WEBinar

MANEJO DE LOS EA DE LOS ITKs - LMC

Desde el SFH.

GARBIÑE LIZEAGA
HU DONOSTIA

ORGANIZA

sefh Sociedad Española de Farmacia Hospitalaria
fefh Fundación Española de Farmacia Hospitalaria
gedefo Grupo de Farmacia Oncológica de la sefh

LMC en 2020


Tratamiento crónico.
Adherencia.
Pacientes frágiles.
Polimedicación.

bjh guidelines

A British Society for Haematology Guideline on the diagnosis and management of chronic myeloid leukaemia

Graeme Smith,[1] Jane Apperley,[2] Dragana Milojkovic,[2] Nicholas C. P. Cross,[3] Letizia Foroni,[2] Jenny Byrne,[4] Andy Goringe,[5] Anupama Rao,[6] Jamshid Khorashad,[2] Hugues de Lavallade,[7] Adam J. Mead,[8] Wendy Osborne,[9] Chris Plummer,[9] Gail Jones,[9,10] Mhairi Copland[11] and behalf of British Society for Haematology

Table V. First-line TKI response milestones.

*BCR-ABL*1 (IS)	3 months	6 months	12 months	>12 months
>10%	Consider TKI switch*	Failure — switch TKI	Failure — switch TKI	Failure — switch TKI
1–10%	Continue same TKI	Consider TKI switch*	Failure — switch TKI	Failure — switch TKI
0·1–1%	Continue same TKI	Continue same TKI	Consider TKI switch*	Consider TKI switch*
<0·1% (MR3;MMR)	Continue same TKI	Continue same TKI	Continue same TKI	Continue same TKI
<0·01% (MR4;DMR)	Continue same TKI	Continue same TKI	Continue same TKI	Consider TFR†

■, optimal response, continue current therapy; ■, suboptimal response, consider change of therapy; ■, treatment failure, change therapy; ■, optimal response and potentially eligible for treatment discontinuation.

*Patients in this category require careful assessment of factors such as age/co-morbidities, baseline prognostic factors, cytogenetic response, trajectory of molecular response, compliance, presence of KD mutation, side effects. This intervention is not currently NICE-approved in the UK.

†see treatment-free remission (TFR) section for details of TFR eligibility. Patients should have been on a TKI for at least three years, and duration of DMR is important.

ITK aprobados para LMC Ph+ en la EMA / FDA

Fármaco	Indicaciones de uso	Posología
gleevec (imatinib mesylate) tablets	• Recién diagnosticados, FC (adulto, pediatrico) • Tras fallo a INFα o en FA, FB (adulto, pediátrico)	FC: 400 mg/día (adultos), 340 mg/m2 al día (pediátrico) FA, FB: 600 mg/día (adultos), 340 mg/m2 al día (pediátrico)
Tasigna (nilotinib)	• Recién diagnosticados, FC (adulto, pediatrico) • Tras resistencia o intolerancia a un tratamiento previo en FC (adulto, pediátrico) + FA (adulto).	FC RD: 300 mg/2 veces al día (adulto) FC tras terapia previa, FA: 400 mg/2 veces al día (adulto) Pediátricos: 230 mg/m2 dos veces al día
SPRYCEL dasatinib	• Recién diagnosticados, FC (adulto, pediátrico) • Tras resistencia o intolerancia a un tratamiento previo en FC, (adulto, pediátrico) + FA o FB (adulto)	FC: 100mg/día (adulto) FA,FB: 140mg/día (adulto) Pediátricos: *tabla en función peso en FT*
▼ Bosulif bosutinib tablets	• Recién diagnosticados, FC (adulto)* • Tras resistencia o intolerancia a uno o más ITK en FC, FA o FB (adulto).	FC RD: 400 mg/día (adulto)* FC tras terapia previa, FA o FB: 400 mg/día (adulto)
▼ ICLUSIG (ponatinib) tablets	• Pacientes con mutación T315I en FC, FA o FB (adulto). • Tras resistencia o intolerancia a dasa o nilo y que no este indicado imatinib en FC,FA o FB (adulto).	FC, FA o FB: 45mg/día. (adulto).

LMC Ph+: Leucemia Mieloide Crónica Filadelfia positiva; FC, fase crónica; FA, fase acelerada; FB, fase blástica; RD, recién diagnosticados

*No comercializado en España oendiente de precio y rembolso.

▼ Este medicamento está sujeto a seguimiento adicional, es prioritaria la notificación de sospechas de reacciones adversas asociadas a este medicamento.

