INTERNATIONAL SEMINAR

REPOSI 2015

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TARGETING THE BURDEN OF POLYPHARMACY IN THE ELDERLY

ORAL COMMUNICATIONS

POLYPHARMACY IN VERY ELDERLY CHRONIC MYELOID LEUKEMIA PATIENTS TREATED WITH TYROSINE KINASE INHIBITORS

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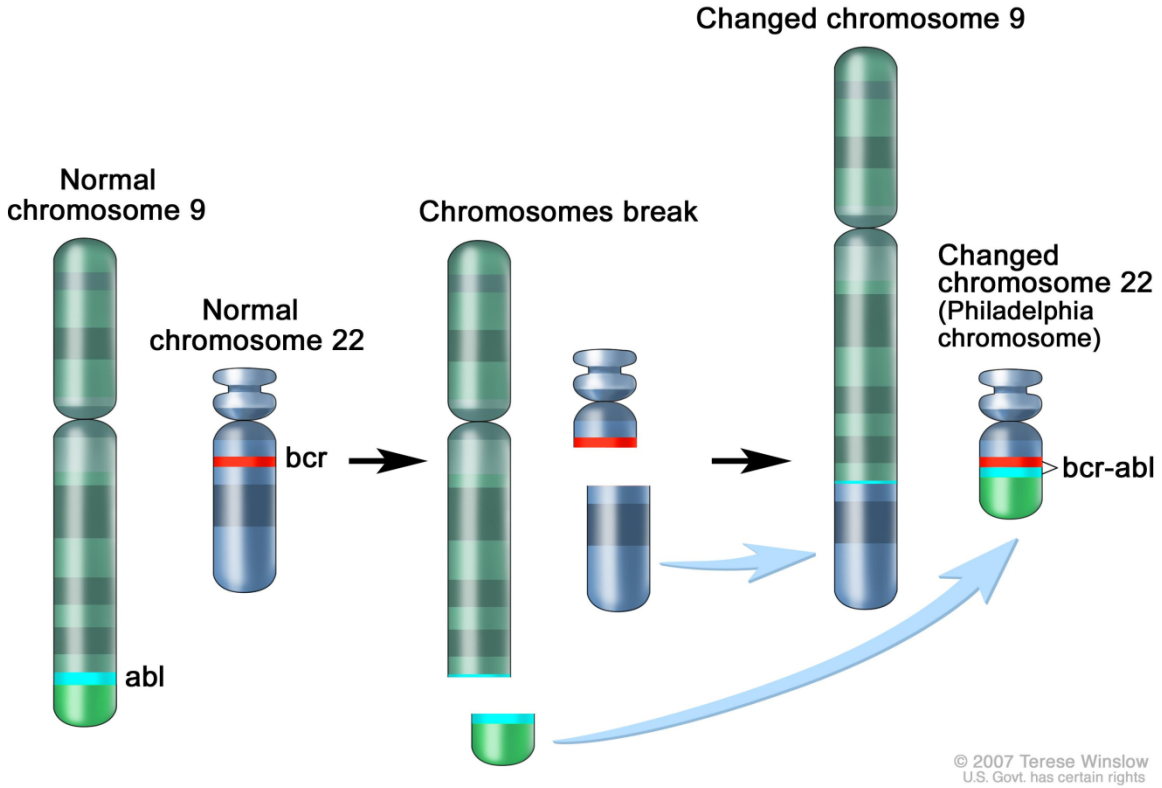
CHRONIC MYELOID LEUKEMIA

Disease of hematopoietic stem cells characterized by the presence of the Philadelphia Chromosome with formation of *BCR-ABL* fusion gene

