Personalized Medicine and Quality of Life: Current Challenges in Patients with Leukemia

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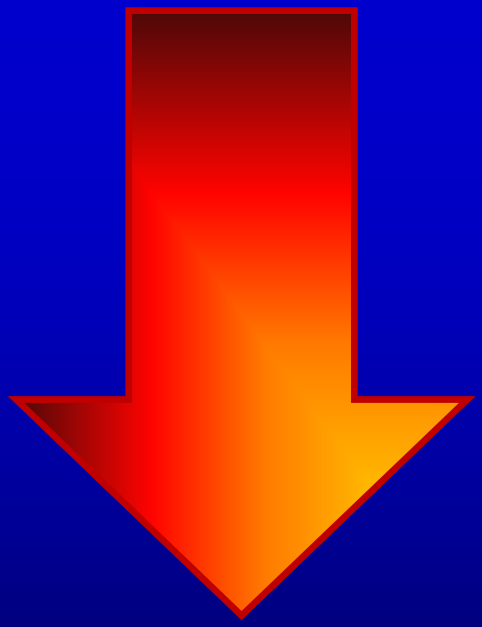
Why a focus on patients with Leukemia?

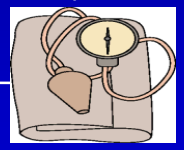


Outstanding Clinical Achievements

WHO SHOULD MEASURE SYMPTOMS OR QOL?

Information → Instrument

Blood pressure cuff

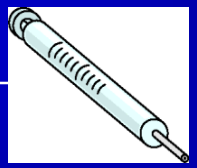


Pressure

Thermometer

Temperature

Syringe



Blood test

FATIGUE

PAIN

NAUSEA

Ask the Patient !

The Patient is the only source of data

QoL Instruments:

-Structured Questionnaires
-Valid
-Reliable (reproducible)

Major Clinical Advances in Patients with Leukemia

-The example of Acute Promyelocytic Leukemia (APL)-

Years…

2000 → **Introduction of a vitamin A plus chemotherapy**

First Line therapy with:

- All-trans retinoic acid (ATRA), plus chemotherapy
- Overall Survival (6 years): **87%**

Lo-Coco F. et al. Blood 2010;116:3171-3179

2013 → **Introduction of a Chemo-free therapy (i.e. arsenic)**

ATRA plus Chemo *vs*. **ATRA plus Arsenic** (New Engl J Med, 2013)

Remarkably, a recently developed first line therapy (without chemo) provide further advantages

The NEW ENGLAND JOURNAL of MEDICINE

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Retinoic Acid and Arsenic Trioxide for Acute Promyelocytic Leukemia

F. Lo-Coco, G. Avvisati, M. Vignetti, C. Thiede, S.M. Orlando, S. Iacobelli, F. Ferrara, P. Fazi, L. Cicconi, E. Di Bona, G. Specchia, S. Sica, M. Divona, A. Levis, W. Fiedler, E. Cerqui, M. Breccia, G. Fioritoni, H.R. Salih, M. Cazzola, L. Melillo, A.M. Carella, C.H. Brandts, E. Morra, M. von Lilienfeld-Toal, B. Hertenstein, M. Wattad, M. Lübbert, M. Hänel, N. Schmitz, H. Link, M.G. Kropp, A. Rambaldi, G. La Nasa, M. Luppi, F. Ciceri, O. Finizio, A. Venditti, F. Fabbiano, K. Döhner, M. Sauer, A. Ganser, S. Amadori, F. Mandelli, H. Döhner, G. Ehninger, R.F. Schlenk, and U. Platzbecker for Gruppo Italiano Malattie Ematologiche dell'Adulto, the German–Austrian Acute Myeloid Leukemia Study Group, and Study Alliance Leukemia

RESULTS

Complete remission was achieved in all 77 patients in the ATRA–arsenic trioxide group who could be evaluated (100%) and in 75 of 79 patients in the ATRA–chemotherapy group (95%) (P=0.12). The median follow-up was 34.4 months. Two-year event-free survival rates were 97% in the ATRA–arsenic trioxide group and 86% in the ATRA–chemotherapy group (95% confidence interval for the difference, 2 to 22 percentage points; P<0.001 for noninferiority and P=0.02 for superiority of ATRA–arsenic trioxide). Overall survival was also better with ATRA–arsenic trioxide (P=0.02). As compared with ATRA–chemotherapy, ATRA–arsenic trioxide was associated with less hematologic toxicity and fewer infections but with more hepatic toxicity.

Major achievements in clinical research in hematology

-Cancer Types of Treatments-

Chemotherapy

Uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. a body cavity such as the abdomen, the drugs mainly affect cancer cells in those areas

Radiation Therapy

Uses a certain type of energy (called ionizing radiation) to kill cancer cells and shrink tumors.

Biological therapy

Uses the patient's immune system to fight cancer. Substances made by the body or made in a laboratory are used [illegible] imm[illegible]

In hematology more and more patients are being treated with targeted therapies.
Many of the FDA cancer targeted therapies approved for use in patients with hematologic malignancies!

Bone [illegible]

G[illegible]es of chemotherapy and/or radiation therapy to destroy, and replacing blood-forming cells dest[illegible] the cancer treatment.

Targeted therapy

Targeted cancer therapies are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules involved in tumor growth and progression, without harming normal cells.

Sources: www.cancerresearchuk.org; National Cancer Institute, www.cancer.gov

MAIN DIFFERENCES BETWEEN TARGETED THERAPIES (HEMATOLOGY)

Broad categories	Type of administration	Timing of administration	Drug interactions	Examples (Drug/disease)
MONOCLONAL ANTIBODIES	Generally **intravenously** *(because their protein structure is denatured in the gastrointestinal tract)*	Usually **once every one to four weeks** *(half-lives ranging from days to weeks)*	**Limited** *(as they do not undergo hepatic metabolism)*	**Alemtuzumab** / CLL **Gemtuzumab** / AML **Rituxan** / NHL & CLL **Ofatumumab** /CLL **Tositumomab** / NHL
SMALL MOLECULE Inhibitors	Generally **orally**	Usually on a **daily basis** *(half-lives of few hours)*	**Significant interactions**	**Bortezomib**/ M. Myeloma **Imatinib** / CML & ALL **Dasatinib** /CML **Nilotinib** / CML

Some new challenges for clinical research:

- **Monitoring adherence to therapy**
  (which is related to outcomes but is not readily assessable as it is with conventional chemotherapy)
- **Determining optimal dosing**
- **Monitoring long -term effects**
  (Lack of long-term data)

