Clinical Pathology Conference

Division of Hematology

History

- 48 y/o female patient
- First visit in July 2014
- No systemic disease except psychiatric dis ease with regular medications in KMUH
- Refer for evaluation of leukocytosis and an emia during healthy examination
- No discomfort

History

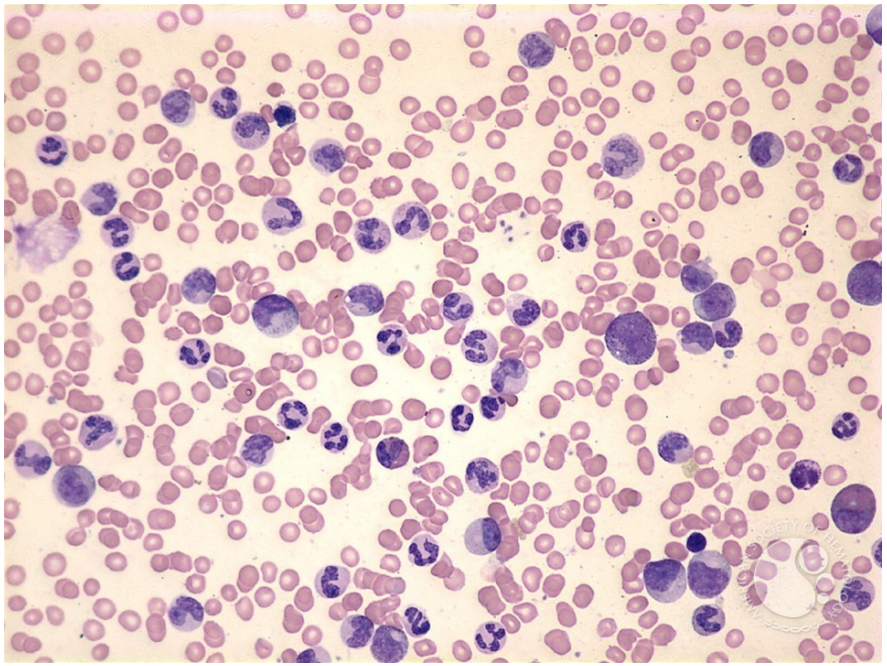
- Mild pale conjunctiva, no hepatosplenome galy
- Abdominal sonography: no abnormality

