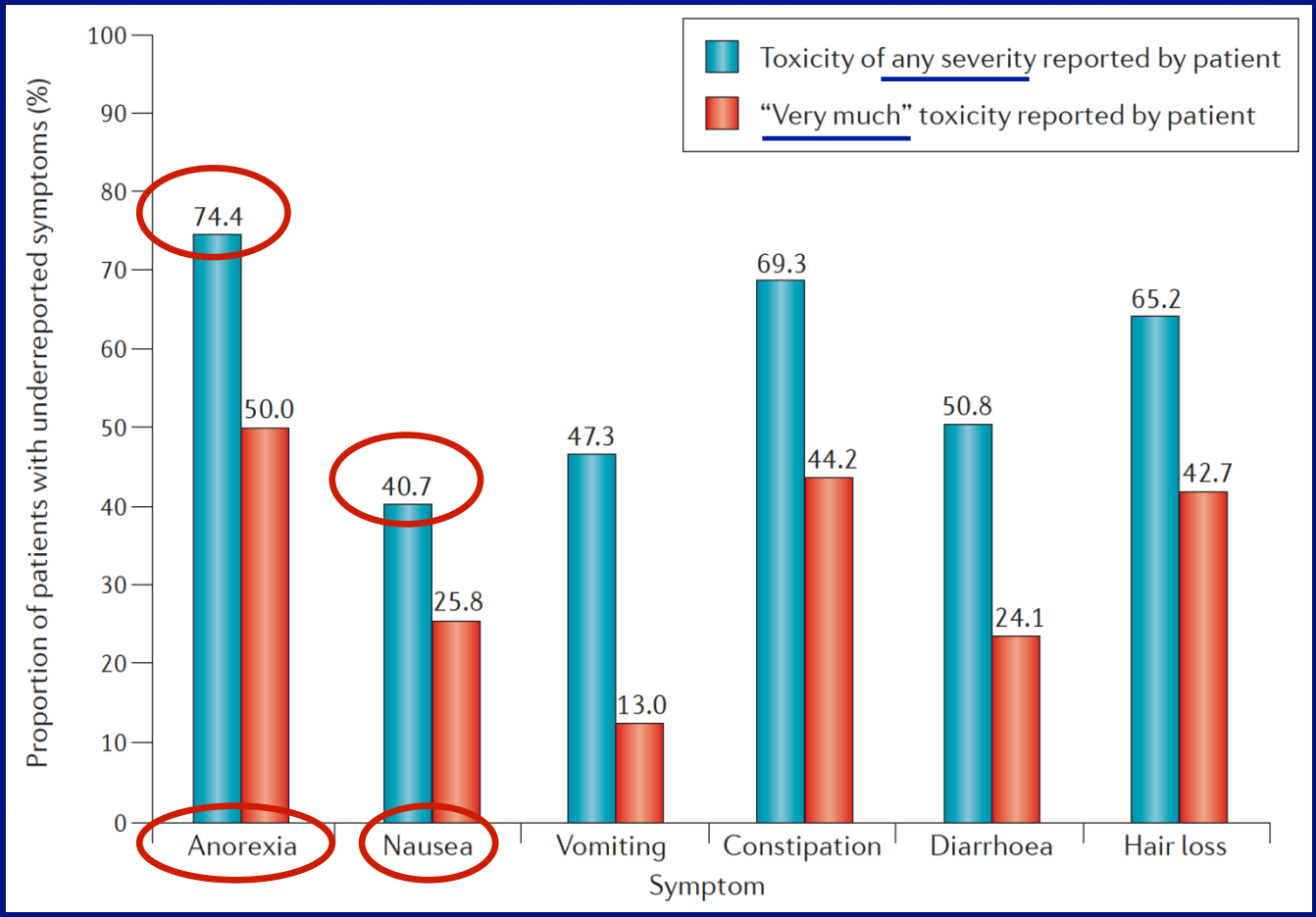


Physician opinion

PAIN

Underreporting of Treatment-Related Toxicities by Physicians

(Di Maio et al., Nat Rev Clin Oncol. 2016 May;13:319-25)



(data taken from three large RCTs in patients with solid tumors)

Toxicity data (symptoms) are not consistent across Clinical Trials

Toxicity (any grade) of imatinib therapy in Chronic Myeloid Leukemia Patients in 5 Pivotal RCTs

Table 1. Percentage of newly diagnosed, chronic phase, CML patients who were reported to complain of the listed side-effects with imatinib.

Side-effects (all grades)	Pivotal trials comparing imatinib (400 mg once daily) versus IFNα or 2nd generation TKI				
	IRIS	ENESTnd	DASISION	SWOG	BELA
FATIGUE (including asthenia, depression)	50	8	10	54	12
MUSCLE PAIN (including cramps, inflammation, spasm, myalgia)	95	34	43	44	50
JOINT/BONE PAIN (including arthralgia)	28	0	0	0	26
EDEMA (including peripheral edema, superficial edema, eyelid edema, periorbital edema, face edema, fluid retention, weight gain)	68	39	86	50	38
NAUSEA and VOMITING (including dyspepsia)	77	45	30	71	68
DIARRHEA	33	21	17	41	21
ABDOMINAL PAIN	27	0	0	0	5
SKIN RASH (including pruritus)	41	16	17	28	15
HEADACHE	31	8	10	19	8
SUM	**450**	**171**	**213**	**307**	**243**

The data are from five prospective, company-sponsored, GCP, CRO-monitored studies testing imatinib versus *IFNα plus low-dose arabinosyl cytosine (IRIS)*[13] versus *nilotinib (ENESTnd)*[14] versus *dasatinib (DASISION and SWOG)*[12,15] *and* versus *bosutinib (BELA).*[16] *In the original reports, the figures represented the proportion or percent of patients complaining of each side-effect. Of course, in all studies, the sum of the figures was higher than 100% because many patients complained of more than one side-effect. The differences among the totals, and among each side-effect, underscore the variability in collecting and reporting the side-effects, although all patients were treated frontline with the same dose (400 mg once daily) of imatinib. The differences among studies are quite impressive. The difference is also impressive for grade 3/4 side-effects: from a total of 18.1% in IRIS*[13] *to a total of 3.6% in ENESTnd*[14] *(data not shown in the Table).*

Baccarani M, Efficace F, Rosti G. *Haematologica*. 2014 Feb;99(2):205-8.

