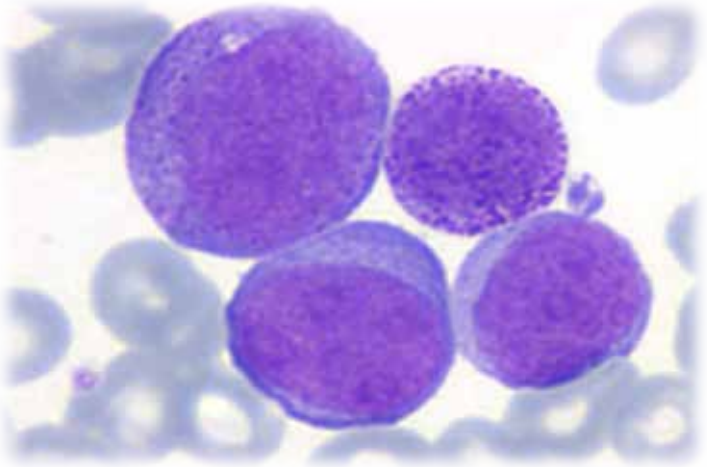
LEUCEMIA MIELOIDE CRONICA EN PEDIATRIA



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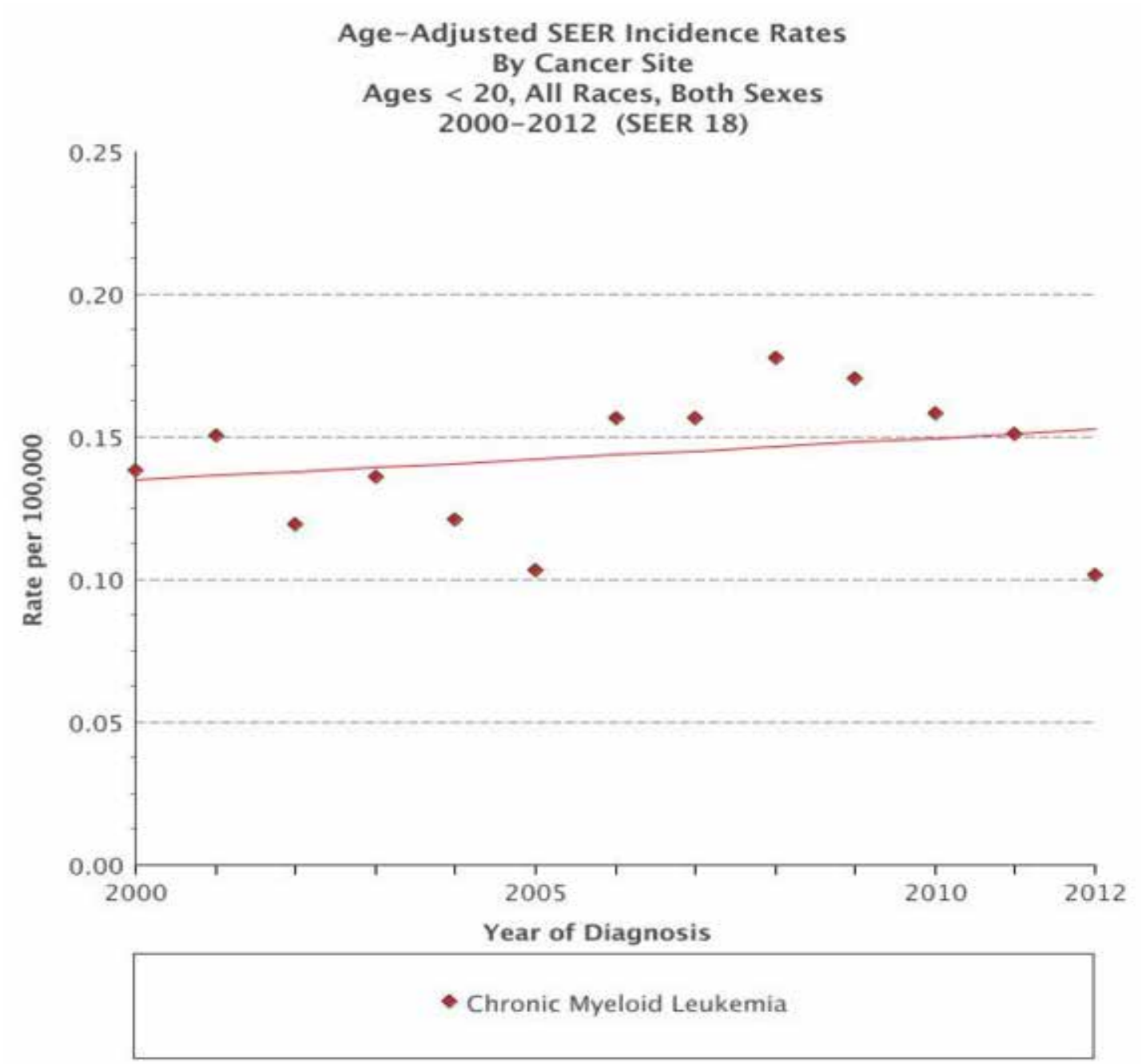
NOVIEMBRE DE 2015

LEUCEMIA MIELOIDE CRONICA

- Es una proliferación descontrolada de granulocitos.
- Diagnosticada en aproximadamente 6000 pacientes cada año en los estados unidos.
- 2% de todas las leucemias en menores de 15 años.
- 9% en pacientes entre 15-19 años.