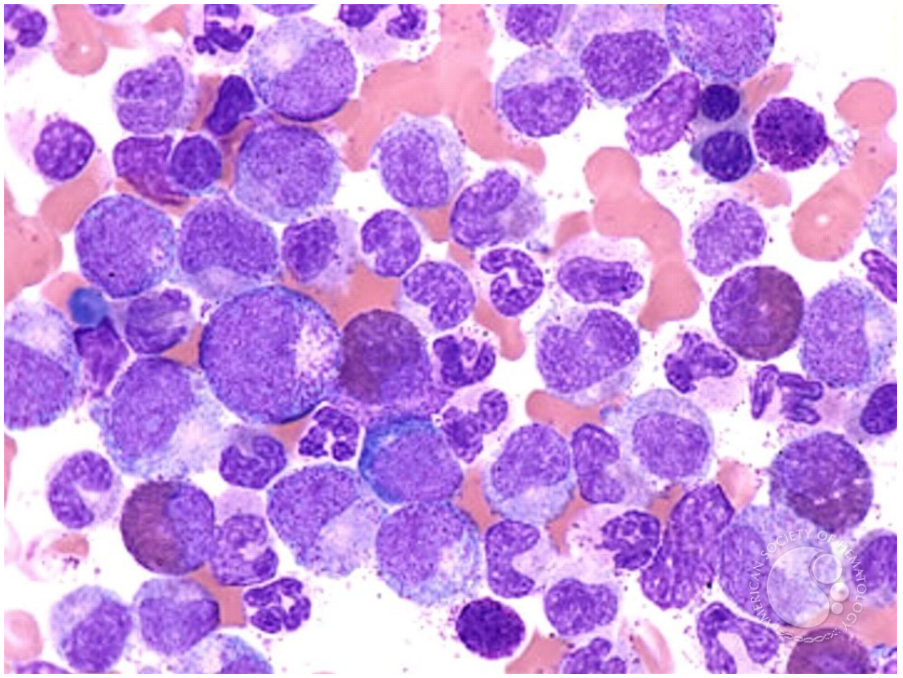
Lab Data

CBC	Value
WBC	49240
Hemoglobin	10.3
Platelet	319k
DC	
Band/Seg	10/49
Lym/Mon	7/1
Eo/Baso	1/8
Myelo/Meta	13/11
Normoblast	2

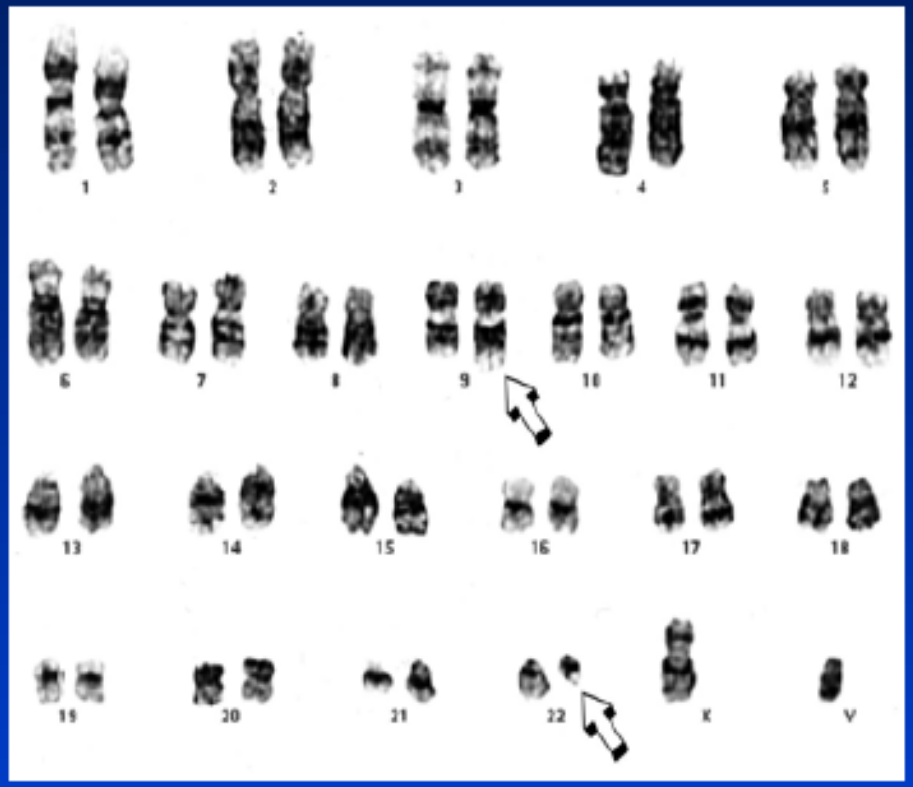
Biochemistry	Value
UA	6.1
Creatinine	0.84
ALT	20
LAP score	54
LDH	768