Creado a partir de Fichas técnicas de Gleevec Imatinib (Novartis), Tasigna Nilotinib (Novartis), Sprycel Dasatinib (Bristol-Myers Squibb Pharma), Bosulif bosutinib, (Pfizer SLU), Iclusig ponatinib (Incyte Biosciences)

	Bosutinib	Dasatinib	Imatinib	Nilotinib	Ponatinib
BCR/ABL	100	105	83	98	101
ABL(E255K)	99	101	38	88	101
ABL(T315I)	93	68	9	15	100
CAMK2G	96	-3	-7	4	-4
VEGFR	100	102	4	17	97
EPHA1	3	101	9	61	97
EPHA2	99	99	6	95	102
FGFR1	79	47	-1	-29	101
C-KIT	23	100	97	96	101
p38α	9	91	-2	92	101
PDGFRα	77	100	98	103	103
PDGFRβ	95	99	91	93	102
RET	95	73	2	31	102
SRC	96	101	5	23	102
TEC	58	101	-3	0	79
TIE2	22	16	0	41	101

Table 2. Relative activity of BCR/ABL inhibitors against different tyrosine kinases (adapted from Uitdehaag[19]).

Activity of BCR/ABL TKIs. The number represents the percentage of inhibition of tyrosine kinase activity at a concentration of 1μmol/l of each inhibitor.

Percentage inhibition of >95-100% noted in Red, 75-95% noted in Orange, 50-75% noted in Yellow, 25-50% noted in Blue, and <25% noted in Green.

BCR/ABL: breakpoint cluster region/Abelson murine leukemia gene; SRC: stored response chain, Sarcoma; TEC: Tec protein kinase; CAMK2G: Calcium/calmodulin dependent protein kinase; C-KIT: Mast/stem cell growth factor receptor; PDGFR: Platelet-derived growth factor receptor; EPHA: Ephrin tyrosine kinase; RET: rearranged during transfection proto-oncogene tyrosine kinase; TIE2: Angiopoietin 1 receptor; FGFR: fibroblast growth factor receptor; VEGFR: vascular endothelial growth factor receptor; TKI: tyrosine kinase inhibitor.

TABLE 3 | Most frequent side effects related to treatment with tyrosine kinase inhibitors in CML patients*.

	Imatinib		Dasatinib		Nilotinib		Bosutinib		Ponatinib	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Fatigue	++++	+	+++	+	++++	–	NR	NR	++++	++
Rash	++++	++	+++	+	++++	–	++++	++	++++	++
Headache	+++	–	++++	–	++++	–	++++	++	++++	++
Myalgia	+++++	–	++++	–	NR	NR	++	–	++++	++
Bone pain	+++	++	NR	NR	NR	NR	++	–	NR	NR
Diarrhea	++++	++	++++	+	+++	+	+++++	++++	NR	NR
Nausea	++++	–	++++	–	+++	+	++++	++	++++	+
Vomiting	+++	–	+++	–	++	–	++++	++	NR	NR
Abdominal pain	++	–	NR	NR	NR	NR	++++	++	++++	+++
Pancreatitis	+	+	NR	NR	++	++	NR	NR	+++	+++
Peripheral edema	++++	++	++++	++	+++	+	+++	++	NR	NR
Pleural effusion	++	+	++++	++	++	+	NR	NR	NR	NR
Elevated lipase	++++	+++	NG	–	++++	+++	++++	+++	++++	++++
Hepatotoxicity	++++	++	NG	+	+++++	+++	+++++	++++	+++	++
Anemia	+++++	+++	+++++	++++	++++	++	+++++	+++	++++	++++
Thrombocytopenia	+++++	++++	+++++	++++	++++	+++	+++++	++++	++++	++++
Neutropenia	+++++	++++	+++++	++++	++++	+++	++++	++++	++++	++++

This table has been adapted from J Apperley (60).

Data derived from studies of first line use with the exception of ponatinib. + ≤ 1% of patients. ++ = 1–5%. +++ = 5–10%. ++++ = 10–50%. +++++ = 50–100%. NR, not reported; NG, data not given.

Garcia-Gutierrez V, Hernandez-Boluda JC. Front.Oncol. 9,603. doi : 10.33897fonc00603

TABLE 3 Surface under the cumulative ranking results for the outcome serious adverse event (grades 3–4)

Drug	Serious adverse event (grades 3–4)			
	Anaemia	Leukopenia	Neutropenia	Thrombocytopenia
Bosutinib 400 mg	52%	47%	22%	71%
Bosutinib 500 mg	60%	27%	21%	34%
Dasatinib 100 mg	74%	84%	74%	79%
Dasatinib 140 mg	90%	87%	91%	97%
Imatinib 400 mg	39%	59%	56%	34%
Imatinib 600 mg	5%	24%	-	20%
Imatinib 800 mg	74%	79%	70%	63%
Nilotinib 600 mg	22%	24%	33%	29%
Nilotinib 800 mg	36%	15%	18%	33%
Ponatinib 45 mg	-	-	21%	65%
Radotinib 600 mg	63%	-	65%	28%
Radotinib 800 mg	35%	-	80%	47%

Fachi MM, Tonin FS, Leonart LP, Rotta I, Fernandez-Llimos F, Pontarolo R. Haematological adverse events associated with tyrosine kinase inhibitors in chronic myeloid leukaemia: A network meta-analysis. Br J Clin Pharmacol. 2019;85:2280–2291. https://doi.org/10.1111/ bcp.13933

- Anemia: ↑dasatinib 100mg
- Leucopenia: ↑dasatinib 100mg
- Neutropenia: ↑ dasatinib 100mg.
- -Trombocitopenia: ↑ dasatinib 100 mg.