Major paradigm-shift in the way the effects of therapy are to be documented: Patient-Reported Outcome (PRO)-CTCAE

In 2008 the NCI began developing a PRO version of the CTCAE in order to bring the patient perspective on toxicity reporting into widespread use in oncology

Dueck AC et al, JAMA Oncol. 2015 Nov;1(8):1051-9

Research

Original Investigation

Validity and Reliability of the US National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

Amylou C. Dueck, PhD; Tito R. Mendoza, PhD; Sandra A. Mitchell, PhD, CRNP, AOCN; Bryce B. Reeve, PhD; Kathleen M. Castro, RN, MS, AOCN; Lauren J. Rogak, MA; Thomas M. Atkinson, PhD; Antonia V. Bennett, PhD; Andrea M. Denicoff, MS, RN, ANP; Ann M. O'Mara, PhD, RN, FAAN; Yuelin Li, PhD; Steven B. Clauser, PhD, MPA; Donna M. Bryant, MSN, ANP-BC, OCN, CCRC; James D. Bearden III, MD, FACP; Theresa A. Gillis, MD; Jay K. Harness, MD; Robert D. Siegel, MD, FACP; Diane B. Paul, AAS; Charles S. Cleeland, PhD; Deborah Schrag, MD, MPH; Jeff A. Sloan, PhD; Amy P. Abernethy, MD, PhD; Deborah W. Bruner, RN, PhD, FAAN; Lori M. Minasian, MD, FACP; Ethan Basch, MD, MSc; for the National Cancer Institute PRO-CTCAE Study Group

The “price” of NOT measuring Patient-Reported QoL

A Real World example in MDS

VOLUME 34 · NUMBER 25 · SEPTEMBER 1, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Phase III Study of Lenalidomide Versus Placebo in RBC Transfusion-Dependent Patients With Lower-Risk Non-del(5q) Myelodysplastic Syndromes and Ineligible for or Refractory to Erythropoiesis-Stimulating Agents

Valeria Santini, Antonio Almeida, Aristoteles Giagounidis, Stefanie Gröpper, Anna Jonasova, Norbert Vey, Ghulam J. Mufti, Rena Buckstein, Moshe Mittelman, Uwe Platzbecker, Ofer Shpilberg, Ron Ram, Consuelo del Cañizo, Norbert Gattermann, Keiya Ozawa, Alberto Risueño, Kyle J. MacBeth, Jianhua Zhong, Francis Séguy, Albert Hoenekopp, C.L. Beach, and Pierre Fenaux

See accompanying editorial on page 2956

ENDPOINTS

Primary: Rate of RBC Transfusion Independen

Secondary: Erythroid response. Progressio[illegible]ML, Overall survival, Toxicity, Quality of Life.

What about toxicity and Quality of Life (QoL)?

Toxicity profile: Lenalidomide *versus* Placebo Group

Table 4. Treatment-Emergent Adverse Events

Adverse Event	Any Grade, No.(%)		Grade 3 or 4, No. (%)	
	Lenalidomide	Placebo	Lenalidomide	Placebo
No. of patients	160	79	160	79
Hematologic				
Neutropenia	103 (64.4)	10 (12.7)	99 (61.9)	10 (12.7)
Thrombocytopenia	63 (39.4)	6 (7.6)	57 (35.6)	3 (3.8)
Infection	83 (51.9)	34 (43.1)	23 (14.4)	3 (3.8)
Bleeding	33 (20.6)	8 (10.1)	3 (1.9)	0
Nonhematologic				
Venous thromboembolism	5 (3.1)	0	3 (1.9)	0
Arterial thromboembolism	4 (2.5)	2 (2.5)	2 (1.3)	1 (1.3)
Hepatic disorder	23 (14.4)	4 (5.1)	8 (5.0)	2 (2.5)
Renal failure	6 (3.8)	0	2 (1.3)	0
Peripheral neuropathy	4 (2.5)	1 (1.3)	0	0
Cardiac failure	8 (5.0)	4 (5.1)	3 (1.9)	1 (1.3)
Cardiac arrhythmia	18 (11.3)	7 (8.9)	2 (1.3)	4 (5.1)
Ischemic heart disease	3 (1.9)	3 (3.8)	3 (1.9)	1 (1.3)
Interstitial lung disease	4 (2.5)	0	0	0
Cutaneous reactions	16 (10.0)	1 (1.3)	2 (1.3)	0
Angioedema	7 (4.4)	1 (1.3)	1 (0.6)	0
Diarrhea	68 (42.5)	18 (22.8)	4 (2.5)	0
Constipation	36 (22.5)	10 (12.7)	0	2 (2.5)

NOTE. Adverse events of interest identified by standardized Medical Dictionary for Regulatory Activities (MedDRA) queries.

Santini V, et al, J Clin Oncol. 2016 Sep 1;34(25):2988-96

However, no QoL difference between treatment arms (Lenalidomide vs Placebo)

ABSTRACT

Purpose

This international phase III, randomized, placebo-controlled, double-blind study assessed the efficacy and safety of lenalidomide in RBC transfusion–dependent patients with International Prognostic Scoring System lower-risk non-del(5q) myelodysplastic syndromes ineligible for or refractory to erythropoiesis-stimulating agents.

Patients and Methods

In total, 239 patients were randomly assigned (2:1) to treatment with lenalidomide (n = 160) or placebo (n = 79) once per day (on 28-day cycles). The primary end point was the rate of RBC transfusion independence (TI) ≥ 8 weeks. Secondary end points were RBC-TI ≥ 24 weeks, duration of RBC-TI, erythroid response, health-related quality of life (HRQoL), and safety.

Results

RBC-TI ≥ 8 weeks was achieved in 26.9% and 2.5% of patients in the lenalidomide and placebo groups, respectively ($P < .001$). Ninety percent of patients achieving RBC-TI responded within 16 weeks of treatment. Median duration of RBC-TI with lenalidomide was 30.9 weeks (95% CI, 20.7 to 59.1). Transfusion reduction of ≥ 4 units packed RBCs, on the basis of a 112-day assessment, was 21.8% in the lenalidomide group and 0% in the placebo group. Higher response rates were observed in patients with lower baseline endogenous erythropoietin ≤ 500 mU/mL (34.0% *v* 15.5% for > 500 mU/mL). At week 12, mean changes in HRQoL scores from baseline did not differ significantly between treatment groups, which suggests that lenalidomide did not adversely affect HRQoL. Achievement of RBC-TI ≥ 8 weeks was associated with significant improvements in HRQoL ($P < .01$). The most common treatment-emergent adverse events were neutropenia and thrombocytopenia.