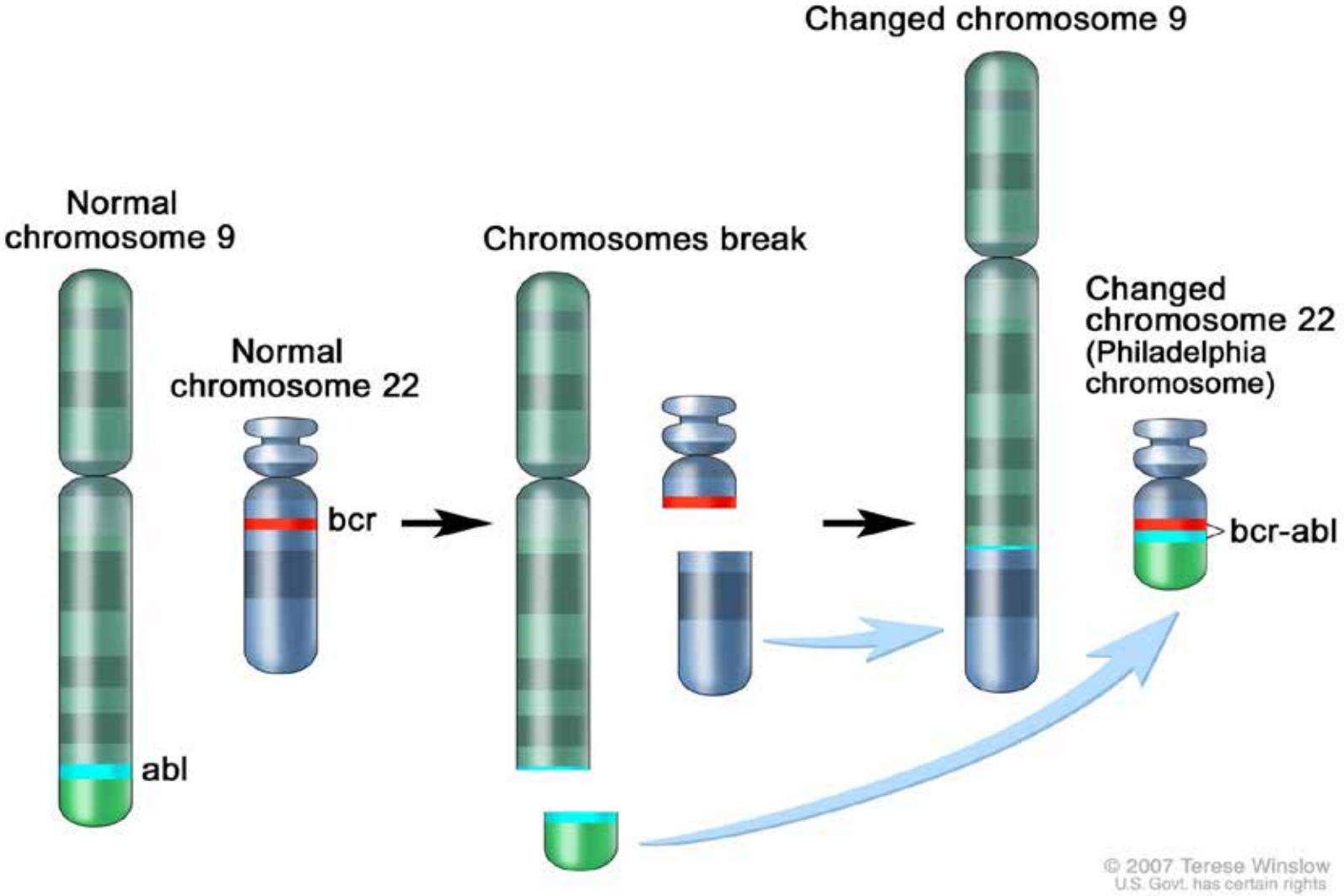
Nobuko Hijiya, Kirk R. Schultz, Markus Metzler, Frederic Millot and Meinolf Suttorp. Pediatric chronic myeloid leukemia is a unique disease that requires a different approach. Blood First Edition Paper, prepublished online October 28, 2015