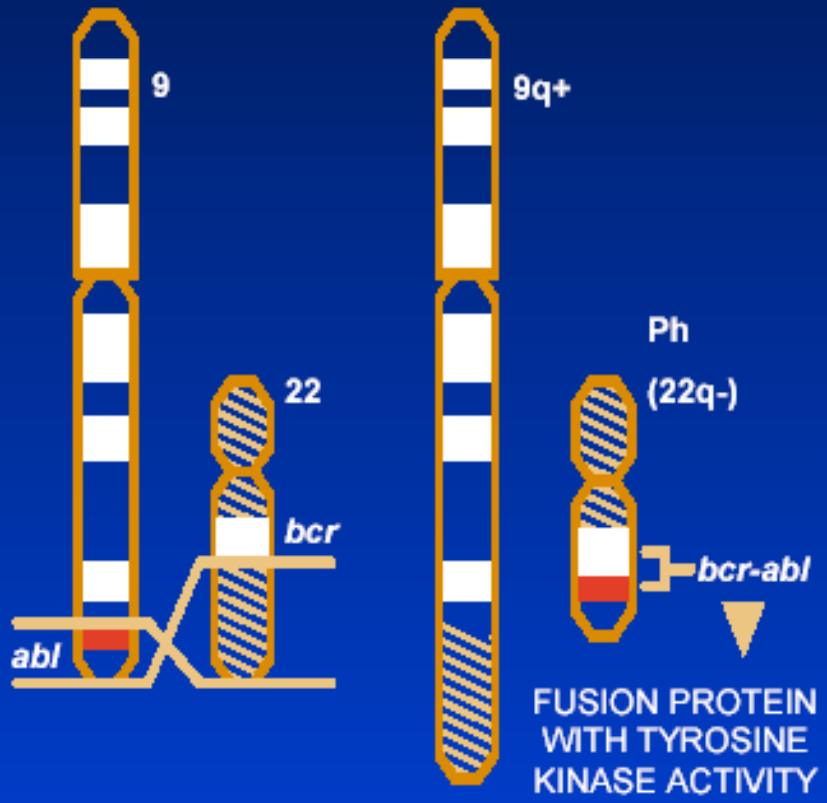
Bone Marrow Examination





CML: Linked to a Single Molecular Abnormality





The Philadelphia (Ph) Chromosome: t(9;22) Translocation

European Leukemia Net: 2009

Overall Response Definitions for Patients With CML-CP Treated With Frontline Imatinib (First 18 Months)

Time	Optimal	Suboptimal	Failure	Warnings
Diagnosis	—	—	—	High risk CCA in Ph+
3 months	CHR, > minor CyR	No CyR	No CHR	N/A
6 months	PCyR	< PCyR	No CyR	N/A
12 months	CCyR	< CCyR (PCyR)	< PCyR	< MMR
18 months	MMR	< MMR	< CCyR	N/A

Baccarani et al. J Clin Oncol. 2009;27:6041-6051.

2013 European LeukemiaNet Definitions of Response to TKIs First Line

Time	Optimal	Warnings	Failure
Diagnosis	—	High risk or CCA in Ph+	—
3 months	BCR-ABL <10% IS and/or Ph+ <= 35%	BCR-ABL >10% IS and/or Ph+ 36-95%R	No CHR and/or > 95% Ph+
6 months	BCR-ABL < 1% IS and/or CCyR	BCR-ABL 1%–10% IS and/or Ph+ 1-35%	BCR-ABL >10% IS and/or Ph+ > 35%
12 months	MMR (BCR-ABL ≤0.1% IS)	0.1% –1% IS	BCR-ABL >1% IS and/or Ph+ >0
At any time	MMR (≤0.1% IS)	CCA/Ph- (-7, or 7q)	Loss of CHR or CCyR; Confirmed loss of MMR ; Mutations; CCA/Ph+

Baccarani M, et al. *Blood*. 2013.