Conclusion

Lenalidomide yields sustained RBC-TI in 26.9% of RBC transfusion–dependent patients with lower-risk non-del(5q) myelodysplastic syndromes ineligible for or refractory to erythropoiesis-stimulating agents. Response to lenalidomide was associated with improved HRQoL. Treatment-emergent adverse event data were consistent with the known safety profile of lenalidomide.

Santini V, et al, J Clin Oncol. 2016 Sep 1;34(25):2988-96

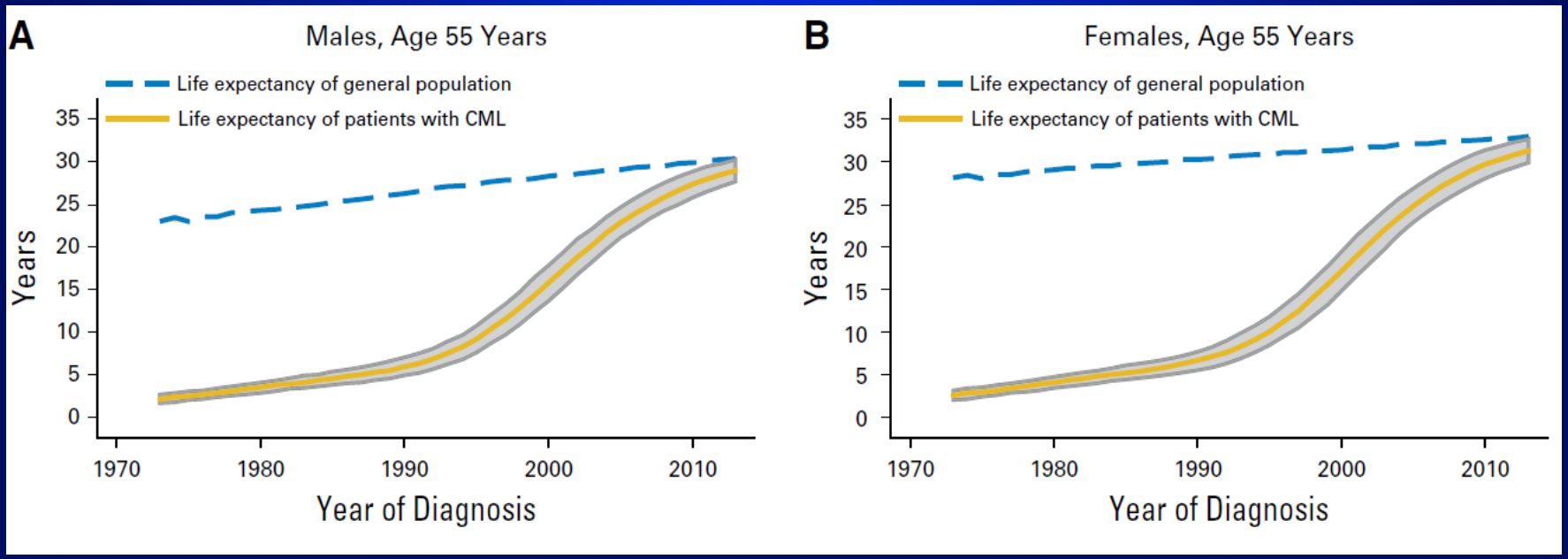
Quality of Life in Chronic Myeloid Leukemia

Background: Why should we assess QoL in CML?

- The progress made in understanding the biology of CML that eventually translated in highly effective therapy is unparalleled in cancer medicine
  (Cortes et al, J Clin Oncol, 29: 524–531, 2011; Saussele S, e tal, Leukemia, 30:1638-47, 2016)

- CML therapy is now lifelong for many patients (Hughes TP et Ross DM, Blood 128:17-23, 2016)

- Life Expectancy of patients with CML approaches that of the general Population
  (Bower H, et al, J Clin Oncol. 2016, 34:2851-7, 2016)



Background: Why should we assess QoL in CML?

The targeted therapies, imatinib first, then the others TKIs, have dramatically changed the scenario and clinical decision-making has become highly challenging

(Jabbour E et al Clin Lymphoma Myeloma Leuk. 15:323-34, 2015; Baccarani G, et al, Haematologica. 2014, 99:205-8)

Approved drugs

First line therapy	**Imatinib**	**Nilotinib**	**Dasatinib**		
Second and further lines	**Imatinib**	**Nilotinib**	**Dasatinib**	**Bosutinib**	**Ponatinib**

Overall Survival (OS) is not different amongst first line therapies

(Rosti G, et al, Nat Rev Clin Oncol, 2016 Oct 18. doi: 10.1038/nrclinonc.2016; Hochhaus A et al Leukemia. 30:1044-54, 2016; Cortes JE et al J Clin Oncol. 34:2333-40, 2016)

Although tyrosine kinase inhibitors (TKIs) provide Quality of Life (QoL) improvements over previous interferon based therapies (IRIS Study), they do impact on patients' QoL

(Hahn EA, et al, J Clin Oncol 21:2138-2146, 2003; Efficace F, et al, Blood, 118:4554-60, 2011; Philips KM et al, Support Care Cancer 21:1097-103, 2013)

Two important data from the literature

1) **Adherence is critical to maximize clinical efficacy**
2) **Adherence to therapy in CML is suboptimal**

Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study

Lucien Noens,[1] Marie-Anne van Lierde,[2] Robrecht De Bock,[3] Gregor Verhoef,[4] Pierre Zachée,[5] Zwi Berneman,[6] Philippe Martiat,[7] Philippe Mineur,[8] Koen Van Eygen,[9] Karen MacDonald,[10] Sabina De Geest,[11] Tara Albrecht,[10,12] and Ivo Abraham[10,13]

