Generalitat de Catalunya
Departament de Salut

ICO
Institut Català d'Oncologia

FEASIBILITY OF TKI TREATMENT IN OLDER PATIENTS WITH Ph+ CML.

A SPANISH GROUP OF CML (GELMC) RETROSPECTIVE STUDY

SIOG

Lisbon, 23-25th October 2014

International Society of Geriatric Oncology Meeting

FEASIBILITY OF TKI TREATMENT IN OLDER PATIENTS WITH Ph+ CML

- **INTRODUCTION**
- PATIENTS AND METHODS
- RESULTS
- CONCLUSIONS

INTRODUCTION (I)

AGE AND CML

Median age at CML presentation is ussually 65 years

Age is included in most prognostic scores

Age is a poor prognosis variable →Lower PFS with Busulfan, HU, IFN and Allogenic Transplant

IFN → More adverse events → Low compliance
CHR, CCR and OS rates similar to younger patients series

Poor prognosis in patients with older age was related to treatment associated factors rather than to an intrinsic different disease

INTRODUCTION (II)

TKI → indicated in Ph+ CML patients regardless of age.

Elderly patients → poorly represented in clinical trials of these drugs

(patients who participate in clinical trials vs who did not are 10,7 years younger, have lower prognostic scores and are managed in hospitals.

IRIS: N= 1106 patients
Patients > 60 years:
20.6% (IM arm)
23.1% (IFN arm + citarabina)

O'Brien et al. NEJM. 2003

ENEST: N= 846 patients
Patients > 65 years:
12.4% (NL 400 arm)
12.8% (NL 300 arm)
10% (IM arm)

Saglio G et al. NEJM. 2010

DASISION: N= 519 patients
Patients > 65 years:
8% Dasatinib arm
9% Imatinib arm

Kantarjian H et al. NEJM. 2010

INTRODUCTION (III)

Cortes et al. 2003

Effects of age on prognosis with IM therapy for patients with CML retrospective one center series

- 26% (49/ 187) patients treated with IM in early CP *with > 60 years*
- *34% (120/351) patients treated in late CP IFN failure > 60 years*
- Response:
  - early CP → Similar CCR and survival (56% vs 44% p=0,05).
  - late CP /IFN failure → Lower incidence of CCR,

In multivariate analysis: Age was not an adverse prognostic factor for survival.

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With Imatinib, older age appears to have lost much of its prognostic relevance

Cortes et al. Cancer 2003.

INTRODUCTION (IV)

Latagliata et al 2005

Toxicity, response and survival in patients treated in only one centre

- 48% (35/72) patients ≥ 60 years: 24 CP (intolerants/resistant IFN), 11 advanced disease (5 AP, 6 BP).
-Response → FC: comparable to results observed in younger patients → 100% CHR, 70,8% CCR.
- Mild toxicity was observed

Elderly patients should receive the same treatment with Imatinib as younger patients.

Latagliata et al. Leukemia Research 2005.

Latagliata et al (2013)

Retrospective analysis in several hospitals

21% late chronic phase
Age ≥ 75 years
One or more comorbidities were present in 93% of patients
Fewer responses (CCR: 64%
4 years survival 78%).
-More adverse events (hematological : 19% and extrahematological toxicity: 21%

Latagliata et al/ Drugs Aging 2013

INTRODUCTION (V)

- **Rosti et al. 2007 (Phase II study of the GIMEMA CML Working Party, sub-analysis)**

- **Response, compliance and toxicity in patients in a multicentre study**

- 20% (58/284) patients ≥ 65 years (late CP after IFN failure or intolerance)

- Fewer responses (CHR :53% vs 74%, CCR: 36%vs 58%).
- Same long-term outcome (PFS and OS with a median follow up of 36 months).
- More adverse events (hematological and extrahematological toxicity

- Differences in response rates from *Cortes et al* → ≠ elderly definition (≥ 60 years), EC multi-institutional vs only one centre

Suggests to define old patients on the basis of age-indpendent reproducible indicators of fragility rather than simply according to age.

INTRODUCTION (V)

ELDERGLI study (*Sánchez-Guijo et al.* 2011)

Multicentre, prospective, observational trial to evaluate Tolerability and response to IM in patients > 65 years

- 36 patients (early CP CML) with median age 76,6 years (65-87).
-52% had HTA and 22% DM

- Response rates and duration of response: comparable to previous reports (*Cortes et al, Latagliata et al*), but different from GIMEMA report (most of the patients were intolerant/resistant to IFN).

-Well tolerated in most patients. Edema (44%), Diarrhea (28%), and musculoesketal (14%) secondary effects were the most frequent.

- 33% interrupted the therapy during the follow up

- Tolerability data comparable to IRIS study but higher infections (25%), Cardiovascular events (16%) and secondary neoplastic diseases (11%) are higher than the reported in CML trials

Sánchez-Guijo et al. Leukemia Research 2011

	SOKAL	HEMATOLOGICAL TOXICITY	NON HEMATOLOGICAL TOXICITY	SUSPENSION RATE	RESPONSE
Cortes 2003 >60y (n=49 ECP and 120 LCP)	NS				87% CCR (CP)
Latagliata 2005 >60y (n= 24 LCP)	Inter /high 75%	33,3% (CP, grade 3-4)	20,8% (grade 3-4)	4,17% (CP)	70,8% CCR
Latagliata 2010 > 65 y (n= 40 ECP)	Inter/High risk mostly	25% (grade 3-4)	27% (grade 3-4)	12,5%	85% CCR
Rosti 2007 ≥65 y n=58 LCP	NS	43% (grade 3-4)	12% (grade 3-4)	6%	36% CCR
Plestch 2009 >65y n=58	n	Superior than younger	Superior than younger	12%	
ELDERGLI 2011 >65 y n=36 ECP	NS	19,4%	91%	33,3%	83%, CCR
Rousselot 2013 > 70 y n=30	-	-	More CV events	37%	79% CCR
GIMEMA 2011 > 65 y n=115	High /inter 91%	-	-	Similar than younger	87% CCR

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PATIENTS AND METHODS

Study → retrospective, multicenter (participants **27 Spanish hospitals**)

OBJECTIVE → To know the TKI treatment applicability in elderly CML patients.