Current Hematologic Malignancy Reports (2019) 14:492–500
https://doi.org/10.1007/s11899-019-00546-4

CHRONIC MYELOID LEUKEMIAS (G SAGLIO, SECTION EDITOR)

Towards a Personalized Treatment of Patients with Chronic Myeloid Leukemia

Florence Rabian[1] · Etienne Lengline[2] · Delphine Rea[2,3,4]

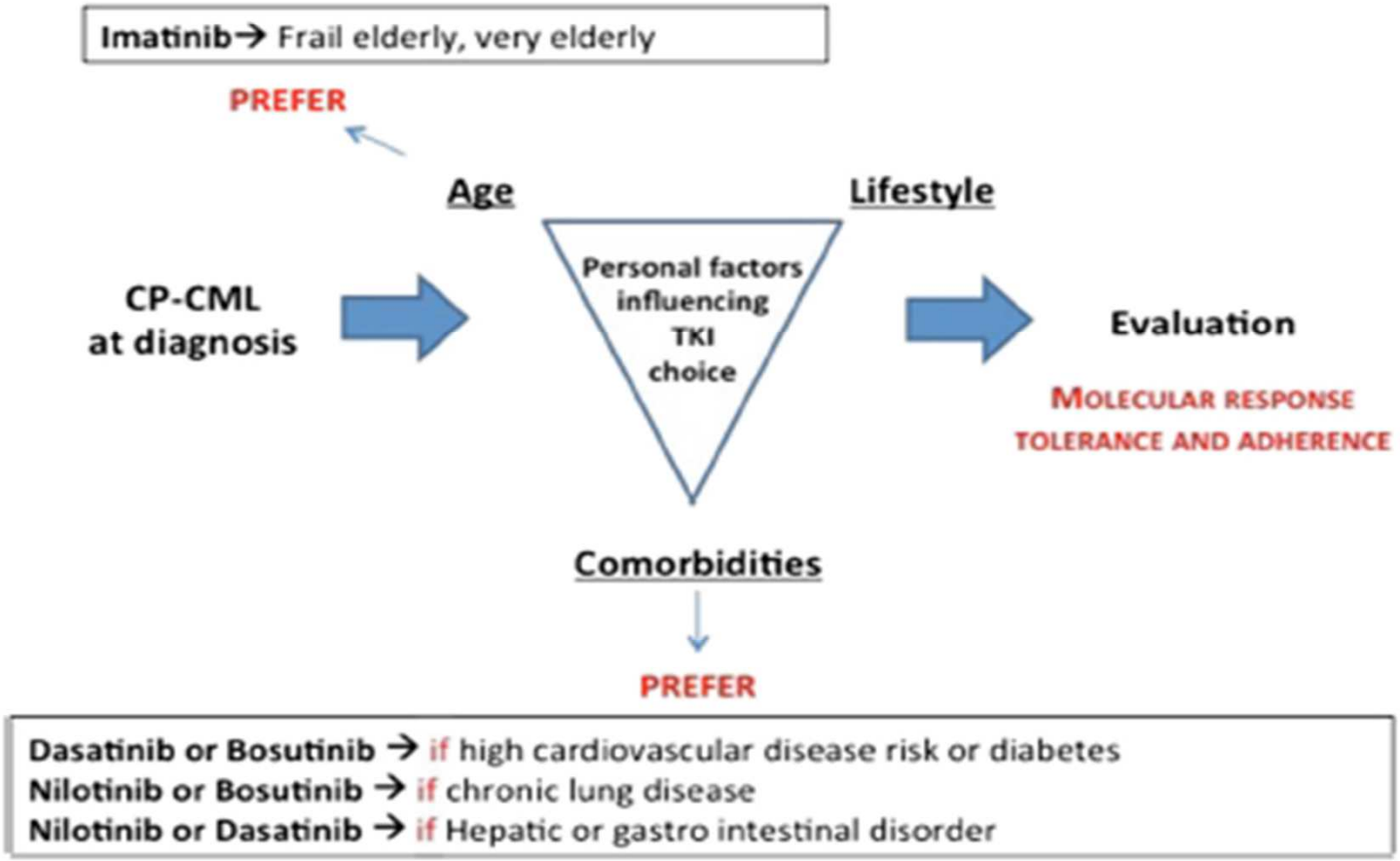

Table II. Guidelines for first-line TKI choice by pre-existing medical condition (adapted from Michael Deininger, personal communication).