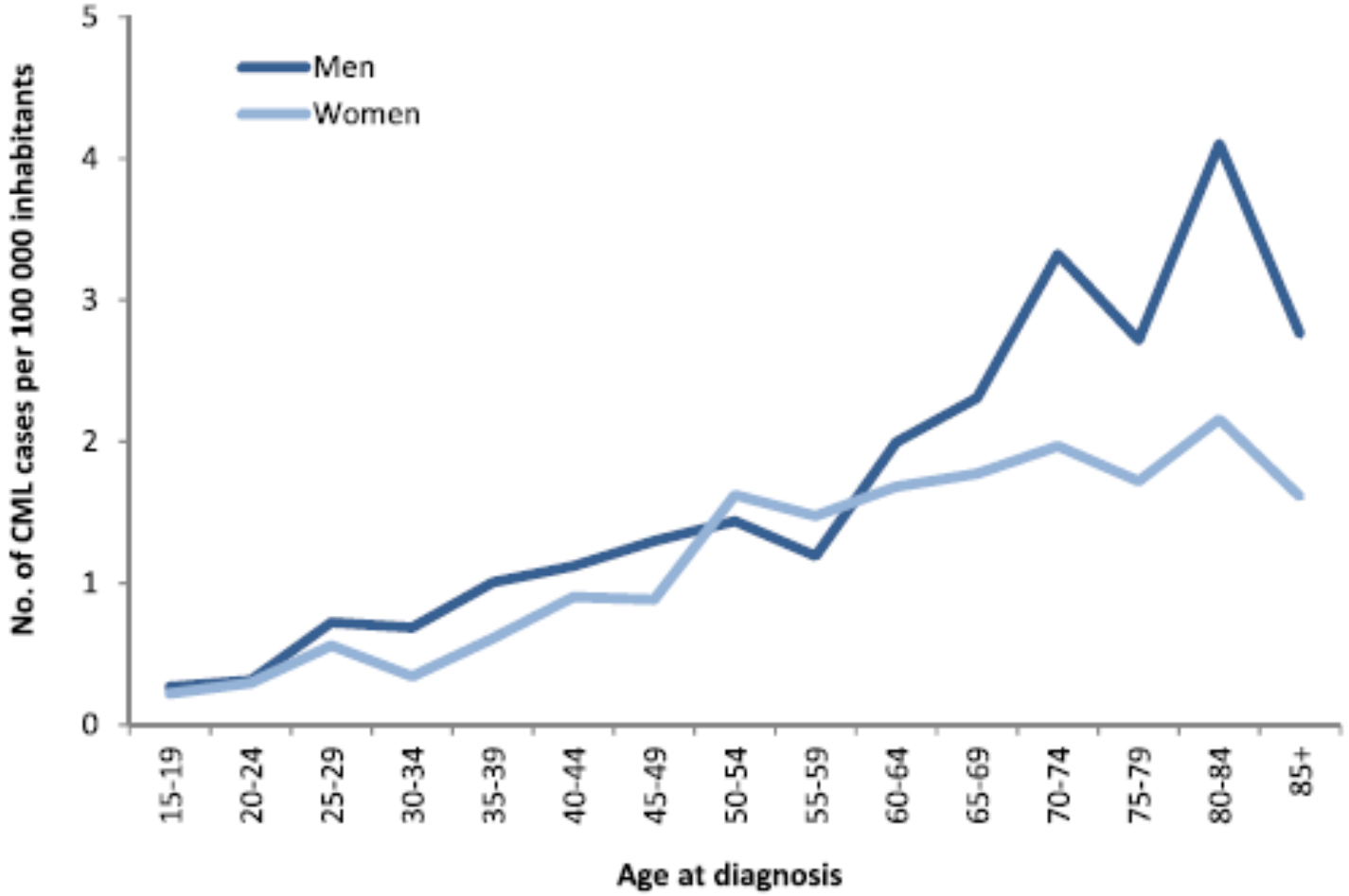
Incidence from 0,6 to 2 per 100.000 inhabitants