FDA-approved targeted therapies for cancer

Drug	Type of agent (target)	Indication(s)	Common toxic effects
Imatinib	TKI (BCR–ABL kinase)	GIST, CML, refractory or recurrent Ph+ ALL, dermatofibrosarcoma protuberans	Fatigue, diarrhea, rash, nausea, cardiotoxicity, granulocytopenia[80,98,140]
Dasatinib	TKI (BCR–ABL kinase)	CML, ALL	Fatigue, diarrhea, rash, nausea, vomiting, edema, anemia, cardiotoxicity[98,140]
Nilotinib	TKI (BCR–ABL kinase)	CML	Fatigue, diarrhea, rash, nausea, vomiting, edema, anemia, cardiotoxicity[89,140]
Trastuzumab	mAb (HER2)	Breast cancer, gastric cancer, gastroesophageal adenocarcinoma	Fatigue, diarrhea, rash, cardiotoxicity, anemia, dyspnea, neutropenia[16,26]
Lapatinib	TKI (HER2, EGFR)	Advanced-stage metastatic breast cancer	Fatigue, diarrhea, rash, cardiotoxicity, hand–foot syndrome[85,103]
Gefitinib	TKI (EGFR)	Advanced-stage NSCLC	Diarrhea, rash, nausea, vomiting, mucositis, dyspnea[32,80,83]
Erlotinib	TKI (EGFR)	mNSCLC, pancreatic cancer	Fatigue, diarrhea, rash, anorexia[80,141]
Cetuximab	mAb (EGFR)	SCCHN, CRC	Fatigue, rash, anorexia, infusion reaction[124,142,143]
Panitumumab	mAb (EGFR)	mCRC	Fatigue, diarrhea, rash, nausea, anorexia, neutropenia[144]
Temsirolimus	mTOR inhibitor (mTOR)	Advanced-stage RCC	Fatigue, diarrhea, rash, nausea, anorexia, stomatitis, anemia, hypertension, dyspnea, edema, pneumonitis, dysgeusia, pyrexia[64]
Everolimus	mTOR inhibitor (mTOR)	Advanced-stage RCC, subependymal giant-cell astrocytoma, pancreatic neuroendocrine tumors	Fatigue, diarrhea, rash, nausea, anorexia, stomatitis, anemia, dyspnea, edema, pneumonitis, hyperglycaemia, oral ulceration[64]
Vandetanib	TKI (EGFR, VEGFR, Ret)	Medullary thyroid cancer	Diarrhea, rash, hypertension, proteinuria, asymptomatic QT prolongation[143,145]
Bevacizumab	mAb (VEGF)	Glioblastoma, NSCLC, metastatic breast cancer, mCRC, mRCC	Fatigue, diarrhea, anorexia, hypertension, abdominal pain, influenza-like illness, pyrexia, gastrointestinal perforation, proteinuria, hemorrhage, congestive heart failure, arterial thromboembolism, wound healing problems[64,92]
Sorafenib	TKI (VEGFR, PDGFR, C-Raf, Flt3)	Advanced-stage RCC, HCC	Fatigue, diarrhea, rash, nausea, vomiting, anorexia, hypothyroidism, cardiotoxicity, hand–foot syndrome, dyspnea[64,98,143]
Sunitinib	TKI (VEGFR, PDGFR, c-Kit, Flt3, Ret)	mRCC, GIST, pancreatic neuroendocrine tumors	Fatigue, diarrhea, nausea, vomiting, anorexia, dyspepsia, stomatitis, hypothyroidism, hypertension, cardiotoxicity, hand–foot syndrome, skin discoloration, dysgeusia[64,98,100,143]
Pazopanib	TKI (VEGFR, c-Kit, PDGFR)	Advanced-stage RCC	Fatigue, diarrhea, nausea, anorexia, hypertension, abdominal pain, arrhythmia, hepatotoxicity, hemorrhage[32]
Crizotinib	TKI (ALK, c-Met)	NSCLC	Mild nausea, vomiting, diarrhea, peripheral edema, very mild visual disturbances (no evidence of ocular pathology), transaminitis, and elevation of alanine aminotransferase[12,13]
Vemurafenib	B-Raf inhibitor (B-Raf, C-Raf, A-Raf)	Metastatic melanoma	Arthralgia, nausea, rash, diarrhea, fatigue, alopecia, squamous-cell carcinoma, and photosensitivity[50,53,54]
Rituximab	mAb (CD20)	NHL, CLL	Fatigue, thrombocytopenia, neutropenia, pneumonitis, edema, dyspnea[146]
Alemtuzumab	mAb (CD52)	B-cell CLL	Neutropenia, anemia, thrombocytopenia, infusion-related reactions, infection[147]
Ofatumumab	mAb (CD20)	CLL	Neutropenia, anemia, thrombocytopenia, infusion-related reactions, infection[148]
Ipilimumab	mAb (CTLA-4)	Metastatic melanoma	Diarrhea, rash, dermatitis enterocolitis, hypophysitis, hepatitis[149,150]

*This is a brief list of targeted anticancer therapies that are currently approved by the FDA; however, there are many other agents in clinical trials and the field is changing rapidly. Abbreviations: ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CRC, colorectal cancer; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; m, metastatic; mAb, monoclonal antibody; NHL, non-Hodgkin lymphoma; NSCLC, non-small-cell lung cancer; Ph+, Philadelphia chromosome positive; RCC, renal-cell carcinoma; SCCHN, squamous-cell carcinoma of the head and neck; TKI, tyrosine kinase inhibitor.

Keefe et al, *Nat. Rev. Clin. Oncol.* 2011

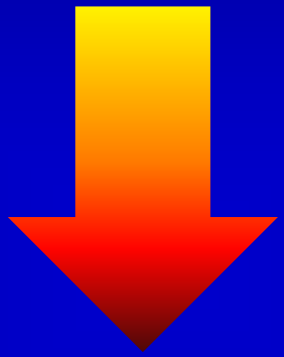
Some others in Hematology:

Bortezomib (Myeloma)

Bosutinib (CML)

Chronic Myeloid Leukemia (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, 2011)



Personalized medicine

refers to tailoring medical treatment to the unique characteristics of each patient.

The promise is that drug therapy targets an individual's genetic makeup.

CML Treatment evolution
Landmark data

►The first drug used for these patients with consistent activity was **busulfan** introduced in 1959 and some 10 years later **hydroxyurea** was also available.