Co-morbidity	Bosutinib	Dasatinib	Imatinib	Nilotinib
Hypertension				
Ischaemic heart disease				
Cerebrovascular thrombosis				
Peripheral arterial occlusive disease				
Prolonged QT interval*				
Congestive cardiac failure				
Diabetes mellitus				
Gastrointestinal bleeding†				
Pulmonary hypertension				
Chronic pulmonary disease				
Pancreatitis				
Abnormal liver function				

, no contra-indication; , low risk of exacerbation of pre-existing condition; , intermediate risk of exacerbation of pre-existing condition; , avoid if possible.

*Some evidence that all 2GTKI prolong QT.

†Imatinib has been associated with the development of gastric antral vascular ectasia (GAVE).

bjh guidelines

A British Society for Haematology Guideline on the diagnosis and management of chronic myeloid leukaemia

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DOI: 10.1002/ajh.25102

CORRESPONDENCE

Cardiovascular toxicity in patients with chronic myeloid leukemia treated with second-generation tyrosine kinase inhibitors in the real-life practice: Identification of risk factors and the role of prophylaxis

- Cohorte 506 pac: dasa/nilo
- Factor riesgo: Historia previa, tratamiento dasa/nilo
- Sin relación entre dosis TKI incidencia EA CV
- A 5 años: incidencia acumulada EA CV todos: 21,7%

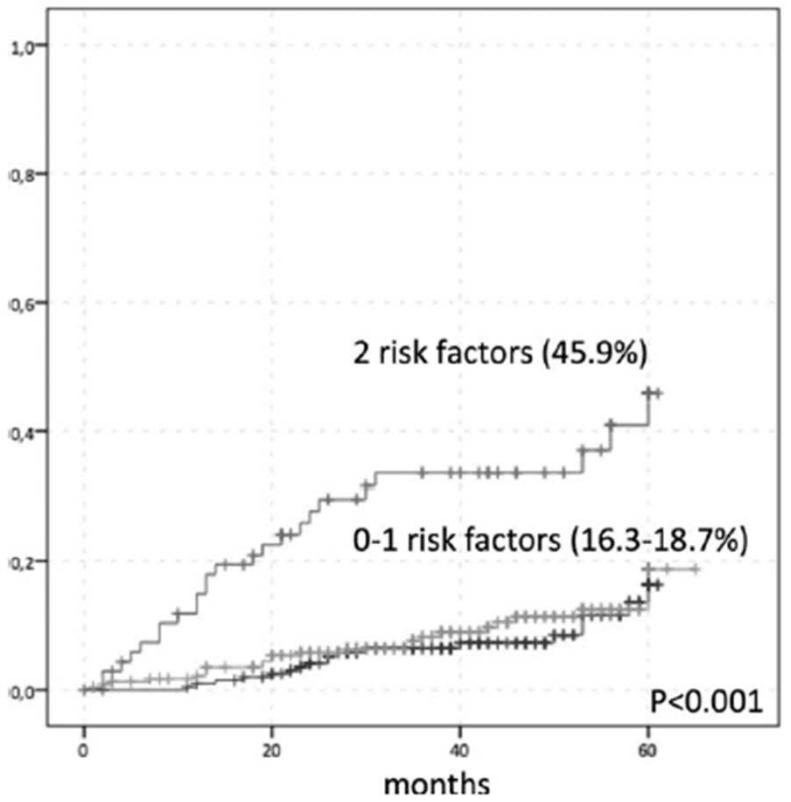

FIGURE 1 Cardio-vascular adverse event incidence in 436 patients with standard risk (0 or 1 risk factor considering a positive anamnesis for CV disease and treatment with 2^{ndG}TKIs administered as second-line or beyond) and 70 patients with high-risk CML- cardiovascular score (both risk factors were present). 2ndGTKI, second-generation tyrosine kinase inhibitor; CML, chronic myeloid leukemia [Color figure can be viewed at wileyonlinelibrary.com]

Blood Reviews 32 (2018) 289–299

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Blood Reviews

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

Review

Cardiovascular, pulmonary, and metabolic toxicities complicating tyrosine kinase inhibitor therapy in chronic myeloid leukemia: Strategies for monitoring, detecting, and managing

Bruno C. Medeiros[a,*], Jennifer Possick[b], Michael Fradley[c]

Venous Thrombosis and Vascular AEs

Hypertension

Assessment	IM	NIL	DAS	BOS	PON
Baseline					
BP	Follow GCP	REC	REC	REC	REC
Ankle-brachial index	GCP	REC	ACI	ACI	REC
1-month follow-up					
BP	GCP	ACI	ACI	ACI	REC
3–6-month follow-up					
BP	GCP	REC	ACI	ACI	REC
Ankle-brachial index	GCP	REC	ACI	ACI	REC