http://seer.cancer.gov/faststats

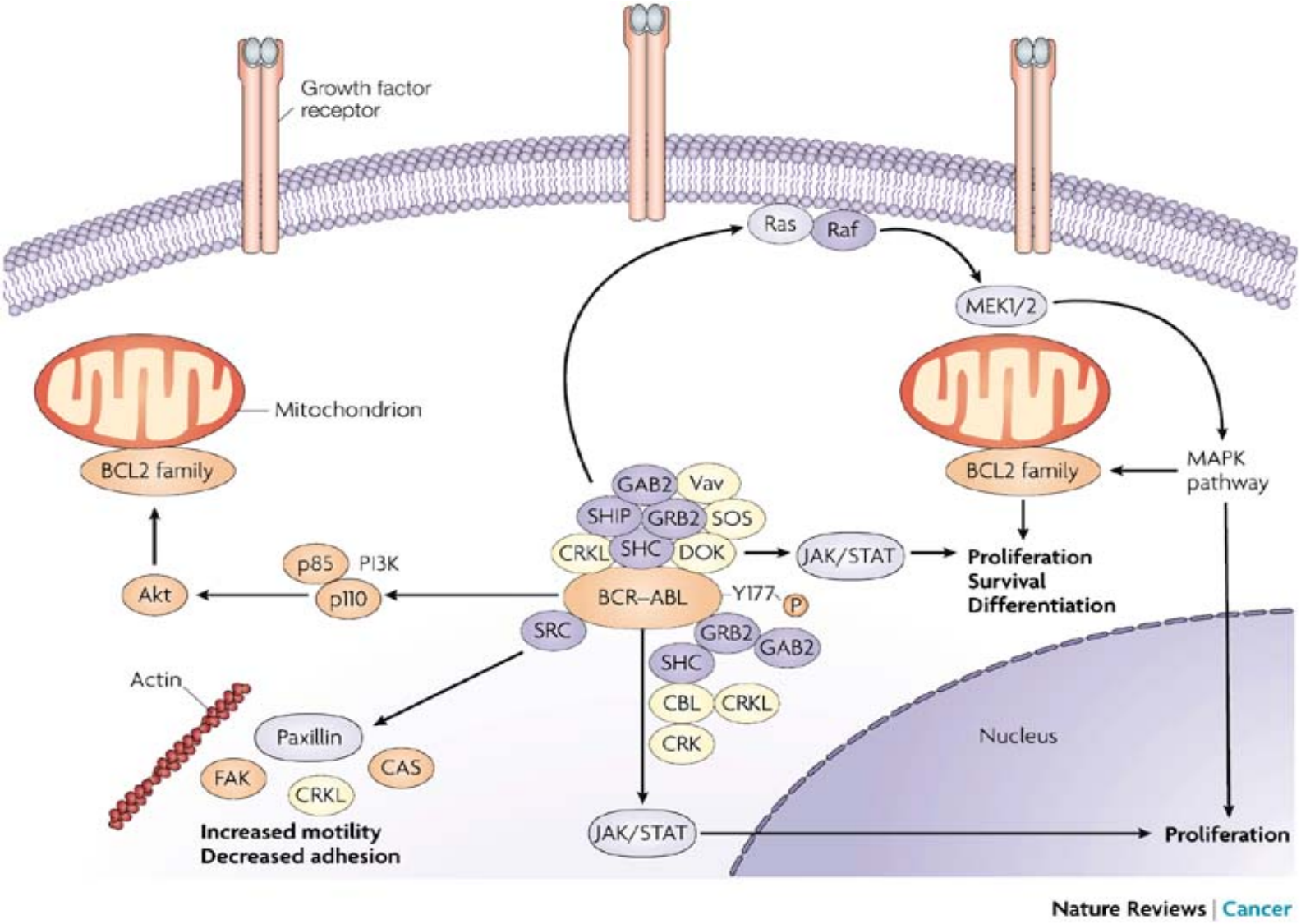
BIOLOGIA DE LMC

CROMOSOMA FILADELFIA



- 100% LMC, LLA: 25-30% Adultos y niños 2-10%

BCR-ABL



Nature Reviews Cancer 7, 345-356 (May 2007)

MANIFESTACIONES CLÍNICAS

Table 1. Comparison of Age-dependent Differences in CML

Ref.	Cohort age (y)*	Patients (No.)	Organo-megaly: Median spleen size (cm BCM)	Blood Counts (median): WBC (cells /µL)	Platelets (cells/µL)	Hgb (g/dL)	Blasts in PB (%)
34	1 - 18	72	6	217	405	10.0	1
30	0.8 - 16.7	25	5	252	n.r.	n.r.	n.r.
	1.9 - 17.3	15	13	378	n.r.	n.r.	n.r.
88	2.8 - 17.9	47	n.r.	171	577	9.9	n.r.
12	16 - 29	120	5	144	430	11.1	2
	30 - 44	383	3	106	369	11.8	1
	45 - 59	495	1	74	364	12.6	1
	>60	526	0	57	381	12.5	0
24	15 – 28	61	39%[‡]	30.5	332	12.2	0
	30 - 85	407	23%[‡]	27.4	343	12.3	0
25	18 - 30	329	4.5	62	370	11.8	1
	30 - 39	444	5.0	66	355	12.1	1
	40 - 49	613	3.0	54	380	12.0	1
	50 - 59	693	2.0	57	350	12.2	1
	60 - 69	473	1.8	54	333	12.3	1
	>70	232	1.0	71	345	12.1	0.7

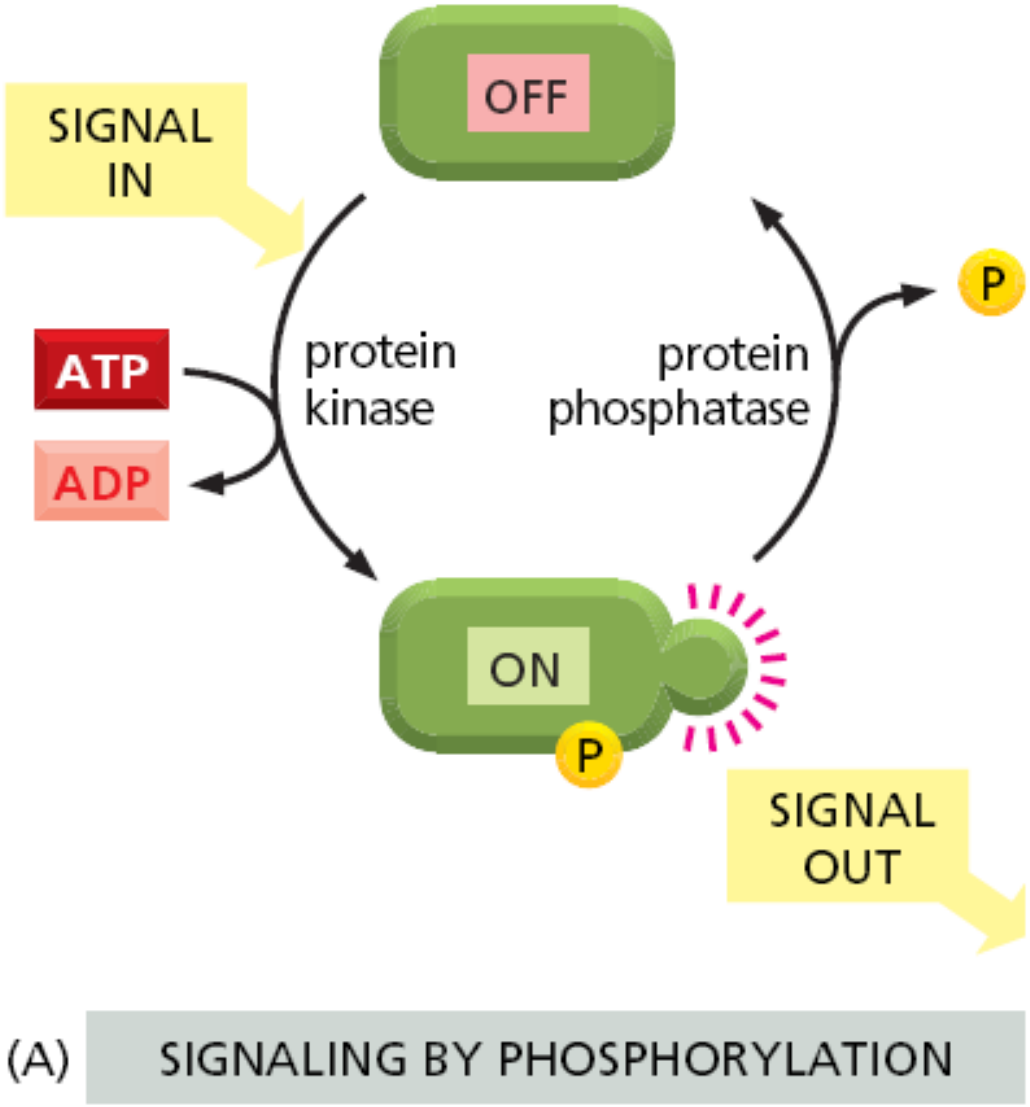
Nobuko Hijiya, Kirk R. Schultz, Markus Metzler, Frederic Millot and Meinolf Suttorp. Pediatric chronic myeloid leukemia is a unique disease that requires a different approach. Blood First Edition Paper, prepublished online October 28, 2015