Median age at diagnosis between 60 and 65 year

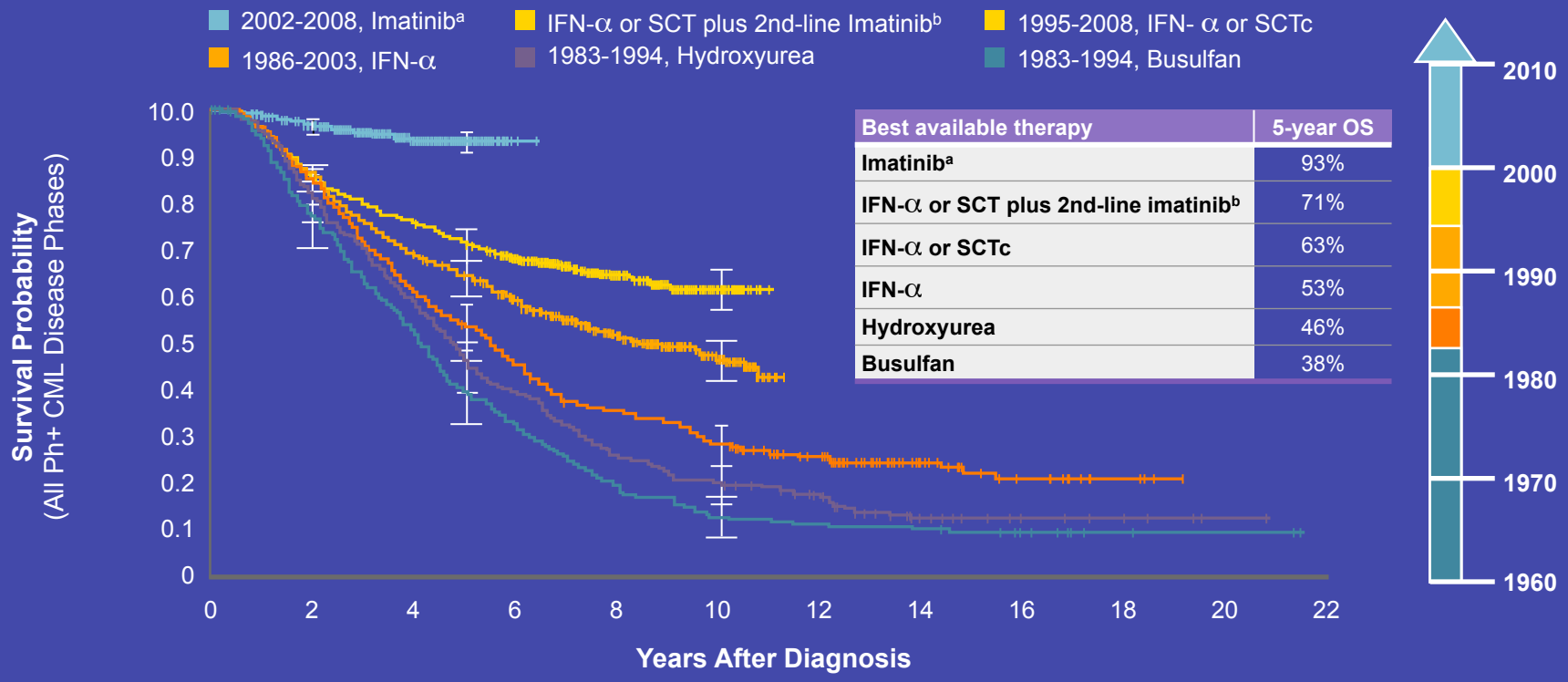


TKIs have significally improved survival of CML patients

Incidence of CML increases with age



IMATINIB: IMPACT ON OUTCOME

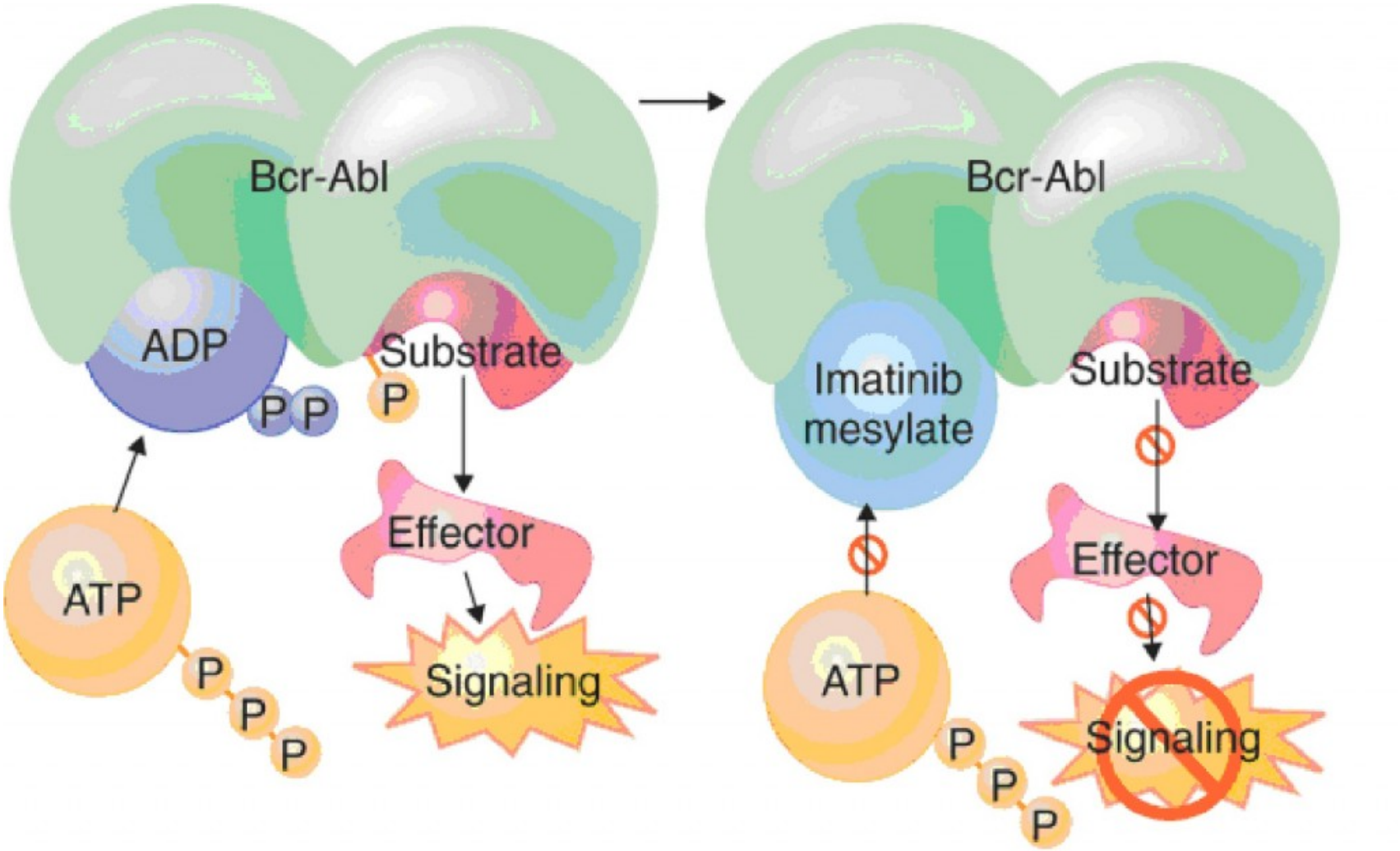


Best available therapy	5-year OS
Imatinib[a]	93%
IFN-α or SCT plus 2nd-line imatinib[b]	71%
IFN-α or SCTc	63%
IFN-α	53%
Hydroxyurea	46%
Busulfan	38%

[a]CML IV; [b]CML IIIA; [c]CML III.
IFN-α, interferon-alpha; OS, overall survival; SCT, stem cell transplant.

Adapted from R. Hehlmann, German CML Study Group.

Imatinib: how it works



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MYELOID NEOPLASIA

e-*Blood*

Drug interactions with the tyrosine kinase inhibitors imatinib, dasatinib, and nilotinib

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Imatinib is metabolized mainly by CYP isoenzyme 3A4

Interactions should be considered when administering inhibitors of the CYP3A family in combination with imatinib