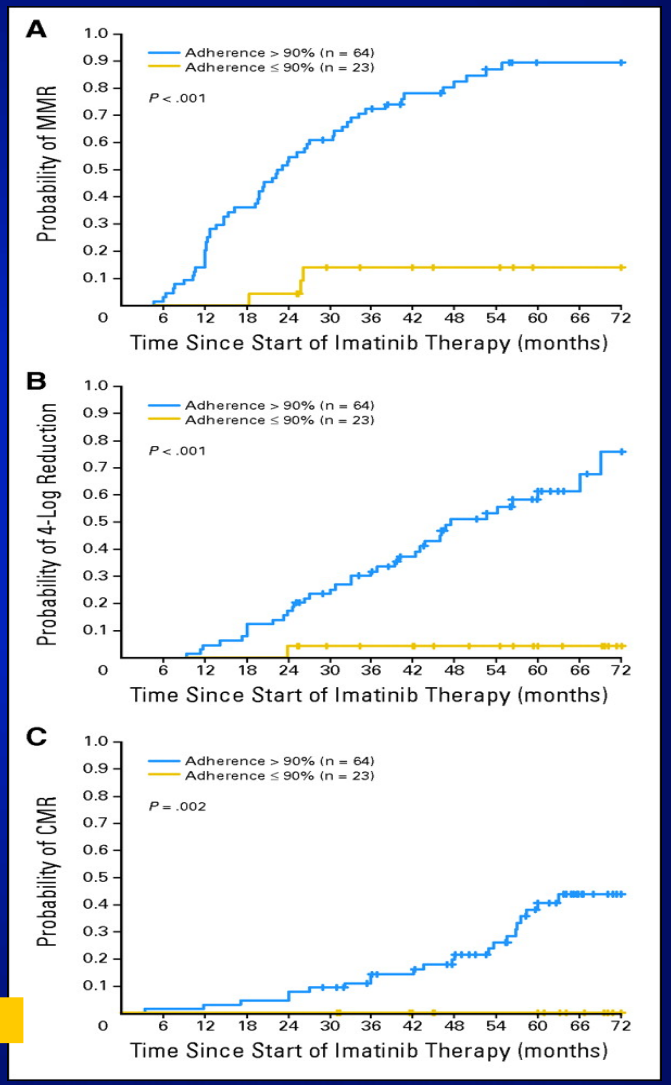
[1]Universitair Ziekenhuis (UZ) Gent, Gent, Belgium; [2]Novartis Pharma, Vilvoorde, Belgium; [3]Ziekenhuisnetwerk Antwerpen (ZNA) Middelheim, Antwerpen, Belgium; [4]UZ Gasthuisberg, Leuven, Belgium; [5]ZNA Stuivenberg, Antwerpen, Belgium; [6]UZ Antwerpen, Antwerpen, Belgium; [7]Institut Jules Bordet, Bruxelles, Belgium; [8]Hôpital St Joseph, Gilly, Belgium; [9]Algemeen Ziekenhuis Groeninge, Kortrijk, Belgium; [10]Matrix45; Earlysville, VA; [11]Institute of Nursing Science, University of Basel, Basel, Switzerland; [12]School of Nursing, University of Virginia, Charlottesville; [13]College of Nursing, and Center for Health Outcomes and PharmacoEconomic Research, College of Pharmacy, University of Arizona, Tucson

Imatinib mesylate (imatinib) has been shown to be highly efficacious in the treatment of chronic myeloid leukemia (CML). Continuous and adequate dosing is essential for optimal outcomes and with imatinib treatment possibly being lifelong, patient adherence is critical. The ADAGIO (Adherence Assessment with Glivec: Indicators and Outcomes) study aimed to assess prospectively over a 90-day period the prevalence of imatinib nonadherence in patients with CML; to develop a multivariate canonical correlation model of how various determinants may be associated with various measures of nonadherence; and to examine whether treatment response is associated with adherence levels. A total of 202 patients were recruited from 34 centers in Belgium, of whom 169 were evaluable. One-third of patients were considered to be nonadherent. Only 14.2% of patients were perfectly adherent with 100% of prescribed imatinib taken. On average, patients with suboptimal response had significantly higher mean percentages of imatinib not taken (23.2%, standard deviation [SD] = 23.8) than did those with optimal response (7.3%, SD = 19.3, $P = .005$; percentages calculated as proportions × 100). Nonadherence is more prevalent than patients, physicians, and family members believe it is, and therefore should be assessed routinely. It is associated with poorer response to imatinib. Several determinants may serve as alert signals, many of which are clinically modifiable. (Blood. 2009;113:5401-5411)

Introduction

Noens L, et al Blood. 2009, 113:5401-11

Only 14% of patients are <u>fully</u> adherent to therapy



The probability of MMR for patients with an adherence rate ≤ 90% was 13.9%, whereas the probability was 93.7% for the patients with an adherence rate greater than 90% (P < .001)

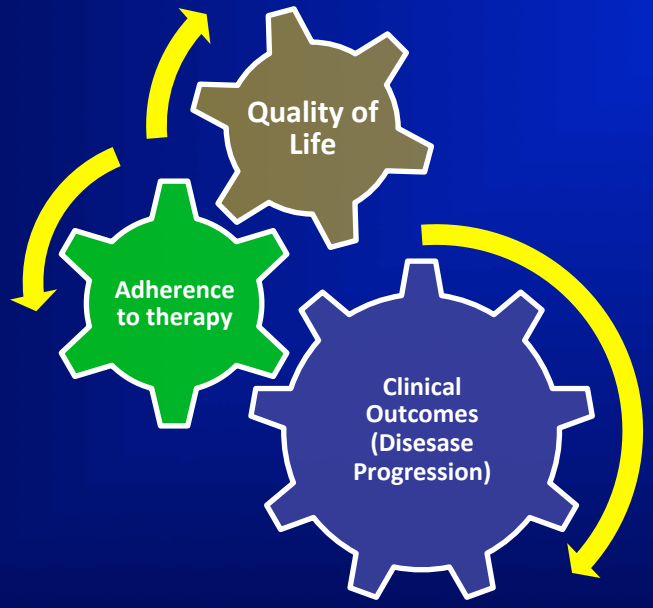
Marin D, et al., J Clin Oncol. 2010, 28:2381-8

Why should we Assess QoL in CML patients?