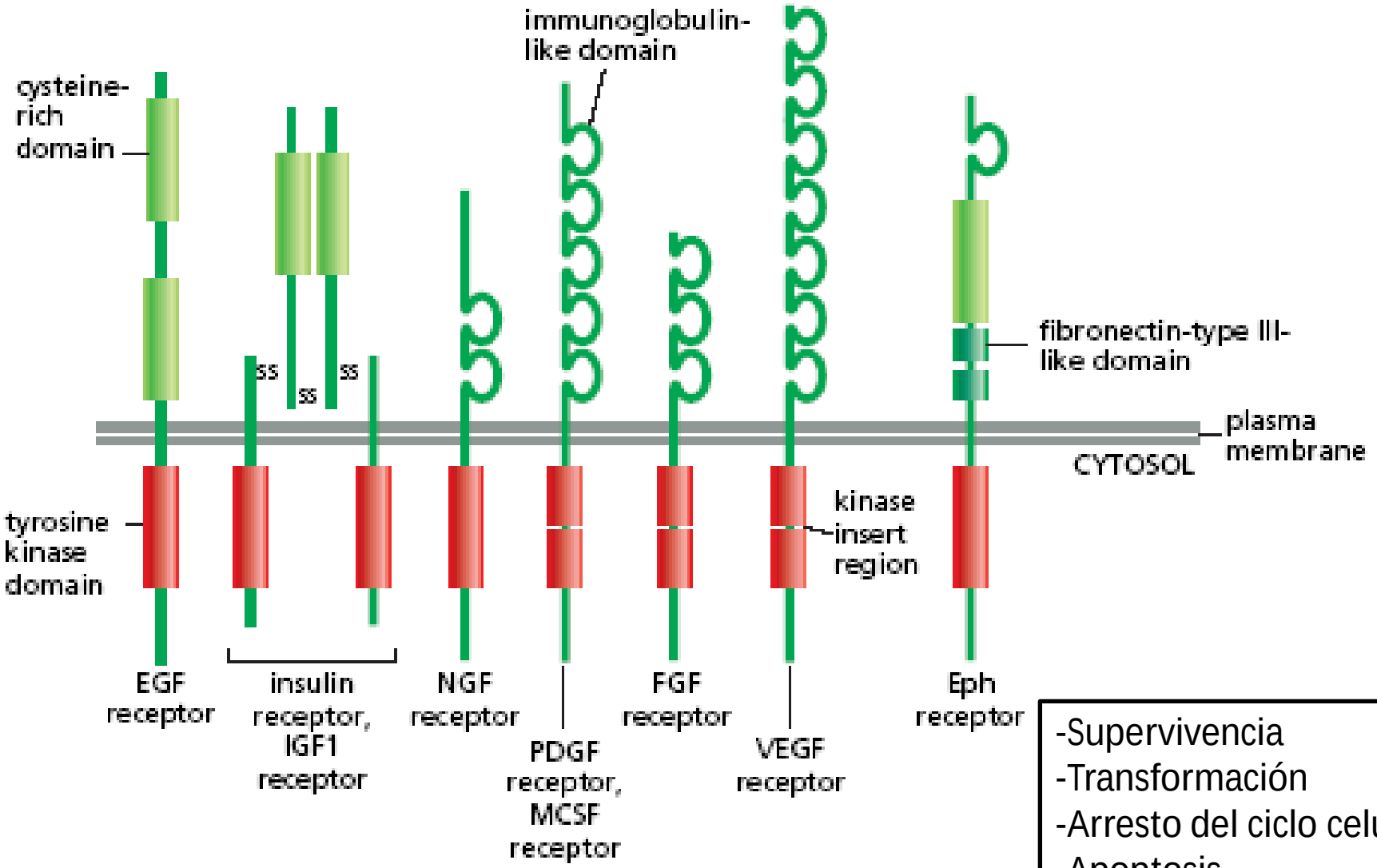
TRATAMIENTO

INHIBIDORES DE TIROSIN KINASA

TRASPLANTE DE PRECURSORES HEMATOPOYETICOS

TIROSIN KINASA





-Supervivencia
-Transformación
-Arresto del ciclo celular
-Apoptosis
-Reparación de ADN
-Crecimiento