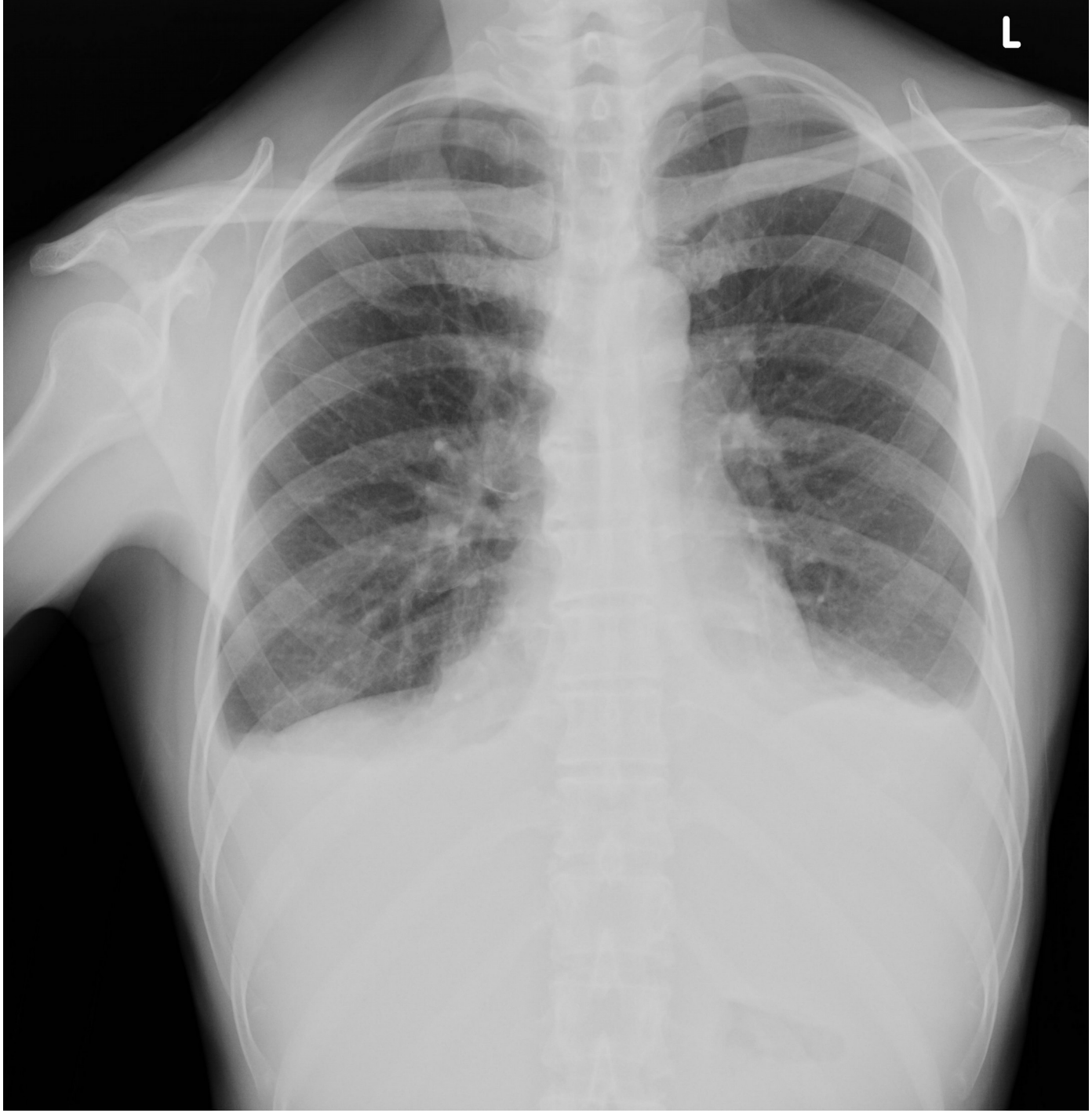
CCA = clonal chromosome abnormalities. Cytogenetic responses: minor >35% Ph+; MCyR (major) 0%–35% Ph+; PCyR (partial) 1%–35% Ph+; CCyR (complete) 0% Ph+.

Diagnosis and Treatment

- CML in chronic phase
- Sokal score 0.62, low risk
- Dasatinib 100 mg qd po since Aug 2014
- Complete hematologic response(CHR) at 1 month
- Molecular response(MR) 4.35 at 6 months
- Complete cytogenetic response(CCyR) at 1 2 month