►1970s **Allogeneic stem cell transplant**: The first observation of cure in CML

►1980s **Interferon α** (IFN-α) was introduced as treatment which provided a significant improvement in overall survival **(Overall survival at ten years=32%)**

► **Targeted Therapies (Tyrosine kinase inhibitors-TKIs), since 2003**

FDA approved therapies:

- **Imatinib** → **Equals to general population** (Gambacorti-Passerini, JNCI, 2011)
- **Dasatinib**
- **Nilotinib**
- **Bosutinib** (only as second line)

Sources: www.cancerresearchuk.org; National Cancer Institute, www.cancer.gov

Clinical outcomes of four Targeted therapies approved for CML patients

Table 2. Results of the randomized trials comparing nilotinib 300 mg twice per day versus imatinib 400 mg once per day (ENESTnd), dasatinib 100 mg once per day versus imatinib 400 mg once per day (DASISION), and bosutinib 500 mg once per day versus imatinib 400 mg once per day (BELA)

	ENESTnd[1,6], %			DASISION[2,8], %			BELA[14], %		
	Imatinib	Nilotinib	Difference	Imatinib	Dasatinib	Difference	Imatinib	Bosutinib	Difference
CCyR at 12 mo	65	80	15*	73	85	12*	68	70	2†
CCyR at 24 mo	77	87	10*	82	85	3†	81	87	6*
MR3 at 12 mo	27	55	28*	28	46	18*	27	41	14*
MR3 at 24 mo	44	71	27*	46	64	18*	52	67	15*
MR4.5 at 12 mo	1	11	10*	~ 5	~ 5	0†			
MR 4.5 at 24 mo	9	25	16*	8	17	9*			
PFS at 24 mo	95	98	3†	92	93	2†			
OS at 24 mo	96	97	1†	95	95	0†	95	97	2†
Patients still on therapy at 24 mo	67	74	7†	75	77	2†	71	63	−8*

The rates of response (CCyR, MR3, and MR4.5) are given as cumulative incidences. MR3 (MMR) is defined as a 3-log reduction in transcript levels or 0.1% on the international scale. PFS and OS are expressed as 2-year probabilities. Patients still on therapy at 24 mos are expressed as proportions. The columns with the heading "difference" indicate the difference in outcome between the second-generation TKI and imatinib.

*Statistically significant difference.

†Statistically nonsignificant difference.

(Marin D, ASH Educational Book, 2012).

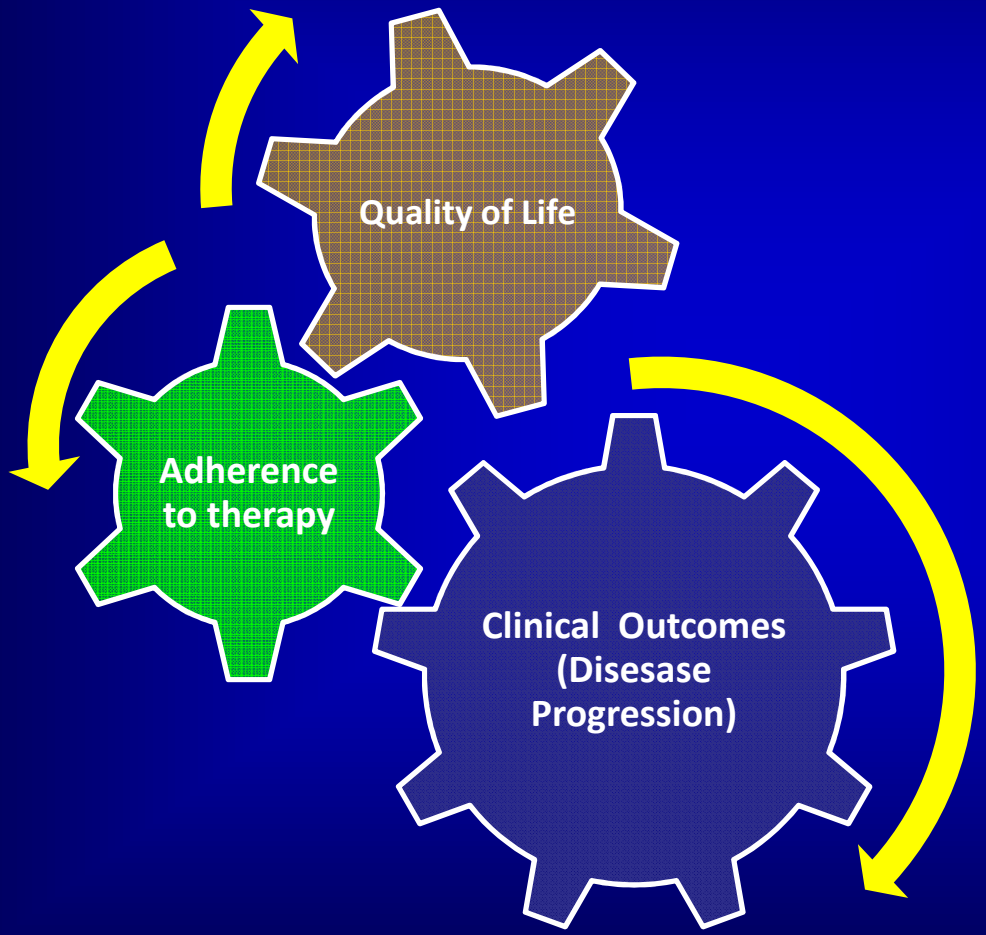
Key Message:

Targeted therapies have similar clinical outcomes in patients with CML.

Thus, in such a scenario, the patient's burden –disease and treatment effects- become crucial to make informed decision on overall value of a given therapy.

Target Therapies in Chronic Myeloid Leukemia

CML target therapies are lifelong, also patients are to take the drug on a daily basis



What we do not know?