INHIBIDORES DE TIROSIN KINASA - TKIs

- INHIBIDOR ENZIMATICO QUE BLOQUEA LA ACCION DE UNA O VARIAS PROTEINAS

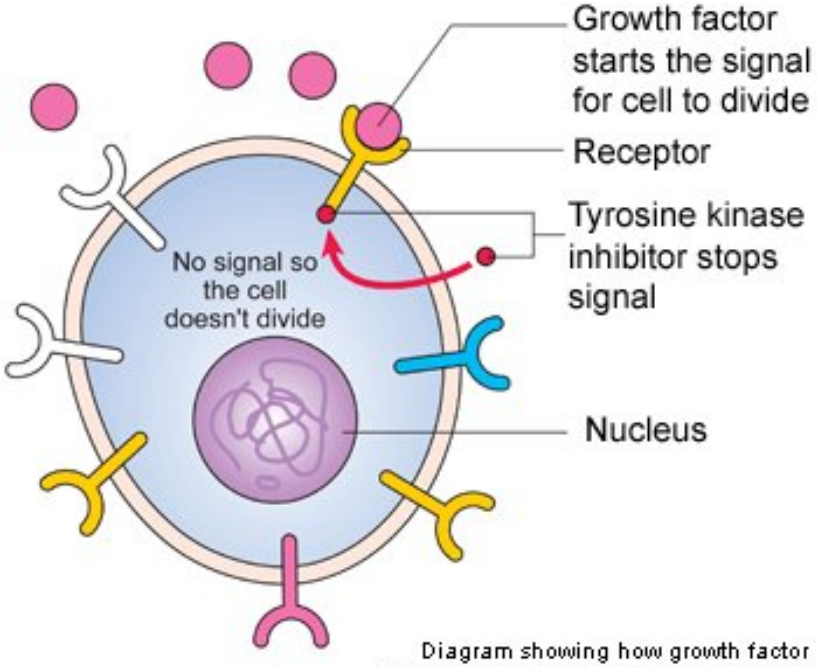


Diagram showing how growth factor inhibitors stop the signal inside the cell
Copyright © CancerHelp UK

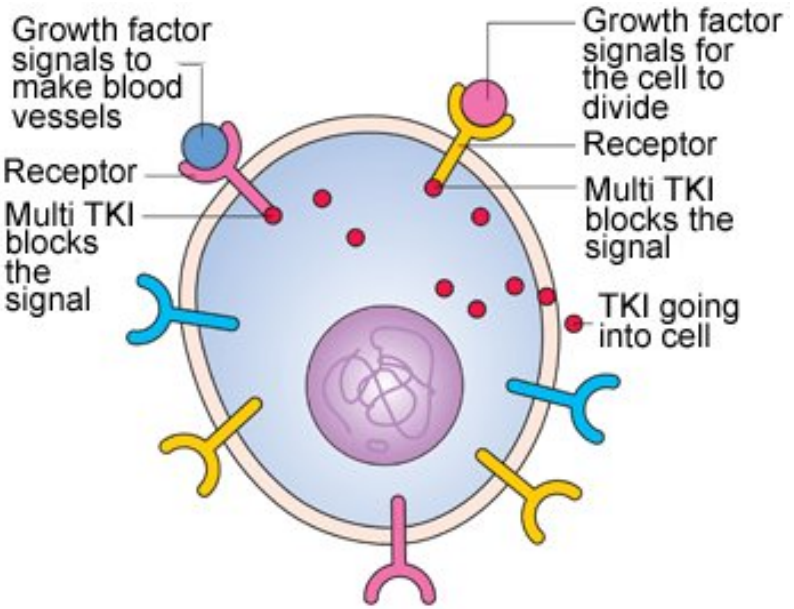
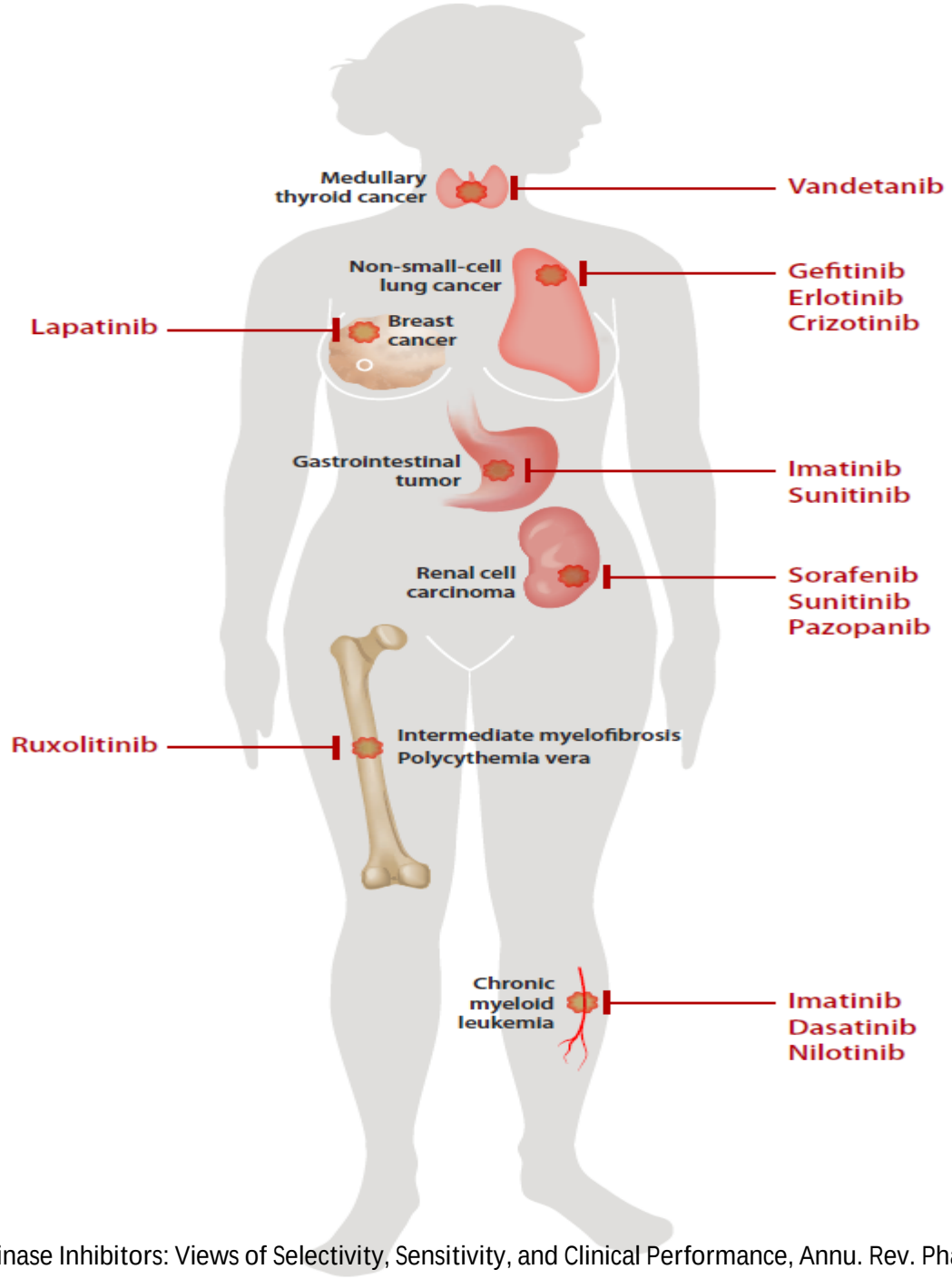