PATIENTS → **129 patients** with Ph+ CML in CP and age ≥ 70 years, diagnosed from January 2005

METHODS → Several variables have been studied analyzing the collected data through the data sheet

Patient
- Cardiovascular risk factors (CVRF)
- Concomitant treatments
- Geriatric syndromes
- Sokal risk

Treatment feseability
- Toxicity
- Adherence
-Discontinuations
-Response

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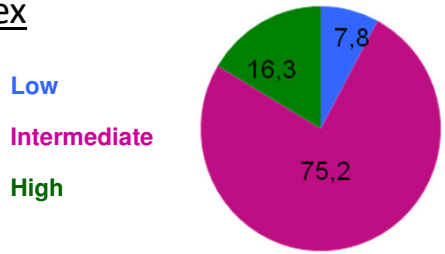
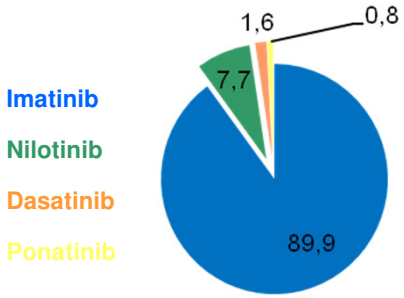
RESULTS

- 129 patients with CP CML coming from 27 different hospitals.
- Median age at diagnosis → 77 years (IR 74-80 years).
- CVRF: HTA, DM, hypercholesterolemia, smoking
  - A 74,4% of patients have CVRF.
  - A 14% of patients had more than 3 (43 evaluated patients)
- Distribution of Sokal index

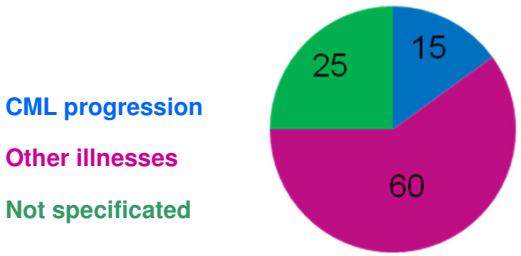


- Geriatric syndromes: Cognitive damage, depression, sleep disorders, walk disorders/falls, incontinence, undernourishment, delirium, osteoporosis/fractures.
  - Present in 47,3%
- Concomitant treatment >5 → 42,6%
- First line treatment



RESULTS II

- Median time from diagnosis until TKI start → 0,69 months (IR 0,23-1,38).
- Toxicity (TKIs at first line) grades 1-4 → Hematological 40,3%, non hematological 71,3%.
  - TKI discontinuation → 45%.
- Adherence → Good 77,5%.
- TKI 2nd or 3rd generation as first line → 38,4% had toxicity
- Of the 97 evaluated patients, 60 (61,8%) were still on treatment at 18 months;
- Of the 97 evaluated patients , 100% had reached CHR, a 96,2% CCR and a 68,3% ≥MMR.
- Overall survival (OS) → 33,1% with a median follow-up of 37 months.
- Causes of death:



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CONCLUSIONS

- High percentage of patients with risk Sokal intermediate-high.

- Most patients have CVRF, geriatric syndromes and multiple concomitant medications at diagnosis

- Response rate comparable to published series.

- Toxicity and TKI suspension rate superior to those reported in studies of patients of all ages.

- Overall survival comparable to that reported in other studies of elderly patients and lower than that observed in patients of all ages.

- Applicability of TKI treatment in older patients would be limited by the high rate of toxicities and treatment interruptions.

- Prospective studies are needed to measure the impact of the specific comorbidities, concomitant treatments or other geriatric patient characteristics on the applicability of the TKI treatment.

We need to define patients age-independent reproducible indicators of fragility and comorbidities (specially the cardiovascular risk factors) to better know patients who will really benefit of TKI treatment.

HOSPITALES PARTICIPANTES EN EL ESTUDIO

HOSPITAL	Nº PACIENTES
ICO-L'Hospitalet de Llobregat	15
Hospital Universitario de Gran Canaria Dr. Negrín	11
Hospital Universitario de Salamanca	8
Hospital Parc Taulí	8
Hospital de León	8
Hospital Clínico Universitario de Santiago de Compostela	7
ICO-Badalona	6
Hospital Universitario Central de Asturias	6
Hospital Clínico de Valencia	5
Hospital Doce de Octubre (Madrid)	5
Hospital Universitario Infanta Leonor (Madrid)	5
Hospital La Fe de Valencia	5
ICO-Girona	5
Hospital Morales Meseguer	4

HOSPITAL	Nº PACIENTES
Hospital Universitario Príncipe de Asturias	4
Hospital Insular de Las Palmas	4
Hospital Clínico Universitario de Valladolid	3
Hospital Severo Ochoa (Madrid)	3
Hospital Universitari Mutua de Terrassa	3
Hospital Universitario Madrid Sanchinarro	3
Hospital de Sant Pau i Santa Tecla	3
Hospital Peset	3
Hospital Son Llàtzer	2
Consorci Sanitari de Terrassa	2
Hospital Universitario Infanta Sofía	1
Hospital Universitario de Burgos	1
Hospital de la Merced (Osuna)	1
Hospital POVISA	1