Plasma concentrations of imatinib appear correlated with efficacy and toxicity

New methodologies and monitoring tools for chronic myeloid leukemia

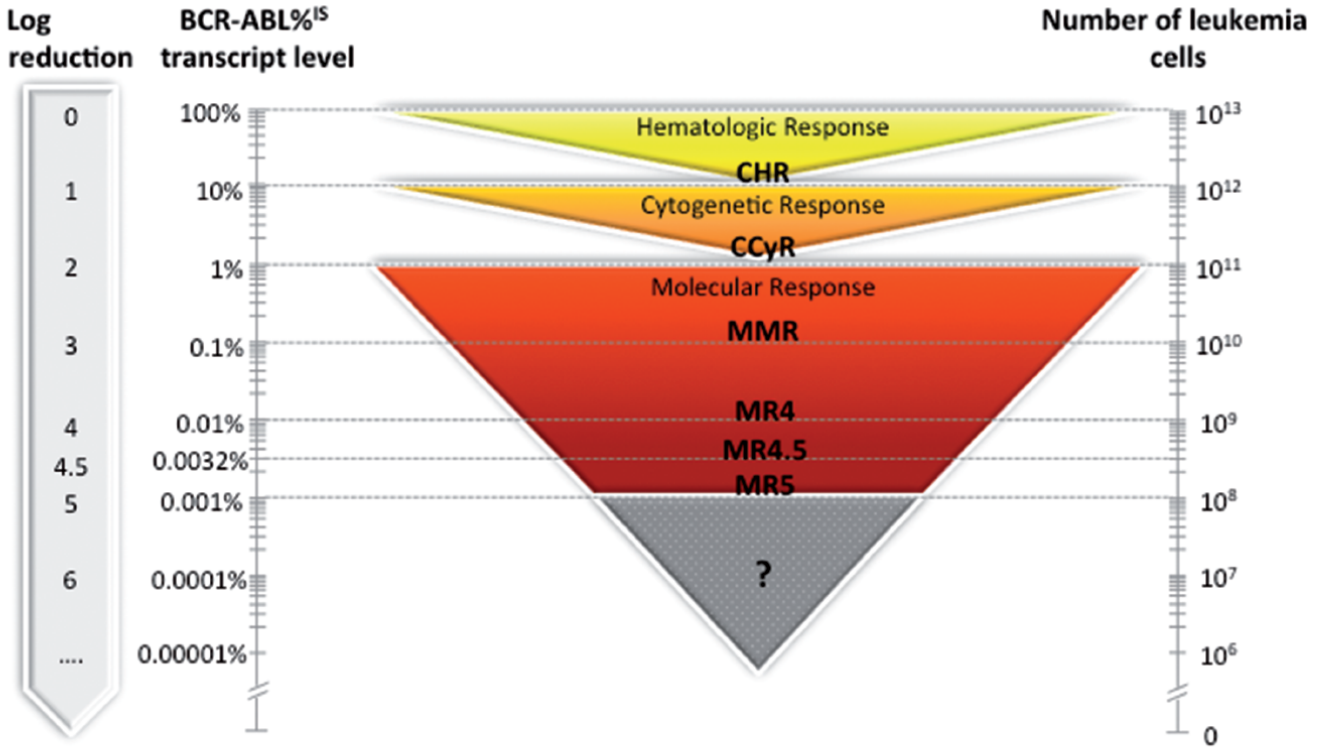


Figure 1. Levels of hematologic, cytogenetic, and molecular response in chronic myeloid leukemia. In gray and the question mark indicate that, below MR5, residual leukemia cells are present but are generally not detectable by RQ-PCR. Novel technologies (such as digital PCR) and/or approaches (such as assessing genomic DNA rather than RNA), however, might extend the dynamic range of MR detection beyond MR5 (BCR-ABL1<0.001%). IS: International Scale; CHR; complete hematologic response; CCyR: complete cytogenetic response; MMR: major molecular response; MR: molecular response with the number indicating log-reduction (4, 4.5 or 5) from the standardized baseline.

Soverini S EHA 2015

DELAY IN CCyR ACHIEVEMENT INCREASES RISK OF PROGRESSION

Months on treatment	Patients not in CCyR (n)	Eventual outcome in patients not in CCyR at the specified time (%)		
		CCyR	MMR	Event
3	109	75	62	23
6	47	57	43	34
12	26	42	31	38

Event = loss of CHR or MCyR, increasing white blood cell count, progression to accelerated/blast-phase CML, or death