Diagram showing an example of how growth inhibitors can block more than one action in a cell (multi TKI)
Copyright © CancerHelp UK

http://www.cancerresearchuk.org/about-cancer/cancers-in-general/treatment/biological/types/cancer-growth-blockers#tki



Levitzki A., Tyrosine Kinase Inhibitors: Views of Selectivity, Sensitivity, and Clinical Performance, Annu. Rev. Pharmacol. Toxicol. 2013.53:161-185.

Table 1 Registered kinase inhibitors

Compound	Kinase target	Disease
Imatinib (STI571, Glivec®, Gleevec®)	ABL1-2, PDGFR, KIT	CML, Ph+ B-ALL, CMML, CEL, GIST
Gefitinib (ZD1839, Iressa®)	EGFR	NSCLC
Erlotinib (OSI-774, Tarceva®)	EGFR	NSCLC, pancreatic cancer
Lapatinib (GW2016, Tykerb®)	EGFR, ERBB2	Breast cancer
Dasatinib (BM-354825, Sprycel®)	ABL1-2, PDGFR, KIT, SRC	CML
Nilotinib (AMN107, Tasigna®)	ABL1-2, PDGFR, KIT	CML
Sunitinib (SU11248, Sutent®)	VEGFR1-3, KIT, PDGFR, RET,CSF1R, FLT3	RCC, GIST
Sorafenib (Bay 43-9006, Nexavar®)	VEGFR2, PDGFR, KIT, FLT3, BRAF	RCC
Pazopanib (GW-786034, Votrient®)	VEGFR1-3, PDGFR, KIT	RCC
Crizotinib (PF-02341066, Xalkori®)	MET and ALK	NSCLC
Vandetanib (ZD6474, Caprelsa®)	RET, VEGFR1–2, FGFR, EGFR	Medullary thyroid cancer
Ruxolitinib (INC424, Jakafi®)	JAK2	IMF
Tofacitinib (CP-690550, Tasocitinib)	JAK3	Rheumatoid arthritis

Abbreviations: ALL, acute lymphoblastic leukemia; CEL, chronic eosinophilic leukemia; CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; GIST, gastrointestinal stromal tumor; IMF, intermediate- or high-risk myelofibrosis; NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma.

Levitzki A., Tyrosine Kinase Inhibitors: Views of Selectivity, Sensitivity, and Clinical Performance, Annu. Rev. Pharmacol. Toxicol. 2013.53:161-185.

Table 2. Studies of TKI Therapy for Pediatric CML

TKI	Sponsor and Collaborator	Phase	Year Published	Author and References
Imatinib	COG	1	2004	Champagne[95]
Imatinib	COG	2	2012	Champagne[96]
Imatinib	French	4	2011	Millot[97]
Dasatinib	COG	1	2011	Aplenc[98]
Dasatinib	BMS/ITCC	1	2013	Zwaan[99]
Dasatnib	BMS	2	Unpublished	www.clinicaltrials.gov (NCT00777036)[100]
Nilotinib	Novartis	1	Unpublished	www.clinicaltrials.gov (NCT01077544)
Nilotinib	Novartis/COG/ITCC	2	Unpublished	www.clinicaltrials.gov (NCT01844765)

CML indicates chronic myelogenous leukemia; COG, Children's Oncology Group; BMS, Bristol-Myers Squibb; and ITCC, Innovative Therapies for Children with Cancer Consortium.