Very little…

Facts vs. Assumptions

- Outstanding clinical outcomes (response rates and overall survival)

- Patient are fully adherent with treatment schedules
- No side effects (or in any case acceptable)
- Optimal Quality of Life

Adherence Is Critical to maximize clinical effectiveness of Target therapies in CML

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]

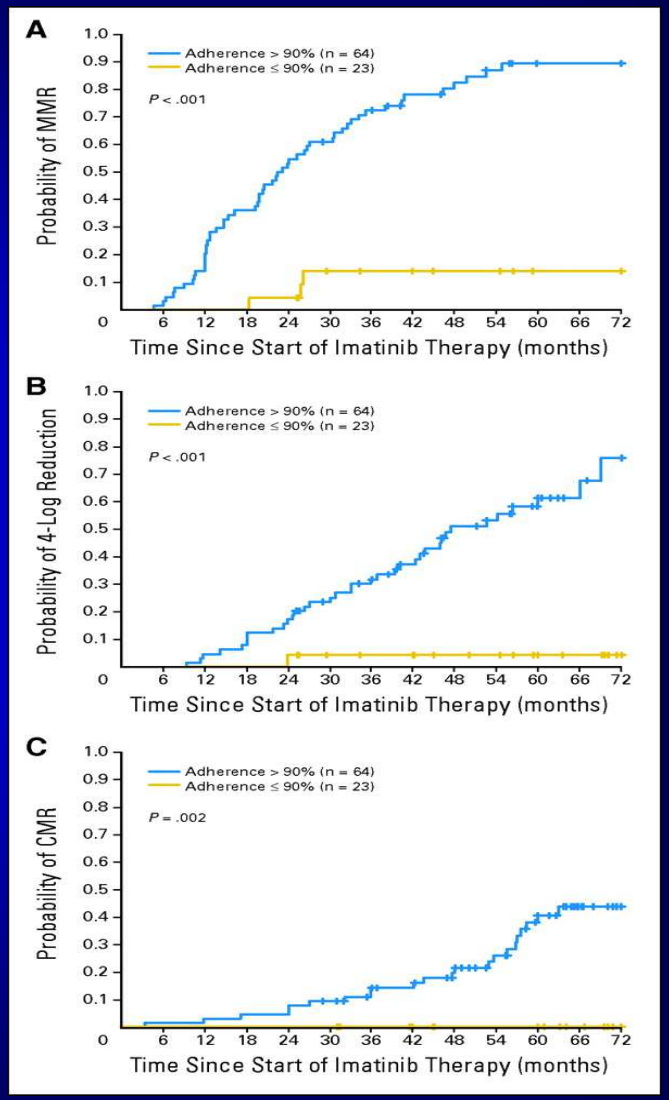
[1]Universitair Ziekenhuis (UZ) Gent, Gent, Belgium; [2]Novartis Pharma, Vilvoorde, Belgium; [3]Ziekenhuisnetwerk Antwerpen (ZNA) Middelheim, Antwerpen, Belgium; [4]UZ Gasthuisberg, Leuven, Belgium; [5]ZNA Stuivenberg, Antwerpen, Belgium; [6]UZ Antwerpen, Antwerpen, Belgium; [7]Institut Jules Bordet, 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 et al, Blood, 2009

Only 14% of patients are fully 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. JCO 2010

Towards a better understanding of the challenges of Personalized Medicine in CML

1. **Patients vs. Physicians: a different perspective ?**

   Efficace F, Rosti G, Aaronson NK et al, *Haematologica,* 2013

2. **How is long-term Quality of Life of these patients?**

   Efficace F, Baccarani M, Breccia M, et al, *Blood* , 2011

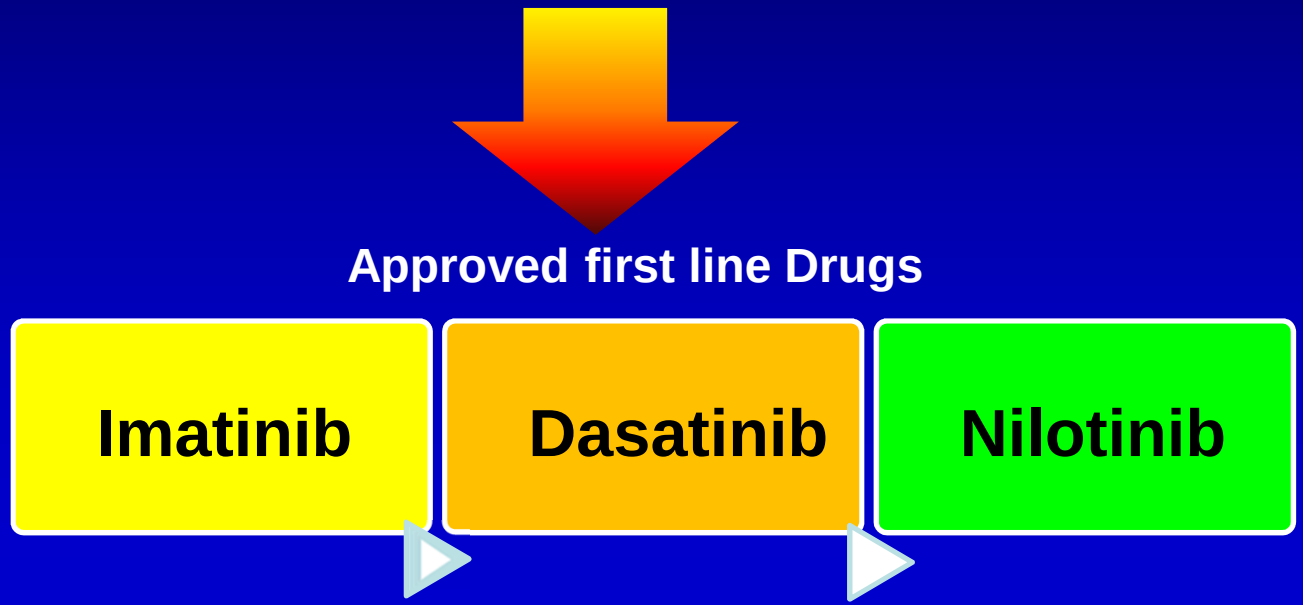
3. **Which factors contribute to a better adherence to therapy?**

   Efficace F, Baccarani M, Rosti G, et al, *Br J Cancer, 2012*

Patients vs. Physicians: a different perspective ?

Efficace F, Rosti G, Aaronson NK et al, *Haematologica,* 2013

Target therapies have introduced several challenges in the management of CML Patients



How one could best evaluate “intolerance” to a given TT in clinical practice?

Current parctice is to use CTCAE to define "intolerance" in CML patients

Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

GASTROINTESTINAL Page 10 of 10

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Ulcer, GI – *Select*: – Anus – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Ulcer, GI – *Select*	Asymptomatic; radiographic or endoscopic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Vomiting	Vomiting	1 episode in 24 hrs	2 – 5 episodes in 24 hrs; IV fluids indicated <24 hrs	≥6 episodes in 24 hrs; IV fluids, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Dehydration.						
Gastrointestinal – Other (Specify, __)	GI – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

Mild severity

Patient *versus* Physician

Efficace F, Rosti G, Aaronson NK, et al, *Haematologic*a, 2013

How accurate are Hematologists in estimating Symptom severity of their patients?