Venous thrombosis

- Recommend appropriate lifestyle modifications
- For black patients with no CKD, initiate thiazide-type diuretic or CCB, alone or in combination
- For nonblack patients with no CKD, initiate thiazide-type diuretic or ACEI or ARB or CCB, alone or in combination
- In CKD patients with or without diabetes, initiate ACEI or ARB, alone or in combination with another drug class
- Treatment with low-molecular weight heparin is recommended over vitamin K antagonist
- Routine prophylaxis is not recommended in patients in the outpatient setting with no additional risk factors for venous thromboembolism

Arterial vascular events, including peripheral artery occlusive disease

- Consider prophylaxis with a daily dose of aspirin or clopidogrel
- Consider switching TKIs or TKI dose reduction for more serious peripheral artery occlusive disease instances that would require interventional revascularization procedures

ACEI = angiotensin-converting enzyme inhibitor; ACI = as clinically indicated; AE = adverse event; AF = atrial fibrillation; ARB = angiotensin-receptor blocker; BOS = bosutinib; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CKD = chronic kidney disease; CV = cardiovascular; DAS = dasatinib; DM = diabetes mellitus; ECG = electrocardiogram; GCP = good clinical practice; GLP-1 = glucagon-like peptide-1; HbA_{1c} = hemoglobin A_{1c}; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HTN = hypertension; ICD = implantable cardioverter-defibrillator; IM = imatinib; MCS = mechanical circulatory support; NIL = nilotinib; PON = ponatinib; REC = recommended; TKI = tyrosine kinase inhibitor.

Table VIII. Cardiovascular and respiratory side effects of TKIs.

	Imatinib	Bosutinib	Dasatinib	Nilotinib	Ponatinib	Treatment options
Hypertension	Uncommon* (<1%)	Common* 3·9% G1–2 1·6% G3 0% G4	Common (<10%)	Common (<10%)	Very* common (≥10%)	NICE guidance[3], start or increase treatment at >160/100 mm Hg, suspend TKI at >180/110 mm Hg
Pleural effusions	Uncommon (<1%)	Common 4·3% G1–2 1·6% G3 0·1% G4	Very common 23% G1–2 5% G3–4	Uncommon (<1%)	Common (<10%)	Suspend TKI, restart TKI at lower dose when resolved. Drainage should not usually be required.
Pericardial effusion	Rare* (<0·1%)	Common 1·5% G1–2 0·2% G3 0·1% G4	Common 3% G1–2 1% G3–4	Uncommon (<1%)	Common (1·3%)	Suspend TKI, symptomatic treatment as required, restart TKI at lower dose when resolved
Pulmonary oedema	Uncommon (<1%)	Uncommon 0·1% G1–2 0·1% G3 0·1% G4	Common 1% G1–2 1% G3–4	Uncommon (<1%)	Not reported	Suspend TKI, symptomatic treatment as required, restart TKI at lower dose when resolved
Pulmonary hypertension	Rare (<0·1%)	Uncommon 0·4% G1–2 0·1% G3 0 G4	Common 1% G1–2 1% G3–4	Not known	Common (<10%)	Suspend TKI, consider alternative TKI at standard dose when resolved
Heart failure	Uncommon (<1%)	Not reported	Common 1% G1–2 0% G3–4	Uncommon (<1%)	Common (2%)	Suspend TKI, heart failure symptoms due to left ventricular systolic dysfunction require cardiological investigation and treatment according to

Table VII. Side effects of TKIs and their management.

General	Fatigue, insomnia, oedema, sub-conjunctival haemorrhage	Co[illegible]der
Skin and subcutaneous tissue	Severe cutaneous adverse reactions (SCARs), rash, dry skin, itch, alopecia, sweats	Dose reduction of TKI for side effects Antihistamines Switching TKI as little cross-reactivity of side effects is seen in clinical practice Topical steroids for symptomatic treatment of skin rash Corticosteroids for elevated liver transaminases Oral steroids for pleural effusion Diuretics may be helpful in the management of peripheral oedema Loperamide for diarrhoea
Musculoskeletal	Myalgia, cramp arthralgia	
Gastrointestinal	Nausea, vomiting, anorexia, diarrhoea, constipation	
Hepatobiliary	Abnormal LFTs,* pancreatitis,	
Haematological	Bone marrow suppression	
Renal	Renal impairment	
Infection	Increased risk of infection (due to cytopenia) and possible hepatitis B reactivation	
Metabolism/endocrine	Thyroid function abnormalities, glucose intolerance/diabetes, gynaecomastia, erectile dysfunction, effects on fertility and gametogenesis	
Neurological	Headache, migraine, rarely dizziness, paraesthesia, PRES†	
Cardiorespiratory	Hypertension, pleural or pericardial effusion, heart failure, pulmonary arterial hypertension, arterial or venous thromboembolism, QT prolongation	

*Liver function tests — a rise in bilirubin is commonly noted with nilotinib and may uncover patients with undiagnosed Gilbert's disease. This is not clinically significant and uridine-diphosphoglucuronate glucuronosyltransferase (UDPGT-1A1) genotyping is not indicated.
†Posterior reversible encephalopathy syndrome.