We need additional information to facilitate clinical-decision making

Some Key QUESTIONS:

- **Which is the best TKI frontline?**
- **When should we consider changing drug?**
- **How do we evaluate "intolerance"** (considering the number of available drugs) **?**
- **How can we improve adherence in a lifelong therapy ?**
- **How valuable are physician-reported toxicity data?**



A Complex Interplay:

Quality of Life
Adherence to Therapy
Clinical Effectiveness in CML

Patient-Reported Quality of Life is associated with Adherence to therapy

Unnikrishnan R , et al, Clin Lymphoma Myeloma Leuk 2016, 16:366-371

Original Study

Comprehensive Evaluation of Adherence to Therapy, Its Associations, and Its Implications in Patients With Chronic Myeloid Leukemia Receiving Imatinib

Radhika Unnikrishnan,[1] Surendran Veeraiah,[1] Samson Mani,[2] Rejiv Rajendranath, Swaminathan Rajaraman,[4] Grace Sahaya Vidhubala Elangovan,[1] Venkatraman Radhakrishnan,[3] Trivadi S. Ganesan,[3] Tenali G. Sagar,[3] Prasanth Ganesan[3]

N=221 CML patients treated with Imatinib

QoL Assessement:
EORTC QLQ-C30 and EORTC QLQ-CML 24

Table 2 Univariate Analysis of Adherence in Association With Global Health Status, Functional Scales, and Symptom Scales Based on EORTC QLQ C30 and EORTC CML 24

EORTC QLQ C30	Mean Score (±SE) Adherent (N = 99)	Nonadherent (N = 122)	*P* Value[a]
Global Health Status	78.9 ± 19.8	64.4 ± 24.7	**<.001**[b]
Functioning scales			
Physical functioning	79.1 ± 21.2	71.0 ± 21.8	**.006**[b]
Role functioning	84.5 ± 25.7	76.7 ± 28.6	**.038**[b]
Emotional functioning	71.0 ± 31.7	62.6 ± 33.8	.061
Cognitive functioning	80.8 ± 29.7	79.3 ± 29.3	.720
Social functioning	83.8 ± 25.9	79.1 ± 29.1	.209
Symptom Scales			
Fatigue	25.2 ± 29.9	36.9 ± 33.7	**.007**[b]
Nausea and vomiting	8.0 ± 18.9	16.3 ± 23.0	**.004**[b]
Pain	16.4 ± 24.5	28.9 ± 33.4	**.002**[b]
Dyspnea	12.4 ± 27.5	21.8 ± 34.2	**.028**[b]
Insomnia	14.1 ± 30.1	20.2 ± 33.3	.161
Appetite loss	5.0 ± 18.6	12.5 ± 24.7	**.013**[b]
Constipation	3.0 ± 14.3	3.8 ± 14.34	.683
Diarrhea	8.7 ± 25.4	12.5 ± 26.5	.280
Financial difficulties	46.1 ± 37.7	58.1 ± 39.1	**.021**[b]
EORTC CML QLQ 24			
Symptom burden	17.1 ± 18.5	26.5 ± 19.6	**<.001**[b]
Impact on worry/mood	19.2 ± 20.4	32.3 ± 25.6	**<.001**[b]
Impact on daily life	24.0 ± 26.8	35.9 ± 28.1	**.002**[b]
Satisfaction with care and information	87.7 ± 20.9	76.0 ± 25.0	**<.001**[b]
Body image problems	9.7 ± 22.4	21.3 ± 34.0	**.004**[b]
Satisfaction with social life	82.4 ± 29.4	74.4 ± 33.1	.060

Abbreviations: EORTC CML 24 = European Organisation for Research and Treatment of Cancer Chronic Myeloid Leukemia 24; EORTC QLQ C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; SE = standard error.
[a]Independent samples *t* test.
[b]Significant *P* value.

Worse CML specific Quality of Life Aspects are associated with non-adherence to therapy (results from univariate analysis using the EORTC QLQ-CML24)

EORTC CML QLQ 24	Adherent	Non-Adherent	
Symptom burden	17.1 ± 18.5	26.5 ± 19.6	**<.001**[b]
Impact on worry/mood	19.2 ± 20.4	32.3 ± 25.6	**<.001**[b]
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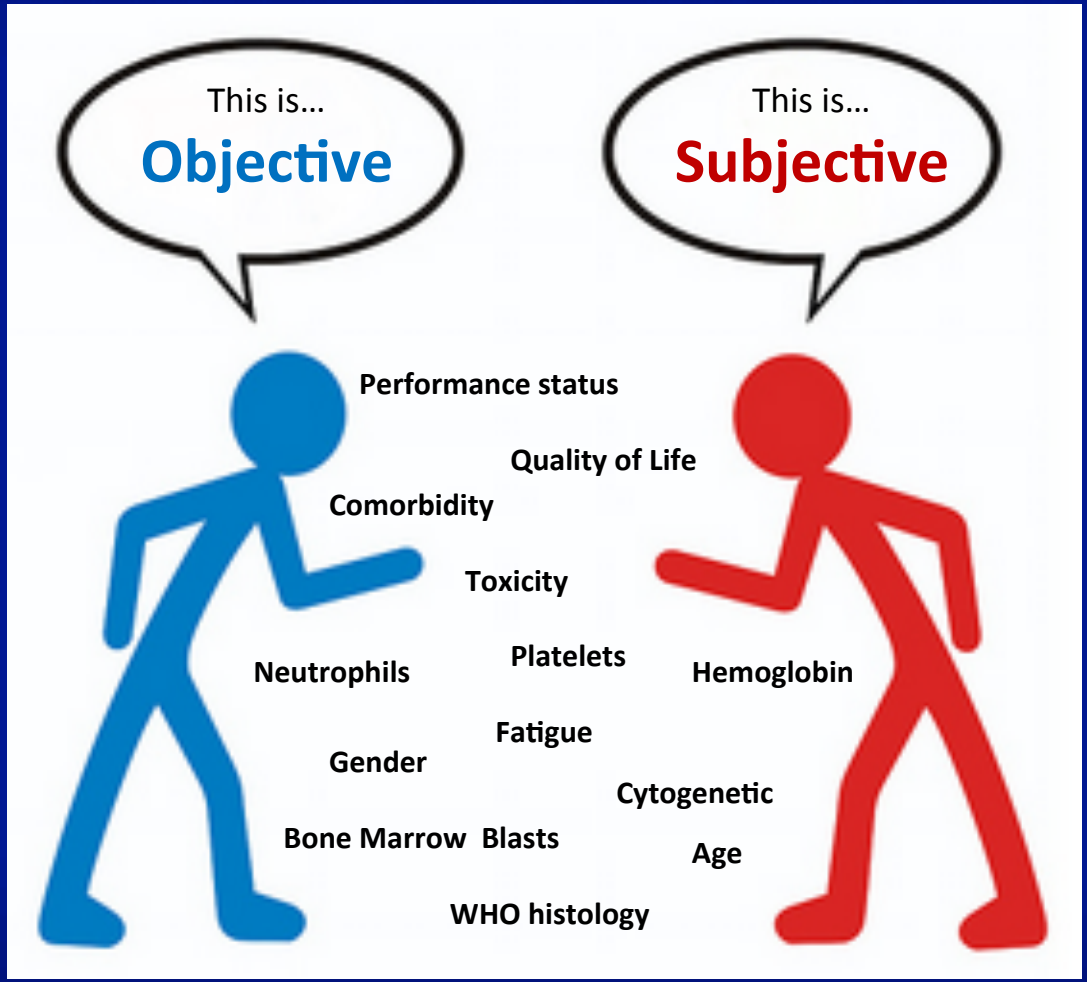
Satisfaction with social life	82.4 ± 29.4	74.4 ± 33.1	.060