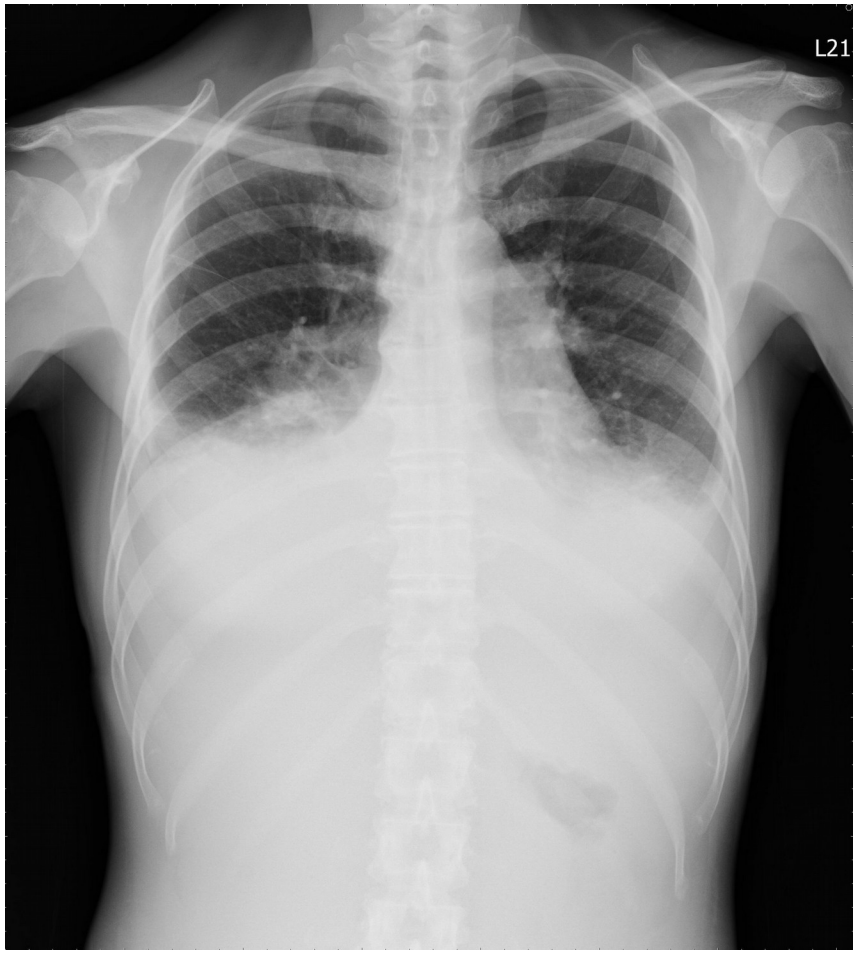
Treatment

- Keep deep molecular response (DMR) 4-4.5
- Follow every 3 month
- No apparent adverse effect until June 2017, 34 months after dasatinib
- Grade 2 pleural effusion
- Improved with stop of dasatinib, drainage with low dose corticosteroid


