

## EORTC Quality of Life -Chronic Myeloid Leukemia

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# Targeted Therapies

**Targets:** The development of targeted therapies requires the identification of good targets—that is, targets that are known to play a key role in cancer cell growth and survival.

Targeted therapies are mainly divided in:

**1. Monoclonal antibodies:** usually cannot penetrate the cell's plasma membrane and are directed against targets that are outside cells or on the cell surface.

- ✓ Monoclonal antibody therapy is a cancer treatment that uses antibodies made in the laboratory from a single type of immune system cell.
- ✓ Act by helping the immune system to destroy cancer cells.

**2. Small-molecule Inhibitors:** are typically able to diffuse into cells and can act on targets that are found inside the cell.

- ✓ Some targeted therapies block specific enzymes and growth factor receptors involved in cancer cell proliferation.
- ✓ **Tyrosine kinase inhibitors:** they block an enzyme called tyrosine kinase that causes stem cells to develop into more white blood cells (granulocytes or blasts) than the body needs.

# Chronic Myeloid Leukemia (CML)

- CML is a slowly progressing blood and bone marrow disease
- The bone marrow makes an enzyme, called **tyrosine kinase**, that causes too many stem cells to develop into white blood cells (granulocytes or blasts).
- Most people with CML have a gene mutation called the **Philadelphia chromosome**. Part of the DNA from one chromosome moves to another chromosome.
- The disease is classified by phase: **chronic phase (CP)**, **accelerated phase (AP)**, or **blastic phase (BP)**. (Depending on the percentage of the cells in the blood and bone marrow that are blast cells .)

Sources: [www.cancerresearchuk.org](http://www.cancerresearchuk.org); National Cancer Institute, [www.cancer.gov](http://www.cancer.gov)

# 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  $\alpha$**  (IFN- $\alpha$ ) was introduced as treatment which provided a significant improvement in overall survival
- ▶ **Targeted Therapies (Tyrosine kinase inhibitors-TKIs)**

### First Line Treatment

**Imatinib (IM)** (2002 FDA approval as 1<sup>st</sup> line treatment)

**First generation TKIs**

### Second Line Treatments

**Dasatinib** (2006 FDA approval)

**Nilotinib** (2007 FDA approval)

**Second generation TKIs**

# Background-Rationale (1)

## Why devising a CML Questionnaire on QoL?

- ▶ TKIs have dramatically changed the treatment of this disease by markedly improving patients survival and by making QoL more acceptable. (Hahn et al, J Clin Oncol, 2003)
- ▶ While it is known that targeted therapies provide better QoL outcomes compared with previous Interferon based treatments (Hahn et al, J Clin Oncol, 2003), toxic effects are still present. For example Imatinib toxic effect includes:
  - muscle cramps,
  - fluid retention;
  - skin problems;
  - headache ;
  - fatigue.
- ▶ Preliminary data suggest that symptoms might still be present in CML patients treated with first line targeted therapies even after years since diagnosis (Efficace, Baccarani, Breccia et al, EHA submitted, 2010) .
- ▶ No Patient-Reported Outcome instrument is currently available for CML patients.
- ▶ **CML patient associations** are highly pushing to have data on expected impact of cancer diagnosis and treatment on their own Quality of Life (CML Adovcates Network)
- ▶ Patients are to continue treatment indefinitely to control the disease (Baccarani et al, Blood, 2006) and this is on a daily basis: might have a significant impact on psychosocial outcomes?

## Background-Rationale (2)

### Why devising a CML Questionnaire on QoL?

#### ➔ **IMATINIB.**

##### **Landmark data:**

2002- FDA approval of Imatinib (IM) as first line treatment of CML patients.

**Follow-up at 7 years with IM** (O'Brien et al, Blood 2008; 112: abstr 186).

Overall Survival: 86%

Cumulative Complete Cytogenetic Response (CCgR): 89%

**CLINICAL DECISION-MAKING IN CML PATIENTS IS GETTING MORE AND MORE CHALLENGING**

#### **2009. Will IM remain the first line treatment for these patients?**

Saglio et al, (phase III ENEST Trial), American Society of Hematology (ASH), 2009			
	Nilotinib (N=281)	Nilotinib (N=282)	Imatinib (N=283)
Dose →	800 mg/day	600 mg/day	400 mg/day
<b>Clinical outcomes</b>			
CCgR (at 12 months)	78%	80%	65%
MMR (at 12 months)	43%	44%	22%

#### **Yet...**

- There are already data on: IM+ Interferon (Palandri et al, ASH 2009)
- it is likely that phase II explorative studies on the association of 2<sup>nd</sup> generation of TKIs (e.g. Nilotinib) and Interferon are in preparation.