MANEJO EA:

STOP.

Manejo síntomas: loperamida, dieta, antihistamínicos, corticoides tópicos.

Evaluación interacciones.

Multidisciplinaridad, monitorización.

Reintroducción a dosis reducidas.

Evaluación.

	Enzymes	Metabolites	Metabolite activity
Bosutinib	CYP3A4	Oxide chlorinated derivative (M2) Demethylated derivative (M5)	Very reduced Very reduced
Dasatinib	CYP3A4	Oxide derivatives Derivatives conjugated with glucoronic acid	Inactive
Imatinib	CYP3A4, CYP1A2, CYP2D6, CYP2C9, CYP2C19	N-desmetilimatinib	Similar to imatinib
Nilotinib	CYP3A4, CYP2C8, UGT1A1	Oxide derivatives Derivatives conjugated with glucoronic acid	Probably inactive
Ponatinib	Amidases, esterases CYP3A4, CYP2C8, CYP2D6, CYP3A5	N-demethylated	Inferior

Table 4: Metabolism and metabolite activity of BCR/ABL inhibitors.

Extraído de Azanza et al. Int J Clin Pharmacol Pharmacother 2018, 3: 134

MANEJO EA:

STOP.

Manejo síntomas: loperamida, dieta, antihistamínicos, corticoides tópicos.

Evaluación interacciones.

Multidisciplinaridad, monitorización.

Reintroducción a dosis reducidas.

Evaluación.

Current Hematologic Malignancy Reports (2019) 14:337–345
https://doi.org/10.1007/s11899-019-00524-w

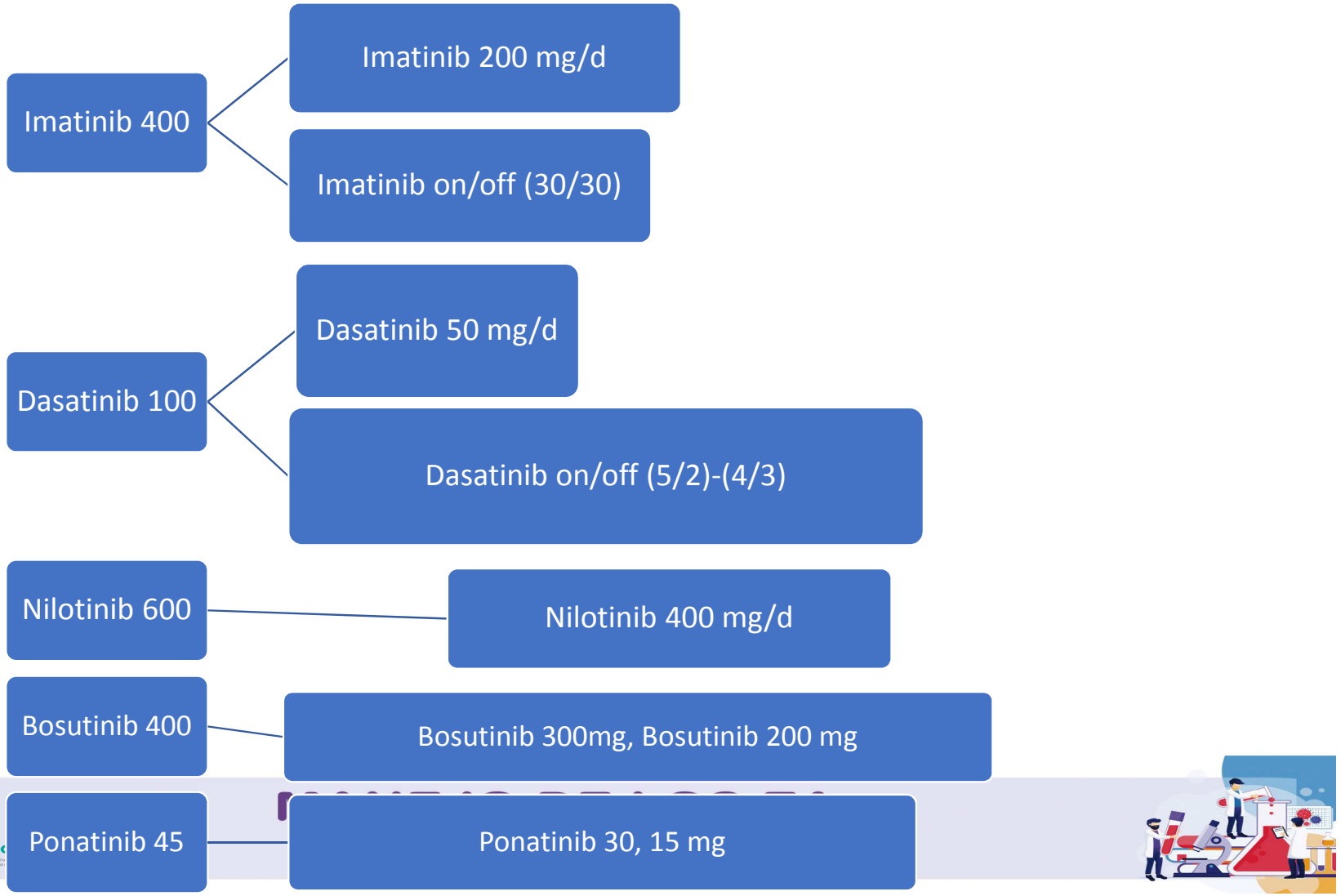
CHRONIC MYELOID LEUKEMIAS (M MAURO, SECTION EDITOR)