Higher scores= worse outcomes

Higher scores= better outcomes

Unnikrishnan R , et al, Clin Lymphoma Myeloma Leuk 2016, 16:366-371

Quality of Life as prognostic/predictive value



How reliable is the information we can obtain from patient's self-reports?

Findings About 500 000 participants were included in the UK Biobank. We excluded participants with more than 80% variables missing (n=746). Of 498 103 UK Biobank participants included (54% of whom were women) aged 37–73 years, 8532 (39% of whom were women) died during a median follow-up of 4·9 years (IQR 4·33–5·22). Self-reported health (C-index including age 0·74 [95% CI 0·73–0·75]) was the strongest predictor of all-cause mortality in men and a previous cancer diagnosis (0·73 [0·72–0·74]) was the strongest predictor of all-cause mortality in women. When excluding individuals with major diseases or disorders (Charlson comorbidity index >0; n=355 043), measures of smoking habits were the strongest predictors of all-cause mortality. The prognostic score including 13 self-reported predictors for men and 11 for women achieved good discrimination (0·80 [0·77–0·83] for men and 0·79 [0·76–0·83] for women) and significantly outperformed the Charlson comorbidity index (p<0·0001 in men and p=0·0007 in women). A dedicated website allows the interactive exploration of all results along with calculation of individual risk through an online questionnaire.

across England, Wales, and Scotland with standardised procedures. In this prospective population-based study, we assessed sex-specific associations of 655 measurements of demographics, health, and lifestyle with all-cause mortality

Biostatistics, Karolinska Institutet, Stockholm, Sweden

Interpretation Measures that can simply be obtained by questionnaires and without physical examination were the strongest predictors of all-cause mortality in the UK Biobank population. The prediction score we have developed accurately predicts 5 year all-cause mortality and can be used by individuals to improve health awareness, and by health professionals and organisations to identify high-risk individuals and guide public policy.

Self-reported health (C-index including age 0·74 [95% CI 0·73–0·75]) was the str t predictor of all-cause mortality in men and a previous cancer diagnosis (0·73 [0·72–0·74]) was the str t predictor of all-cause mortality in women. When excluding individuals with major diseases or disorders (comorbidity index >0; n=355 043), measures of smoking habits were the strongest predictors of all-cause mo ity. The prognostic score including 13 self-reported predictors for men and 11 for women achieved good discrimination (0·80 [0·77–0·83] for men and 0·79 [0·76–0·83] for women) and significantly outperformed the Charlson comorbidity index (p<0·0001 in mo and p=0·0007 in women). A dedicated website allows the interactive exploration of all results along with calculation of individual risk through an online questionnaire.

Interpretation Measures that can simply be obtained by questionnaires and without physical examination were the strongest predictors of all-cause mortality in the UK Biobank population. The prediction score we have developed accurately predicts 5 year all-cause mortality and can be used by individuals to improve health awareness, and by health professionals and organisations to identify high-risk individuals and guide public policy.

Funding Knut and Alice Wallenberg Foundation and the Swedish Research Council.

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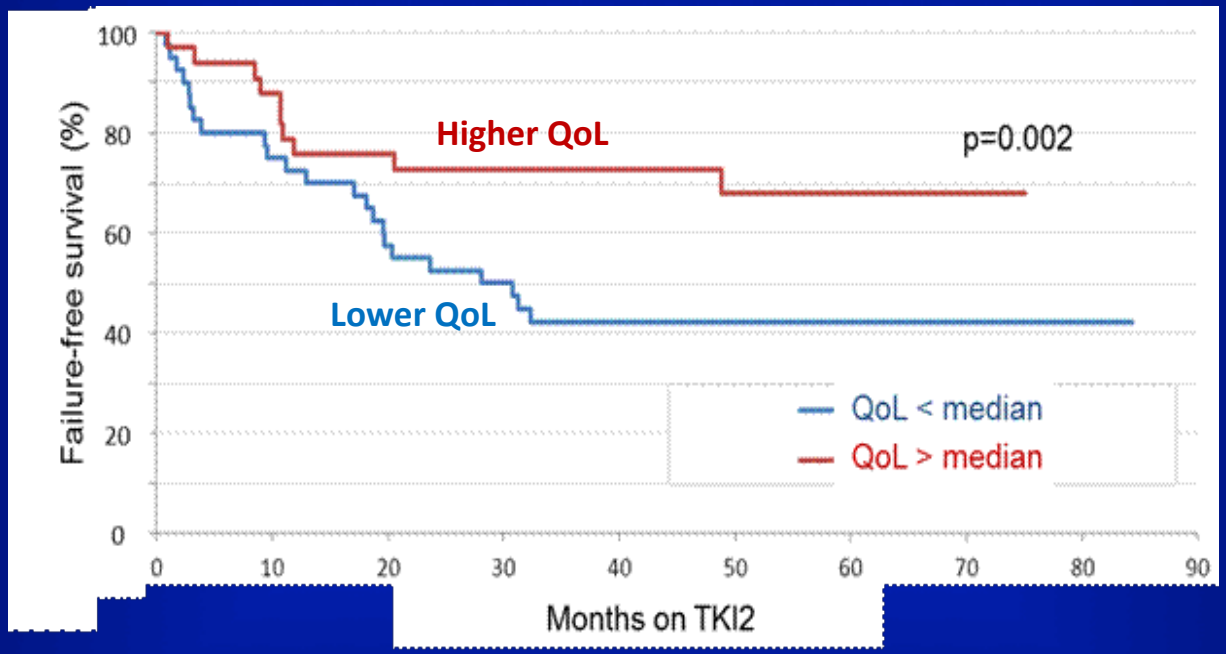
"Subjective" data do provide important and unique information.