## Study Objective

- **To develop an EORTC questionnaire to measure QoL in patients with CML**
- **To develop a CML Symptom Checklist**

## Patient Groups

CML patients in the following treatment groups :

1. undergoing first line treatment with 1<sup>st</sup> generation of TKIs (i.e. IM).
2. undergoing first line treatment with 2<sup>nd</sup> generation of TKIs (e.g., dasatinib or nilotinib).
3. in second line treatment with TKIs (as previously resistant or intolerant to IM).
4. receiving TKIs with previous HSCT, as relapsed from previous treatment lines.
5. receiving treatment for more than five years, regardless of the treatment group.

# Module Development: EORTC QoL Group Guidelines

Development of **modules** specific to tumor site, treatment modality, or a QL dimension, to be administered in addition to the core questionnaire (the EORTC QLQ-C30).

## EORTC QLG Guidelines (main steps)

**Phase 1: Generation of QL issues** Identify a list of relevant QL issues through:

- (i) Literature searches
- (ii) Interviews with health care providers
- (iii) Patients' interviews

**Phase 2: Operationalisation** Operationalise the issues into questions:

- Consult existing items
- Construct new item: major rules
- Review by health care providers

**Phase 3: Pre-Testing** Pretesting the questionnaire for acceptability and relevance

1. Patients complete module with interview
2. Analysis of quantitative and qualitative data
3. Modification of questionnaire

### Phase 4: Field-Testing

Psychometric testing (internationally) of *reliability*, *validity*, and *sensitivity* of the module

# Where are we now?

## Phase 1 - Generation of QOL issues

### Literature search - Articles

#### Methods:

1. Studies including any kind of PROs (QoL, symptom burden, psychosocial issues)
2. Two independent reviewers (F. Efficace and K. Cocks)
3. The following databases were used (1980-2009):
  - ✓ PubMed
  - ✓ CINHAL
  - ✓ SCOPUS
  - ✓ PsycINFO
  - ✓ PsycARTICLES

#### Results:

Initial: 400 articles

Eligible articles: 15

- Treatment effect on QoL
- QoL as prognostic factor
- QoL incidence
- Only 2 dealing with targeted therapies



# Where are we now?

## Phase 1 - Generation of QOL issues

### Literature search - Questionnaires

#### Methods:

Existing questionnaires

The following databases were consulted :

- ✓ FACIT.org
- ✓ www.EORTC.org
- ✓ PROQOLID

#### Results:

- none was CML specific
- EORTC: QLQ – HDC29 (High-dose chemotherapy and stem cell transplantation)  
QLQ – CLL16 (Chronic Lymphocytic Leukaemia)
- FACT : BRM (For patients receiving Biologic Response Modifiers )  
Leu (Leukaemia) Abstract only
- Diabetes
- HIV



## CML Questionnaire development

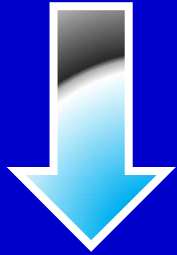
- ✓ A list of 74 issues summarized into the following domains:  
(based on literature review)

Symptoms (disease and treatment related)	37 items
Psychosocial	17 items
Infertility	1 items
Body image	4 items
Adherence to therapy	9 items
Satisfaction	5 items

- ✓ The list is currently being circulated to HCPs from:

Norway, Austria, Australia, Germany, UK, Italy, Netherlands, Taiwan, Greece

- The relevance of each issue
- Select core issues
- Report missing items.



# WHAT'S NEXT?

Finalize phase I and start with phase II

Continue administration of the list to HCPs.

Start administration to patients

In addition, to make sure that Content Validity of the questionnaire will be robust....

CML Patients Association will be involved as well.

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