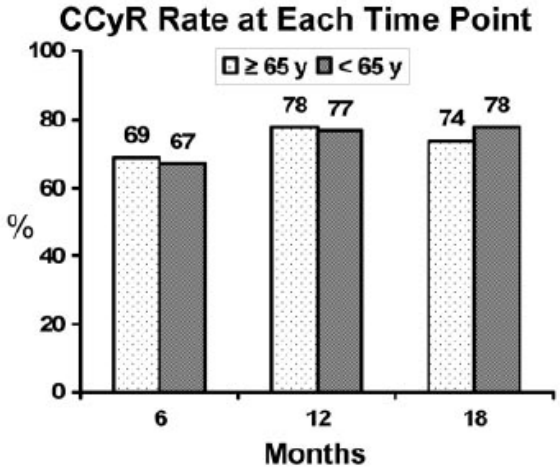
In patients not achieving CCyR at 12 months, probability of achieving CCyR at any time during treatment is about 42%, similar to the rate of loss of response, progression or death (38%)

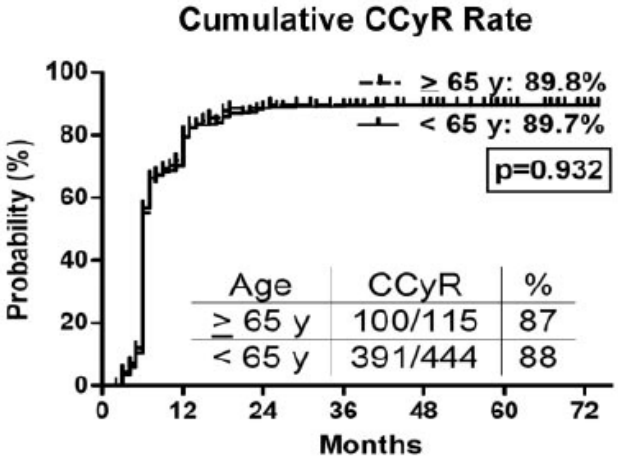
Adapted from Quintas-Cardama A, et al. Blood 2009

blood
2011 117: 5591-5599
doi:10.1182/blood-2010-12-324228 originally published online March 30, 2011

Frontline imatinib treatment of chronic myeloid leukemia: no impact of age on outcome, a survey by the GIMEMA CML Working Party

Gabriele Gugliotta, Fausto Castagnetti, Francesca Palandri, Massimo Breccia, Tamara Intermesoli, Adele Capucci, Bruno Martino, Patrizia Pregno, Serena Rupoli, Dario Ferrero, Filippo Gherlinzoni, Enrico Montefusco, Monica Bocchia, Mario Tiribelli, Ivana Pierri, Federica Grifoni, Giulia Marzocchi, Marilina Amabile, Nicoletta Testoni, Giovanni Martinelli, Giuliana Alimena, Fabrizio Pane, Giuseppe Saglio, Michele Baccarani, Gianantonio Rosti and on behalf of the Gruppo Italiano Malattie Ematologiche dell'Adulto CML Working Party





Long-term safety and efficacy of imatinib mesylate (Gleevec®) in elderly patients with chronic phase chronic myelogenous leukemia: Results of the AFR04 study

Philippe Rousselot,[1,2]* Pascale Cony-Makhoul,[3] Franck Nicolini,[4] François Xavier Mahon,[5] Christian Berthou,[6] Delphine Réa,[7] Josy Reiffers,[8] Anne Bornand,[9] Olivier Saint-Jean,[10] Joelle Guilhot,[11] and François Guilhot[11]; on behalf of the French Intergroup For Chronic Myelogenous Leukemia (Fi-LMC)

Am J Hematol 2014

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journal homepage: www.elsevier.com/locate/ejim

Original article

Comorbidities and polypharmacy impact on complete cytogenetic response in chronic myeloid leukaemia elderly patients

Alessandra Iurlo [a,*], Anna Ubertis [b], Silvia Artuso [a], Cristina Bucelli [a], Tommaso Radice [a], Manuela Zappa [a], Daniele Cattaneo [a], Daniela Mari [b], Agostino Cortelezzi [a]

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[b] Geriatrics, Foundation IRCCS Ca' Granda — Ospedale Maggiore Polidinico and Department of Clinical Sciences and Community Health, University of Milan, Italy