Nobuko Hijiya, Kirk R. Schultz, Markus Metzler, Frederic Millot and Meinolf Suttorp. Pediatric chronic myeloid leukemia is a unique disease that requires a different approach. Blood First Edition Paper, prepublished online October 28, 2015

Brief Report

MYELOID NEOPLASIA

Impact of early molecular response in children with chronic myeloid leukemia treated in the French Glivec phase 4 study

Frédéric Millot,[1] Joelle Guilhot,[1] André Baruchel,[2] Arnaud Petit,[3] Yves Bertrand,[4] Françoise Mazingue,[5] Patrick Lutz,[6] Cecile Vérité,[7] Christian Berthou,[8] Claire Galambrun,[9] Nicolas Sirvent,[10] Karima Yakouben,[11] Claudine Schmitt,[12] Virginie Gandemer,[13] Yves Reguerre,[14] Gérard Couillault,[15] Françoise Mechinaud,[16] and Jean-Michel Cayuela[17]

Blood. 2014;124(15):2408-2410)

- Cohorte de 40 pacientes pediatricos
- Transcriptos del BRC-ABL
- A los 3 meses de iniciado el tratamiento >o <10%

Table 2. Rates of CCyR and MMR at 12 months and PFS at 36 and 48 months, according to the molecular response at 3 months, in 40 children with CML

BCR-ABL1/ABL transcript level at 3 mo*						Molecular response rate outcome over 12 mo**			
						BCR-ABL1/ABL level*			
BCR-ABL1/ABL at 3 mo, %	n (%)	CCyR at 12 mo (%)	MMR at 12 mo (%)	PFS at 36 mo (%)	PFS at 48 mo (%)	at 3 mo, %	at 6 mo, %	n (%)	No. of patients achieving MMR at 12 mo (%)
≤10	25 (63)	19*** (76)	12 (48)	100	100	>10	>10	4 (10)	0
>10	15 (37)	7 (47)	1 (7)	92	61	>10	<10	11 (27.5)	1
				(95% CI, 54-99)	(95% CI, 7-91)	<10	>10	1 (2.5)	1
		P = .177	*P* = .0128	*P* = .028 (overall)		<10	<10	24 (60)	11

mo, months.

*Data from 15 highly standardized French laboratories (ie, following tightly standardized procedures, having at their disposal a conversion factor and participating in the French external quality assessment program organized by the Group of Molecular Biologists for Malignant Hemopathies which requires biannual evaluation of interlaboratory reproducibility and accuracy) were collected and centrally reviewed for updating molecular response level attribution according to the latest recommendations of the ELN.[12]

**This portion of the table shows that achieving a <10% cutoff ratio at 3 mo is in favor of a higher rate of MMR at 12 mo. However, it is also documented that a delayed cutoff ratio achievement of this <10% cutoff ratio at 6 mo with favorable outcome may exist. The small sample size of children does not allow providing robust rate estimates within subgroups.

***One patient with no conventional cytogenetic assessment at 12 mo achieved $MR^{4.5}$ at this time point and was considered as having a CCyR.

RESISTENCIA A LOS INHIBIDORES DE TIROSINA KINASA

MECANISMOS DE RESISTENCIA

Mutaciones dentro del dominio quinasa, común LMC (BCR-ABL)

Evolución de los mecanismos de bypass

Mayor número de copias de la quinasa oncogénica

Aumentó del flujo de salida del fármaco.

Levitzki A., Tyrosine Kinase Inhibitors: Views of Selectivity, Sensitivity, and Clinical Performance, Annu. Rev. Pharmacol. Toxicol. 2013.53:161-185.

European Journal of Cancer (2014) 50, 3206–3211

Available at www.sciencedirect.com

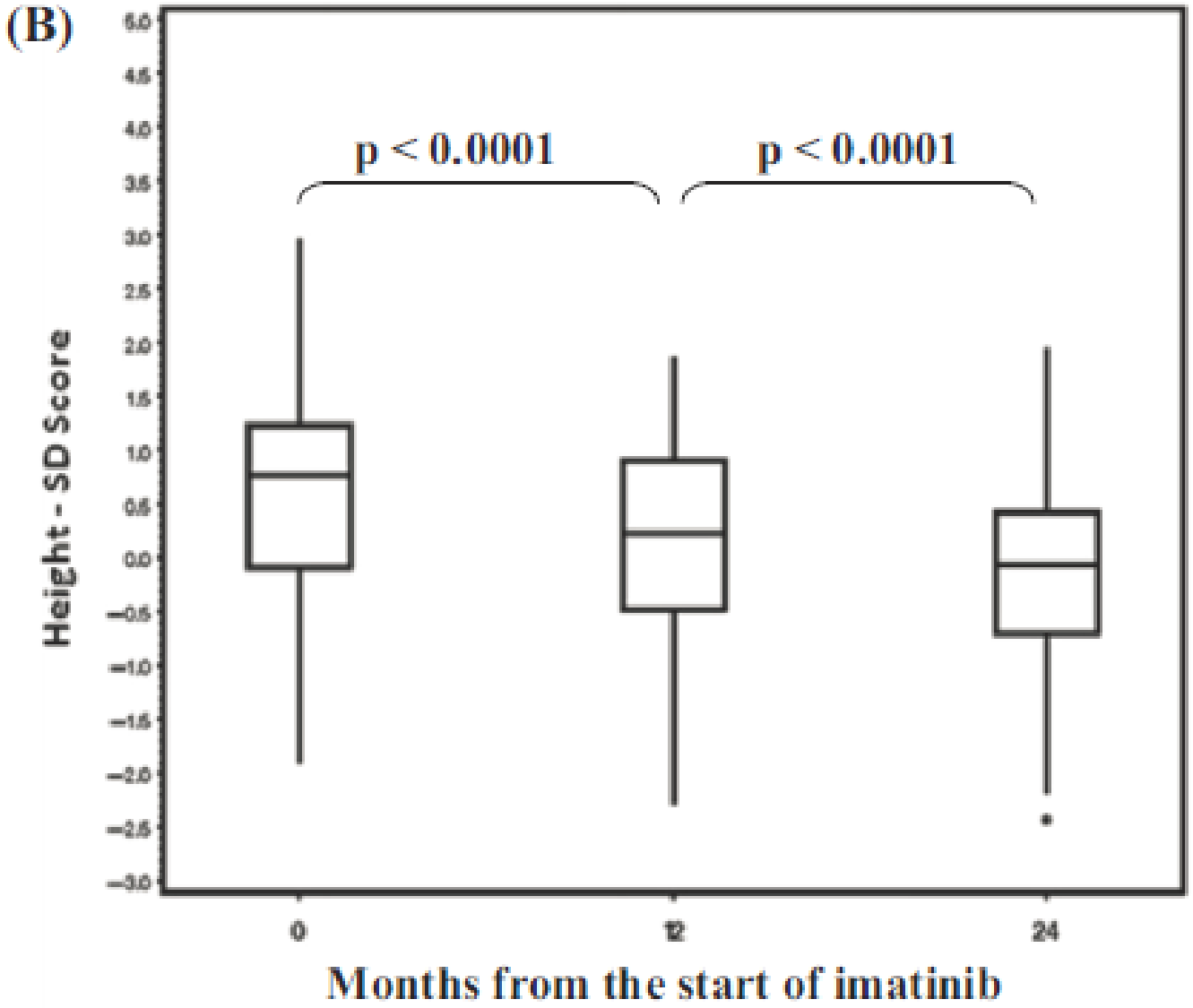
ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Growth deceleration in children treated with imatinib for chronic myeloid leukaemia ☆