Is There a Role for Dose Modification of TKI Therapy in CML?

M. Copland[1]

Table 1 Seminal dose-optimization studies of dasatinib and nilotinib

TKI	Setting	Doses	% MMR at any time	Accepted TKI dose	Reference
Dasatinib CA180-034 study	Resistance/intolerance	50 mg bd	44%	100 mg od for all chronic phase indications	[24•]
		100 mg od	46%		
		70 mg bd	44%		
		140 mg od	46%		
Dasatinib DASISION	Newly diagnosed	100 mg od versus	76%		[25]
		imatinib 400 mg od	64%		
Nilotinib ENESTnd study	Newly diagnosed	300 mg bd	77%	300 mg bd in newly diagnosed and 400 mg bd for resistance/intolerance	[26]
		400 mg bd versus	77%		
		imatinib 400 mg od	60%		
Bosutinib BELA	Newly diagnosed	500 mg versus	59% at 24 months	400 mg od in newly diagnosed and 500 mg od for resistance/intolerance	[27]
		imatinib 400 mg od	49% at 24 months		
Bosutinib BFORE	Newly diagnosed	400 mg versus	61.2% at 24 months		[28•, 29]
		imatinib 400 mg od	50.7% at 24 months		


Imatinib 400
Imatinib 200 mg/d
Imatinib on/off (30/30)
Dasatinib 100
Dasatinib 50 mg/d
Dasatinib on/off (5/2)-(4/3)
Nilotinib 600
Nilotinib 400 mg/d
Bosutinib 400
Bosutinib 300mg, Bosutinib 200 mg
Ponatinib 45
Ponatinib 30, 15 mg

Received: 6 May 2020 | Revised: 8 June 2020 | Accepted: 12 June 2020
DOI: 10.1002/ajh.25908

CORRESPONDENCE

Low-dose ponatinib is a good option in chronic myeloid leukemia patients intolerant to previous TKIs