Background

✓ Several studies conducted in patients with solid tumors have shown that patients more frequently report worse symptom severity than physicians.

✓ Based on this, we hypothesized this would be true in a chronic myeloid leukemia (CML） clinical setting.

Study Objectives

✓ The main objective of this study was to compare the reporting of health status and symptom severity, for a set of core symptoms related to first line imatinib therapy, between patients and their treating physicians.

✓ A secondary objective was to investigate whether either physician or patient-reported symptoms best reflected the patient's overall health status.

Study Population

Physicians' characteristics (=29)

Variable	Category	Total
Age (years)	mean (SD)	43.34 (9.98)
	median	42.00
	range	28.00-58.00
Gender, n (%)	Male	10 (34.48)
	Female	19 (65.52)
Years of practice*	mean (SD)	17.45 (9.64)
	median	17.00
	range	3.00-33.00
Years of experience in treating CML patients, n (%)	mean (SD)	12.45 (8.10)
	median	12.00
	range	1.00-27.00
Overall number of CML patients currently under direct management, n (%)	1-20	5(17.24)
	>20	24(82.76)

Patients' characteristics (=422)

Variable	Total
Gender, N(%)	
Female	172 (40.8)
Male	250 (59.2)
Age at study entry, (years)	
Median	57
Range	19.4 - 86.8
Comorbidity at diagnosis N(%)	
0	269 (63.7)
≥1	153 (36.3)
Sokal risk at diagnosis N(%)	
Low	222 (52.73)
Medium/High	185 (43.94)
Unknown	14 (3.33)
Job problems due to disease and therapy N (%) [a]	
No	228 (66.3)
Yes	116 (33.7)
Time to first CCyR	
Early responders (< 1year)	342 (81.0)
Late responders (≥ 1 year)	80 (19.0)
Imatinib dose at the time of HRQOL evaluation	
400 mg/day	327 (77.5)
Other than 400 mg/day	95 (22.5)

Patient *versus* Physician

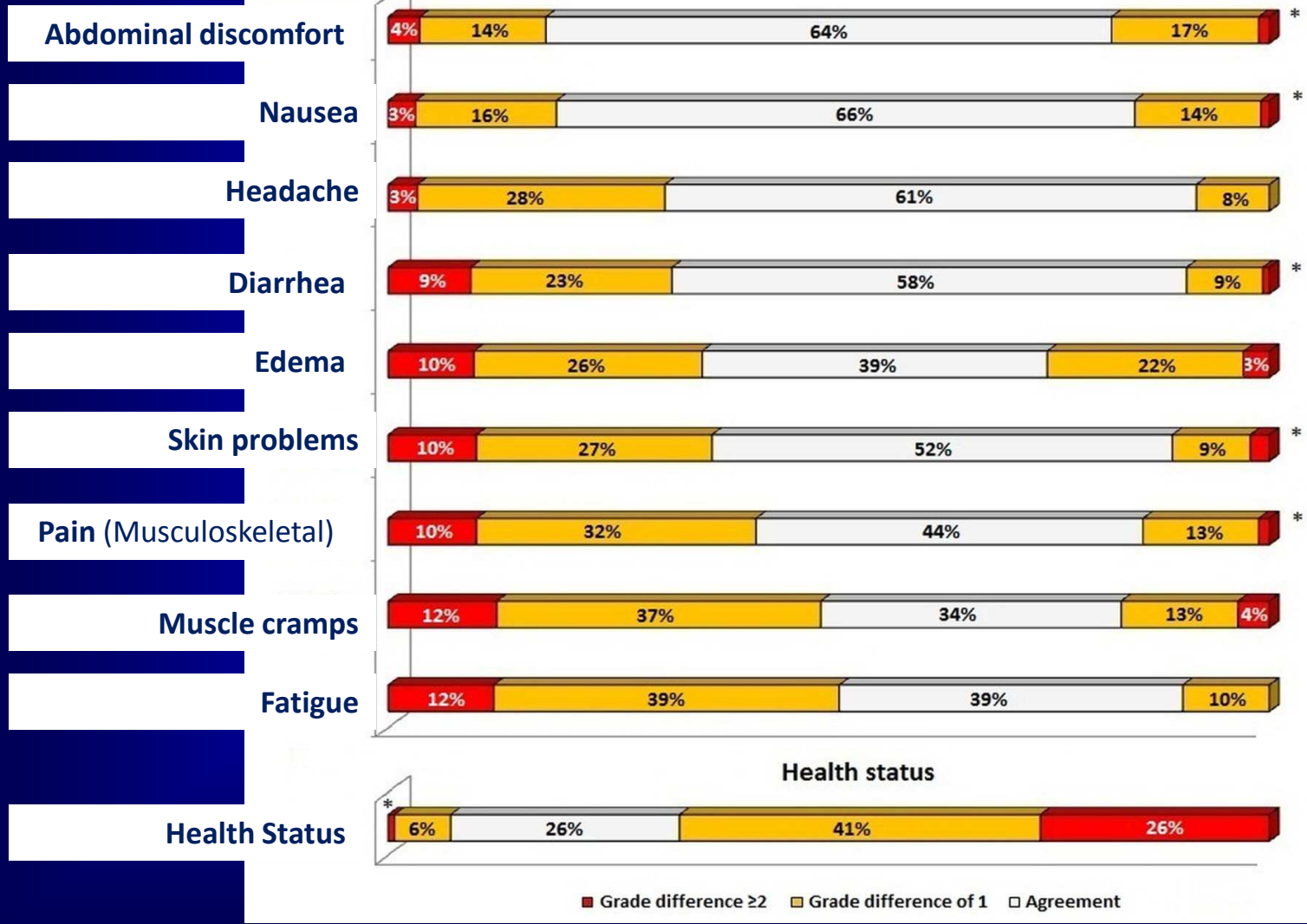
How accurate are Hematologists in estimating Symptom severity of their patients?

How severe is this symptom?