Frédéric Millot [a,*], Joelle Guilhot [a], André Baruchel [b], Arnaud Petit [c], Thierry Leblanc [b], Yves Bertrand [d], Françoise Mazingue [e], Patrick Lutz [f], Cecile Vérité [g], Christian Berthou [h], Claire Galambrun [i], Nicolas Sirvent [j], Karima Yacouben [k], Pascal Chastagner [l], Virginie Gandemer [m], Yves Reguerre [n], Gérard Couillault [o], Tackwa Khalifeh [a], Fanny Rialland [p]



F. Millot et al. / European Journal of Cancer 50 (2014) 3206–3211

Table 4. Results of HSCT in Children (≤18 years of age) with CML in First Chronic Phase*

Author	Year	Patients (No.)	Disease Phase at HSCT	Donor Source	Overall Survival	Notes
Cwynarski[101]	2003	314	CP1, n=253 Other, n=61	MSD VUD	75% (CP1, MSD, n=156) 65% (CP1, VUD, n=97)	EBMT registry data
Suttorp[84]	2009	176	CP1, n=158 Other, n=18	MRD MUD	At 5 years: 87±11% (MSD, n=41) 52±9% (MUD, n=71) 45±16% (MMD, n=55)	
Muramatsu[102]	2010	125	CP1, n=88 Other, n=37	Unrelated	59.3% at 5 years	
Chaudhury[81]	2014	177	CP1 and hematological remission		71% (95%CI, 65–77) at 5 years	CIBMTR data

* Only studies with more than 100 cases are listed.

CP1 indicates first chronic phase; HSCT, hematopoietic stem cell therapy; MSD, matched-sibling donor; MRD, matched-related donor; MUD, matched-unrelated donor; MMD, mismatched donor; VUD, volunteer-unrelated donor; CI, confidence interval; EBMT, European Group for Blood and Marrow Transplantation; and CIBMTR, Center for International Blood and Marrow Transplant Research.

Nobuko Hijiya, Kirk R. Schultz, Markus Metzler, Frederic Millot and Meinolf Suttorp. Pediatric chronic myeloid leukemia is a unique disease that requires a different approach. Blood First Edition Paper, prepublished online October 28, 2015

EXPERIENCIA ONCOLOGIA PEDIATRICA

Pte	Sexo/ Edad	Año	Fase	Glivec	Donante	Resultado	Años SV	
IBR	F/6	1992	FC	No	DR - HNO	VSE	23,6	
MSA	F/12	1995	FC	No	DR - HNO	VSE	20,0	
SM	F/6	1996	CB	No	NO	Fallece	3,5	Enfermedad
DF	M/18	1996	Fc	No	DR - HNO	Fallece	1,1	Hemorragia pulmonar
GZZ	M/7	1997	FC	No	DR - Tia	VSE	17,9	
NS	F/12	1999	FC	No	SCU	Fallece	0,5	CMV
ROB	M/16	2002	FC	Si	DR - Papá	Fallece	0,5	Aspergilosis
MAR	F/8	2010	FC	Si	DNR	VSE	4,8	
IMC	M/9	2012	CB	Si	DNR	VSE	3,8	

RECOMENDACIONES PARA PACIENTES PEDIATRICOS EN TTO CON ITK.

- Monitorizar velocidad de Crecimiento
- Evaluación de taner (Pubertad retardada)
- Evaluar Función Tiroidea
- Ecocardiograma y electrocardiograma
- Consejería en fertilidad para pacientes en edad reproductiva.

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CONCLUSIONES

Niños tienen mayor expectativa de vida: Estudios no han probado que la eficacia de TKIs dure mas de 15 años.

Morbilidades de los TKIs en niños son diferentes que en los adultos.

Tratamiento : Debe ser curativo mas que suprimir la enfermedad.

TSCH: Resultados son mejores en niños

Eficacia de nuevos TKIs no ha sido validada

MUCHAS GRACIAS