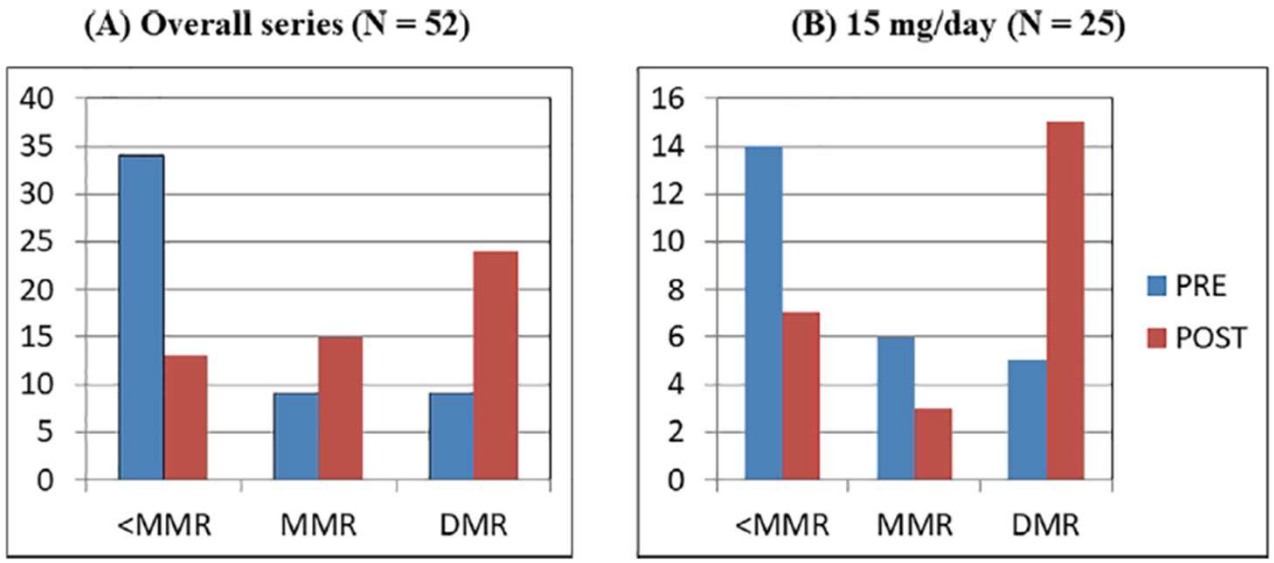
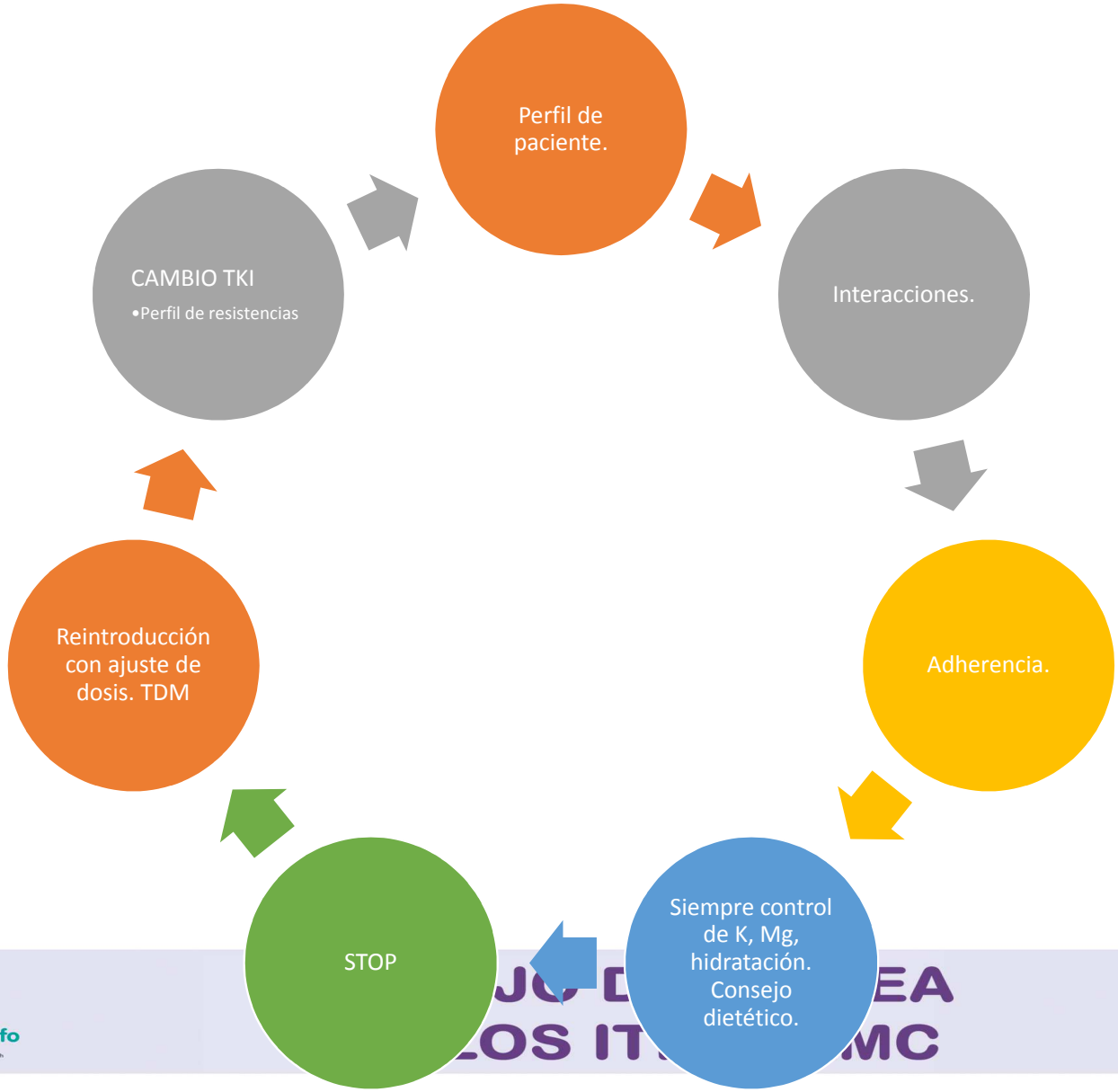


FIGURE 1 Molecular response rate before and after ponatinib start (A, overall series; B, 15 mg/d)

Reducción de dosis…

- Imatinib 200mg /d
- Imatinib on/off (30/30).
- Dasatinib 50 mg/d.
- Dasatinib on/off (3-5/4-3). (5/2).
- Nilotinib 300 mg/d
- Bosutinib 300mg/d y 200mg/d
- Ponatinib 30 mg/d y 15mg/d.

TDM


Perfil de paciente.
Interacciones.
Adherencia.
Siempre control de K, Mg, hidratación. Consejo dietético.
STOP
Reintroducción con ajuste de dosis. TDM
CAMBIO TKI
•Perfil de resistencias

ORGANIZA

sefh fefh gedefo

MANEJO DE LOS EA DE LOS ITKs - LMC