Not at all **A little** **Quite a bit** **Very much**

Efficace F, Rosti G, Aaronson , et al, *Haematologic*a, 2013

N=422 comparison Patient-Physician



Efficace F, Rosti G, Aaronson , et al, *Haematologica*, 2013

Results

Efficace F, et al, *Haematologica*, 2013

Physicians' underestimation by symptom severity

Physicians' rating

Abdominal discomfort

Physicians' rating \ Patients' rating	A little	Quite a bit	Very much
Quite a bit			0.00
A little		8.00	5.33
Not at all	**72.00**	10.67	4.00

Nausea

Physicians' rating \ Patients' rating	A little	Quite a bit	Very much
Quite a bit			1.25
A little		5.00	2.50
Not at all	**77.50**	10.00	3.75

Headache

Physicians' rating \ Patients' rating	A little	Quite a bit	Very much
Quite a bit			0.75
A little		6.02	1.50
Not at all	**82.71**	6.77	2.26

Diarrhea

Physicians' rating \ Patients' rating	A little	Quite a bit	Very much
Quite a bit			2.99
A little		12.69	6.72
Not at all	**55.22**	15.67	6.72

Edema

Physicians' rating \ Patients' rating	A little	Quite a bit	Very much
Quite a bit			4.67
A little		26.67	11.33
Not at all	**41.33**	11.33	4.67

Skin problems

Physicians' rating \ Patients' rating	A little	Quite a bit	Very much
Quite a bit			2.60
A little		7.14	4.55
Not at all	**62.99**	16.88	5.84

Musculo-skeletal pain

Physicians' rating \ Patients' rating	A little	Quite a bit	Very much
Quite a bit			4.57
A little		21.14	7.43
Not at all	**50.29**	15.43	1.14

Muscular cramps

Physicians' rating \ Patients' rating	A little	Quite a bit	Very much
Quite a bit			3.41
A little		24.88	10.73
Not at all	**46.34**	10.73	3.90

Fatigue

Physicians' rating \ Patients' rating	A little	Quite a bit	Very much
Quite a bit			3.27
A little		24.77	8.41
Not at all	**48.60**	13.08	1.87

Patients' rating

Legend: for each symptom, the table shows the distribution of physicians underestimation by each permissible pair of scores. Each cell shows the joint frequency of physicians' score (vertical ratings) versus patients' score (horizontal ratings).
The levels of underestimation are represented on the diagonals from left to right. For example, the main diagonal represents the possible pairs of the smallest score difference (-1).

How is long-term Quality of Life of these patients?

Efficace F, Baccarani M, Breccia M, et al, *Blood* , 2011

How is Quality of Life of CML patients treated with **Imatinib** and in CCyR compared to the general population?

Efficace F, Baccarani M, Breccia M, *Blood*, 2011

Patients' Quality of Life

SF-36
Questionnaire

PHYSICAL HEALTH

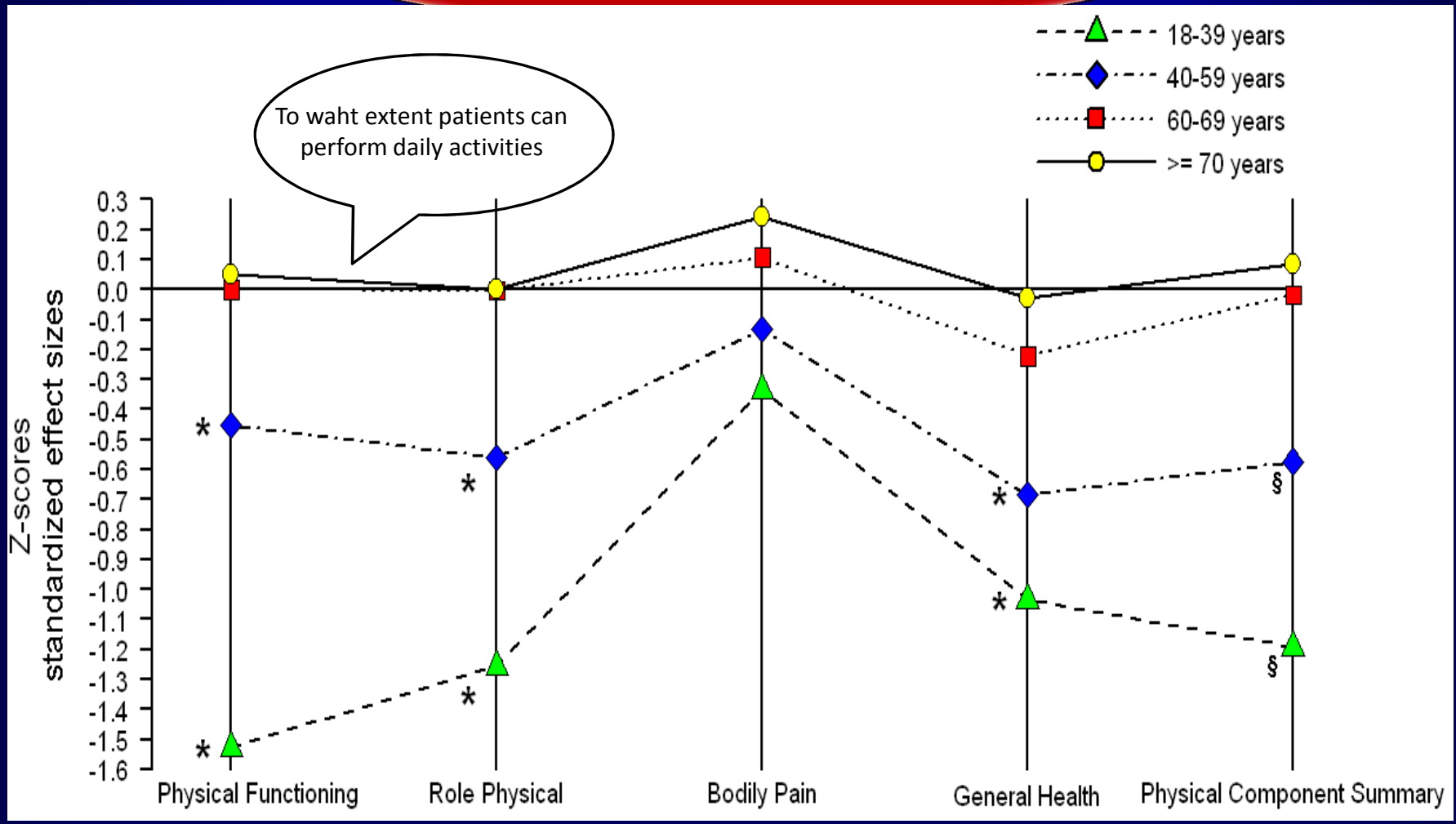
- Physical functioning (PF)
- Role limitations due to physical health problems
- Bodily pain
- General health perceptions