Therefore are important as "objective "data

Failure free survival since TKI2 (nilotinib or dasatinib) initiation according to the FACT questionnaire result (Patients have been split into 2 groups according to the median value of the QoL score). Nicolini F, et al, **ASH, 2014** (meeting Abstracts)

Failure-free survival (FFS): defined as no hematologic or cytogenetic response, CHR, CCyR, PCyR MMR or MR4.5 loss, death, progression to AP/BC, definitive TKI2 cessation for resistance or intolerance, allogeneic stem cell transplantation].



Key findings:

1) **A better QoL is associated with significantly longer FFS since TKI2 initiation.**

2) **No QoL differences existed between patients treated with nilotinib or dasatinib.**

Three well-established Prognostic Indices

International Scoring System for Evaluating Prognosis in Myelodysplastic Syndromes

By Peter Greenberg, Christopher Cox, Michelle M. LeBeau, Pierre Fenaux, Pierre Morel, Guillermo Sanz, Miguel Sanz, Teresa Vallespi, Terry Hamblin, David Oscier, Kazuma Ohyashiki, Keisuke Toyama, Carlo Aul, Ghulam Mufti, and John Bennett

IPSS
(Blood, 1997)

Revised International Prognostic Scoring System for Myelodysplastic Syndromes

Peter L. Greenberg,[1] Heinz Tuechler,[2] Julie Schanz,[3] Guillermo Sanz,[4] Guillermo Garcia-Manero,[5] Francesc Solé,[6] John M. Bennett,[7] David Bowen,[8] Pierre Fenaux,[9] Francois Dreyfus,[10] Hagop Kantarjian,[5] Andrea Kuendgen,[11] Alessandro Levis,[12] Luca Malcovati,[13] Mario Cazzola,[13] Jaroslav Cermak,[14] Christa Fonatsch,[15] Michelle M. Le Beau,[16] Marilyn L. Slovak,[17] Otto Krieger,[18] Michael Luebbert,[19] Jaroslaw Maciejewski,[20] Silvia M. M. Magalhaes,[21] Yasushi Miyazaki,[22] Michael Pfeilstöcker,[2] Mikkael Sekeres,[20] Wolfgang R. Sperr,[15] Reinhard Stauder,[23] Sudhir Tauro,[24] Peter Valent,[15] Teresa Vallespi,[25] Arjan A. van de Loosdrecht,[26] Ulrich Germing,[11] and Detlef Haase[3]

IPSS-Revised
(Blood, 2012)

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

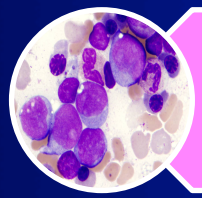
Time-Dependent Prognostic Scoring System for Predicting Survival and Leukemic Evolution in Myelodysplastic Syndromes

Luca Malcovati, Ulrich Germing, Andrea Kuendgen, Matteo G. Della Porta, Cristiana Pascutto, Rosangela Invernizzi, Aristoteles Giagounidis, Barbara Hildebrandt, Paolo Bernasconi, Sabine Knipp, Corinna Strupp, Mario Lazzarino, Carlo Aul, and Mario Cazzola

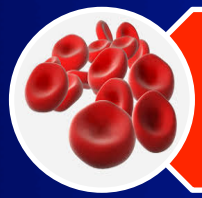
WPSS
(JCO, 2007)

Does Patient-Reported Fatigue add prognostic information for Survival ?

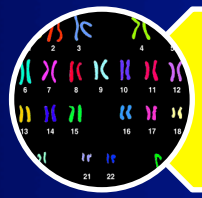
IPSS Index



Bone marrow Blasts

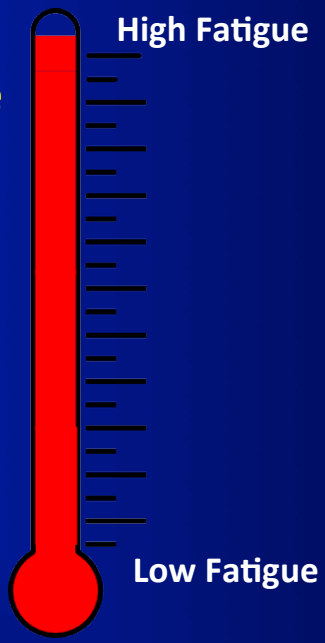


Cytopenia



Karyotype

Patient-reported Fatigue



GIMEMA-PROMYS International Registry

Prognostic value of self-reported fatigue on overall survival in patients with myelodysplastic syndromes: a multicentre, prospective, observational, cohort study

Fabio Efficace, Gianluca Gaidano, Massimo Breccia, Maria Teresa Voso, Francesco Cottone, Emanuele Angelucci, Giovanni Caocci, Reinhard Stauder, Dominik Selleslag, Mirjam Sprangers, Uwe Platzbecker, Alessandra Ricco, Grazia Sanpaolo, Odile Beyne-Rauzy, Francesco Buccisano, Giuseppe A Palumbo, David Bowen, Khanh Nguyen, Pasquale Niscola, Marco Vignetti, Franco Mandelli

Summary

Background The clinical presentation of myelodysplastic syndromes is highly variable and so accurate prediction of outcomes in these patients is crucial. We aimed to assess whether self-reported fatigue severity predicts overall survival beyond gold-standard prognostic indices in patients with higher-risk myelodysplastic syndromes.

Methods We did a multicentre, prospective, observational, cohort study of patients from 37 centres in Europe, USA, and east Asia. Adults (≥18 years) with myelodysplastic syndromes were consecutively enrolled within 6 months of diagnosis with an intermediate-2-risk or high-risk score according to the International Prognostic Scoring System (IPSS). Patients were enrolled irrespective of older age, comorbidities, performance status, and progression from a lower IPSS risk score category. All patients had to complete a quality of life assessment at baseline. With use of univariate and then multivariate Cox proportional hazards regression analysis, we constructed a multivariate model of how prognostic variables, including IPSS and fatigue score from the European Organisation for Research and Treatment of Cancer quality-of-life questionnaire–core 30, predicted overall survival. The primary endpoint was overall survival by baseline self-reported fatigue scale ratings. This study was registered with ClinicalTrials.gov, number NCT00809575.