ORIGINAL RESEARCH ARTICLE

Imatinib in Very Elderly Patients with Chronic Myeloid Leukemia in Chronic Phase: A Retrospective Study

Roberto Latagliata · Dario Ferrero · Alessandra Iurlo · Francesco Cavazzini · Fausto Castagnetti · Elisabetta Abruzzese · Carmen Fava · Massimo Breccia · Mario Annunziata · Fabio Stagno · Mario Tiribelli · Gianni Binotto · Giovanna Mansueto · Antonella Gozzini · Sabina Russo · Laura Cavalli · Enrico Montefusco · Gabriele Gugliotta · Michele Cedrone · Antonella Russo Rossi · Paolo Avanzini · Patrizia Pregno · Endri Mauro · Antonio Spadea · Francesca Celesti · Gianfranco Giglio · Alessandro Isidori · Monica Crugnola · Elisabetta Calistri · Federica Sorà · Stefano Storti · Ada D'Addosio · Giovanna Rege-Cambrin · Luigiana Luciano · Giuliana Alimena

Published online: 17 May 2013

POLYPHARMACY IN VERY ELDERLY CHRONIC MYELOID LEUKEMIA PATIENTS TREATED WITH TYROSINE KINASE INHIBITORS

Iurlo A, Latagliata R, Bucelli C, Ferrero D, Castagnetti F, Breccia M, Abruzzese E, Fava C, Annunziata M, Stagno F, Vigneri P, Tiribelli M, Cavazzini F, Binotto G, Mansueto G, Gozzini A, Russo S, Falzetti F, Montefusco E, Gugliotta G, Cattaneo D, Djade CD, Cedrone M, Russo Rossi A, Avanzini P, Pregno P, Endri M, Spadea A, Celesti F, Giglio G, Isidori A, Crugnola M, Calistri E, Sorà F, Sica S, Storti S, D'Addosio A, Rege-Cambrin G, Luciano L, Saglio G, Rosti G, Alimena G, Nobili A, Mannucci PM, Cortelezzi A

Retrospective analysis of 202 patients from 33 Italian Institutions

Patients aged $\geq$ 75 years in chronic phase CML treated with imatinib frontline

Endpoint: evaluation of impact of concomitant drugs on outcome (CCyR) and toxicity

Baseline clinical features

Clinical parameters	**Patients (n. 202)**
Male, n (%)	109 (54)
Age at diagnosis (year), median (range)	77.6 (65-93)
Sokal score, n (%)	
Low	3 (1.5)
Intermediate	120 (59.3)
High	60 (29.7)
Not available	19 (9.5)
Age at imatinib start (year), median (range)	78.7 (73-93)
Imatinib dosage, n(%)	
< 400 mg die	64 (31.7)
400 mg die	134 (66.3)
> 400 mg die	4 (2)
CCI, n (%)	
0	86 (42.6)
1	50 (24.7)
2	37 (18.3)
>3	29 (14.4)
Concomitant drugs, n (%)	
0	29 (14.4)
1-2	76 (37.6)
3-4	56 (27.7)
≥5	41 (20.3)

Results I

Variables		CYTOGENETIC RESPONSE			
		CCyR (=2) ≤12 MESI 33 (%)	CCyR (=2) >12 MESI 85 (%)	No CCyR (=0) 33 (%)	*P value*
CCI	0	15 (45.5)	41 (48.3)	13 (39.4)	*0.2506*
	1	9 (27.3)	22 (25.9)	7 (21.2)	
	2	5 (15.1)	10 (11.8)	11 (33.3)	
	≥3	4 (12.1)	12 (14.1)	2 (6.1)	
N. of drugs	0	4 (12.1)	13 (15.3)	6 (18.2)	*0.7641*
	1 - 2	24 (72.7)	52 (61.2)	21 (63.6)	
	3 - 4	5 (15.2)	20 (23.5)	6 (18.2)	
	≥5	0	0	0	
Antihypertensive drugs	0=NO	8 (24.2)	28 (32.9)	8 (24.2)	*0.5026*
	1=SI	25 (75.8)	57 (67.9)	25 (75.8)	
Drugs					
ACE-INHIBITORS		9 (39.1)	17 (29.9)	10 (30.3)	*0.4395*
ATII RECEPTOR BLOCKERS		3 (13.0)	20 (35.1)	3 (9.1)	*0.0562*
DIURETICS		13 (56.5)	28 (49.1)	15 (45.5)	*0.4324*
CALCIUM CHANNEL BLOCKERS		5 (21.7)	13 (22.8)	4 (12.1)	*0.8997*
BETA-BLOCKERS		2 (8.7)	22 (38.6)	4 (12.1)	*0.0171*
ALFA-BLOCKERS		2 (8.7)	1 (1.8)	1 (3.0)	*0.3651*
PPIs	2=NO	24 (72.7)	49 (58.3)	20 (60.6)	*0.3345*
	1=SI	9 (27.2)	35 (41.7)	13 (39.4)	
IMATINIB DOSE	< 400	8 (24.2)	21 (24.7)	10 (30.3)	*0.8051*
	≥400	25 (75.7)	64 (75.3)	23 (69.7)	