MENTAL HEALTH

- Vitality
- Social Functioning
- Role limitations due to emotional problems
- Mental health

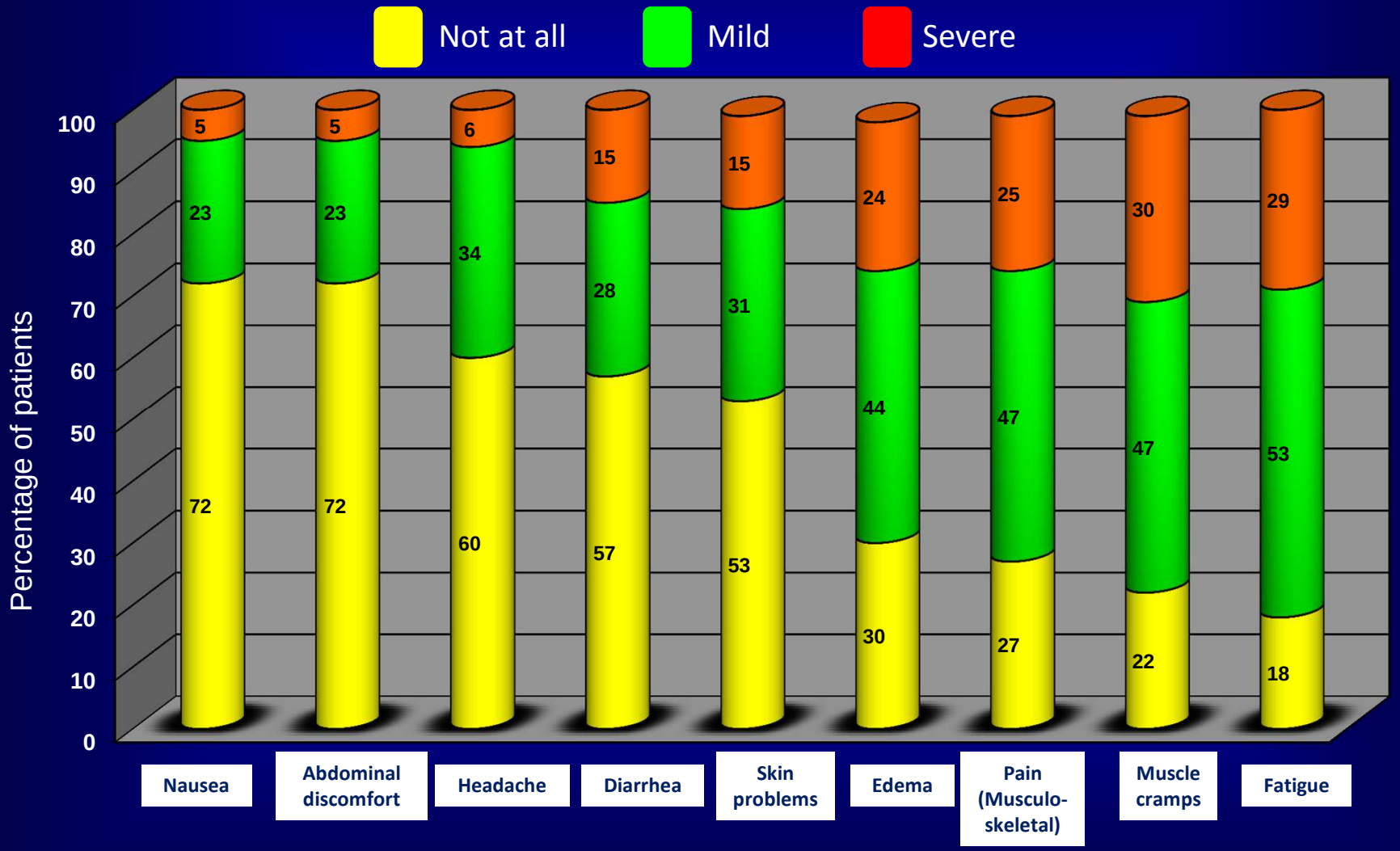
PHYSICAL HEALTH by age categories

Efficace F, Baccarani M, Breccia M, ***Blood***, 2011



Chronic Symptoms in CML Patients treated with TKI (i.e. Imatinib)

Duration of treatment: 5 years (median)



Efficace F, Baccarani M, Breccia M, et al, *Blood* , 2011

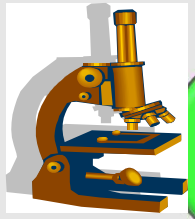
Which factors contribute to a better adherence to therapy?

Efficace F, Baccarani M, Rosti G, et al, *Br J Cancer, 2012*

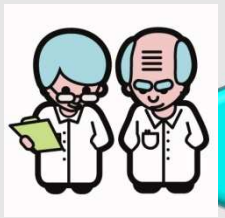
Background-Rationale

Factors possibly associated with Adherence to Treatment

Socio-demographic
(age, gender, comorbidity...)



Clinical and Treatment-related
(duration of therapy, dose of treatment...)



Physician-reported data
(performance status, toxicity)