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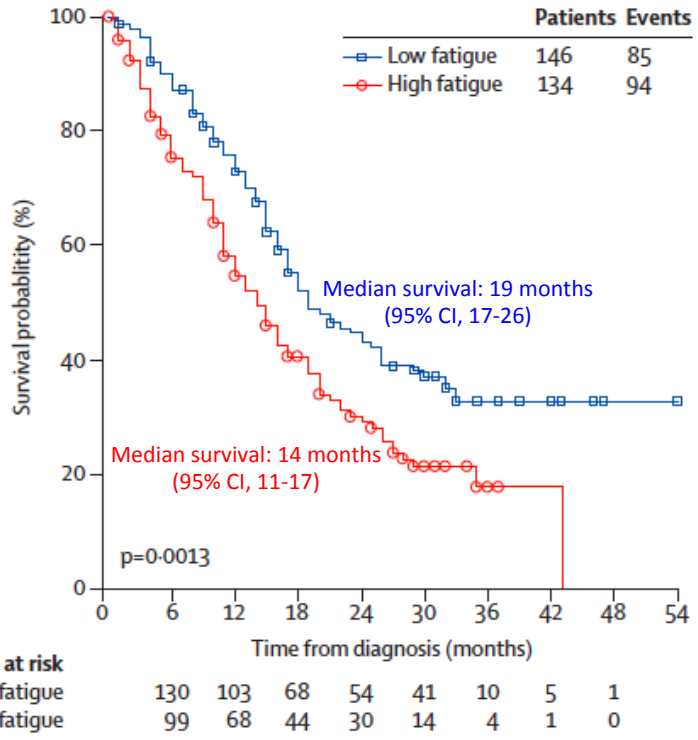
Italian Group for Adult Hematologic Diseases (GIMEMA), Data Center and Health Outcomes Research Unit, Rome, Italy (F Efficace PhD, F Cottone PhD, M Vignetti MD, Prof F Mandelli MD); **Division of Hematology, Department of**

Efficace et al, Lancet Oncology 2015 Nov;16(15):1506-14.

Overall Survival by baseline patient's self-reported Fatigue severity and IPSS risk group

FATIGUE



IPSS Group

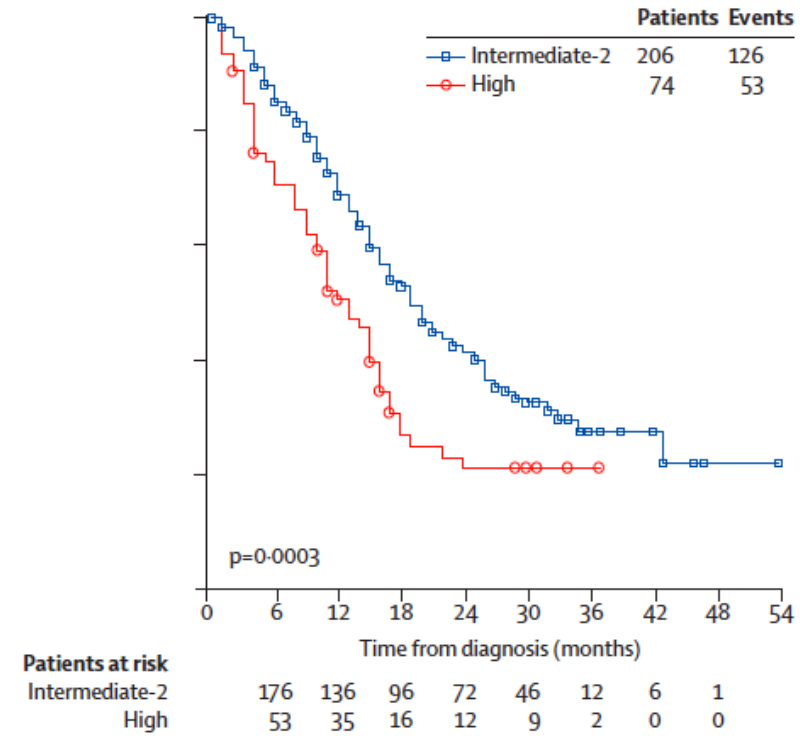


***Figure 1*: Overall survival by baseline patient's self-reported fatigue severity and IPSS risk group**
Low fatigue denotes patients reporting a baseline EORTC QLQ-C30 fatigue score lower than median value (34 points). High fatigue denotes patients reporting a baseline EORTC QLQ-C30 fatigue score equal or higher than the median value. EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer, quality of life questionnaire-core 30. IPSS=International Prognostic Scoring System.

Efficace et al, Lancet Oncology 2015 Nov;16(15):1506-14

Prognostic value for overall survival of IPSS, IPSS-R and WPSS with or without baseline fatigue

	Overall survival	
	Estimate (95% CI), months	Likelihood ratio test
IPSS risk group	..	14·6, p=0·0007
Intermediate-2	20 (17–24)	..
High	13 (9–16)	..
IPSS-R risk group	..	34·5, p<0·0001
Intermediate	35 (27–NR)	..
High	24 (19–28)	..
Very high	14 (12–16)	..
WPSS risk group	..	20·6, p<0·0001
High	20 (17–26)	..
Very high	11 (9–15)	..

FATIGUE ?

Shows whether the inclusion of baseline self-reported fatigue adds statistically significant prognostic information. p<0·05 indicates that additional information provided by baseline fatigue is statistically significant, under the null hypothesis that models with and without fatigue fit the data equally well. IPSS=International Prognostic Scoring System. IPSS-R=Revised International Prognostic Scoring System. NR=not reached. WPSS=WHO classification-based Prognostic Scoring System.

***Table 4*: Prognostic value for overall survival of IPSS, IPSS-R, and WPSS with or without baseline fatigue**

Lancet Oncology 2015 Nov;16(15):1506-14

Take Home Messages

- **Patient-Reported Quality of Life provides unique information** that cannot be captured by standard clinical or laboratory information.
- Subjective toxicities are at **high risk of under-reporting by physicians**, even when collected within RCTs.
- Quality of Life data are essential to f**acilitate clinical decision-making**

Thanks all for your attention!