Results II

Variables		HEMATOLOGIC Toxicity			EXTRA-HEMATOLOGIC Toxicity		
		severe, 40 (%)	mild, 171 (%)	*P value*	severe, 41 (%)	mild, 170 (%)	*P value*
CCI	0	19 (47.5)	72 (42.1)	*0.5835*	13 (31.7)	78 (45.9)	*0.2377*
	1	11 (27.5)	42 (24.6)		15 (36.6)	38 (22.4)	
	2	7 (17.5)	31 (18.1)		8 (19.5)	30 (17.7)	
	≥3	3 (7.5)	26 (15.2)		5 (12.2)	24 (14.1)	
N. of drugs	0	9 (22.5)	20 (11.7)	*0.0638*	7 (17.0)	22 (12.9)	*0.1247*
	1 – 2	26 (65.0)	106 (62.0)		20 (48.8)	112 (65.9)	
	3 – 4	5 (12.5)	45 (26.3)		14 (34.1)	36 (21.2)	
	≥5	0	0		0	0	
Antihypertensive drugs	0=NO	15 (38.4)	53 (31.0)	*0.2804*	16 (39.0)	53 (31.2)	*0.3416*
	1=SI	24 (61.5)	118 (83.1)		25 (61.0)	117 (68.9)	
Drugs							
ACE-INHIBITORS		9 (22.5)	40 (23.4)	*0.9040*	6 (14.6)	43 (25.3)	*0.1309*
ATII RECEPTOR BLOCKERS		6 (15.0)	28 (16.4)	*0.8302*	6 (14.6)	28 (16.5)	*0.7719*
DIURETICS		12 (30.0)	65 (38.0)	*0.3379*	15 (36.6)	62 (80.5)	*0.9891*
CALCIUM CHANNEL BLOCKERS		6 (15.0)	24 (14.0)	*0.8757*	7 (17.1)	23 (15.5)	*0.5673*
BETA-BLOCKERS		4 (10.0)	33 (19.3)	*0.1416*	8 (19.5)	29 (17.1)	*0,7137*
ALFA-BLOCKERS		0	8 (4.7)	*0.0638*	1 (2.4)	7 (4.1)	*0.5949*
PPIs	2=NO	28 (70.0)	103 (61.0)	*0.3345*	23 (59.0)	108 (63.5)	*0.5975*
	1=SI	12 (30.0)	66 (39.1)		16 (41.0)	62 (36.5)	
IMATINIB DOSE	< 400	10 (25.0)	54 (31.4)	*0.4085*	13 (31.7)	51 (30.0)	*0.8315*
	≥400	30 (75.0)	117 (68.4)		28 (68.3)	119 (70.)0	

Conclusions

Our preliminary results confirm the safety and efficacy of imatinib also in very elderly patients despite of polypharmacy

This topic is very important because life expectancy of CML patients is now approcching that of the general healthy population leading to an increasing number of elderly patients dealing with it.

No data available in literature about impact of classes of drugs and TKIs on outcome and toxicity

Ongoing analysis to evaluate impact of the other concomitant single classes of drugs on outcome, toxicity, and molecular response

Thank you for your attention!