Adherence to treatment

Social Support

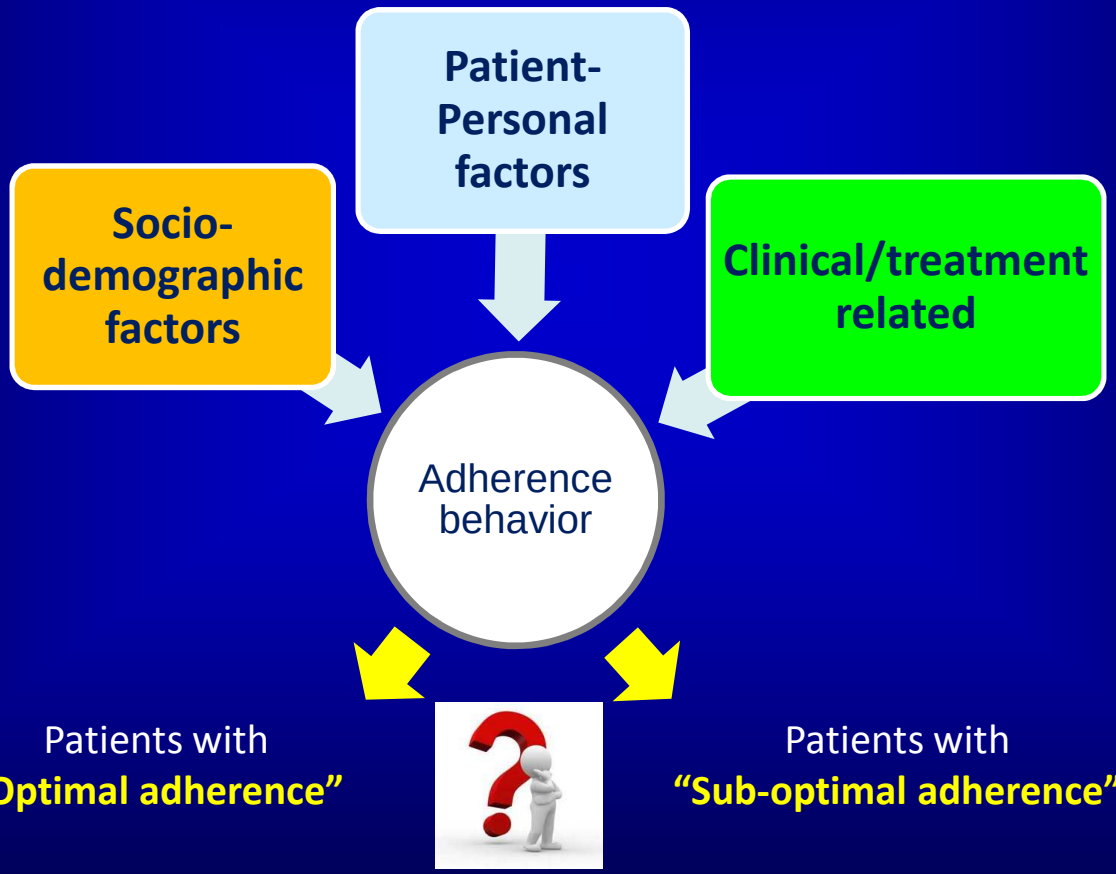
Were we missing something in CML?

Patient's personal factors

- ✓Social Support
- ✓Symptom Burden
- ✓Quality of Life
- ✓Level of Information received

Objective

To investigate patient-reported personal factors associated with “sub-optimal” adherence behavior



Patient Population (N=448) and Study Design

Inclusion criteria

- Age ≥ 18 years
- Started Imatinib (IM) therapy in the early chronic phase (ECP).
- In treatment with IM, as first line therapy, for at least three years regardless of the current dose of IM.
- In complete cytogenetic response (CCyR) and no clinical evidence of disease progression to AP or BC
- Freedom from psychiatric conditions that may confound HRQOL evaluation.
- Informed consent provided.

Exclusion criteria

- CML patients who were initially diagnosed in the AP or BC or those who started therapy with IM in the late chronic phase (LCP).
- Having received any kind of treatment prior to IM therapy (except for hydroxyurea and/or anagrelide)
- Patients with a new primary malignancy.

Study Measures

Adherence measure

Self-reported Morisky Scale (adapted version)

1) Do you ever forget to take your medicine?

2) When you feel better do you sometimes stop taking your medicine?

3) Sometimes if you feel worse when you take the medicine, do you stop taking it?

Answers categories: *Never, Rarely, Sometimes, Often.*

Socio-demographic and clinical factors

Age, Gender, Education, Marital status.

Assumption of concomitant drugs, Performance status, Comorbidity, Sokal risk, Dose of Imatinib. Intolerance to Imatinib, Duration of therapy, Time between start of therapy and CCyR and time from CCyR to study entry, Toxicity within six months to study entry.

Patient-Reported Personal Factors

Social support

Multidimensional scale of perceived social support (MSPSS)

Quality of Life

Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)

Fatigue

FACIT-Fatigue scale

RATIONALE:

Found to be associated with Adherence Behavior in other Chronic Medical Conditions

(DiMatteo MR. Health Psychol. 2004; Jackevicius CA, et al, JAMA 2002; Banta JE, et al, Am J Health Behav 2009; Krousel-Wood M, et al, Curr Opin Cardiol 2004; Kripalani S, et al, Arch Intern Med 2007; Gordillo V, et al, AIDS 1999)

-Would you have wished more information on **side effects of your therapy**?

-Would you have wished more information the **impact of disease and side effects of therapy on your QoL?**

Socio-demographic and clinical characteristics of study population (n=413)

Gender, N (%)	
Female	167 (40.44)
Male	246 (59.56)
Age at study entry (years)	
Median	56.83
Range	19.67 - 86.83
Education, N(%)	
8th grade or less	188 (45.52)
High school	152 (36.8)
University degree or higher	70 (16.95)
Missing	3 (0.73)
Marital Status, N (%)	
Divorced	30 (7.26)
Single	42 (10.17)
Married/living together	304 (73.61)
Widow	31 (7.51)
Missing	6 (1.45)
Comorbdity at diagnosis N (%)	
0	264 (63.92)
≥1	149 (36.08)
Sokal-risk at diagnosis, N (%)	
Low (< 0.8)	217 (52.54)
Intermediate (0.8-1.2)	136 (32.93)
High (>1.2)	46 (11.14)
Missing	14 (3.39)
Current Imatinib dose, N (%)	
< 400 mg/day	59 (14.29)
400 mg/day	320 (77.48)
>400 mg/day	34 (8.23)
Intolerance to Imatinib, N (%)	
No	300 (72.64)
Yes	113 (27.36)
Current concomitant drug not related to CML, N (%)	
No	239 (57.87)
Yes	170 (41.16)
Missing	4 (0.97)
Duration of Imatinib therapy (years)	
Mean (SD)	5.18 (1.48)
Median	5.08
Range	3.00 - 9.33

Patients with
"Optimal adherence"

53%

Patients with
"Sub-optimal adherence"

47%

Final multivariate model of factors associated with “suboptimal” adherence behavior

Variable	OR (95%, CI)	*P* value
Concomitant drug(s) not related to CML (ref. no)	0.549 (0.357; 0.844)	0.006
Social support	0.775 (0.669; 0.899)	< 0.001
Desire for more information on the impact of disease and therapy on QoL (ref. no)	2.297 (1.510; 3.494)	< 0.001

Conclusions

- Target therapies have help moving toward a more personalized treatment approach in oncology.
- Target therapies has provided outstanding clinical benefits.
- However target therapies have introduced a number of "new" challenges in patients management (lifelong therapy and chronic side effects).
- Contrary to what one would have expected target therapies do not necessarily translate into an "optimal QoL".
- Patients are not fully adherent to therapy and actions have to be taken to maximize adherence to therapy.

Thanks all for your attention!