L

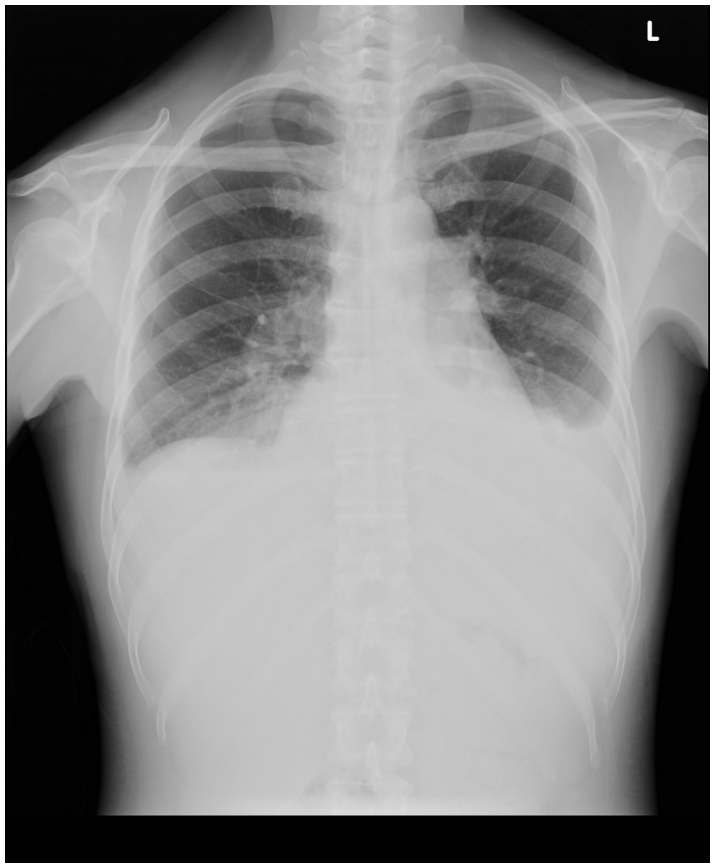
Treatment

- Resume dasatinib 1 mont h later and stop corticoste roid
- Keep DMR(MR 4.5)
- Recurrence of pleural effu sion(PE) in Sep 2018
- Exudate
- Grade 2 PE despite drain age and corticosteroid

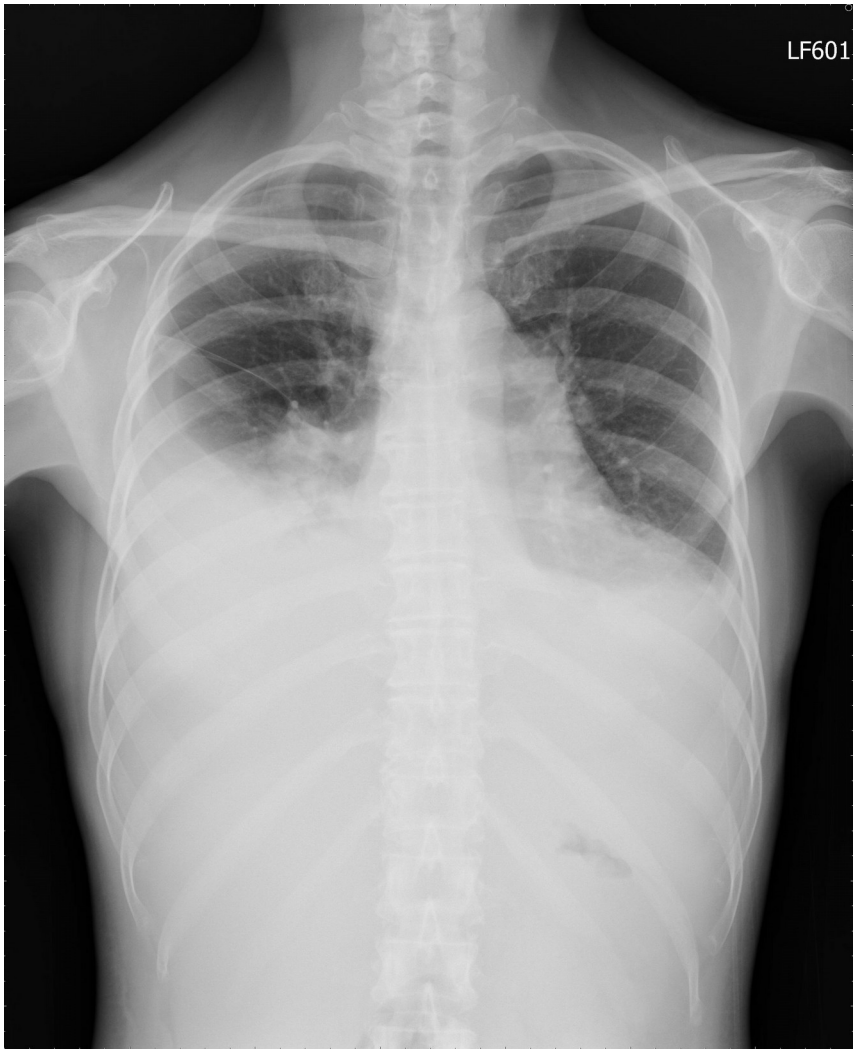


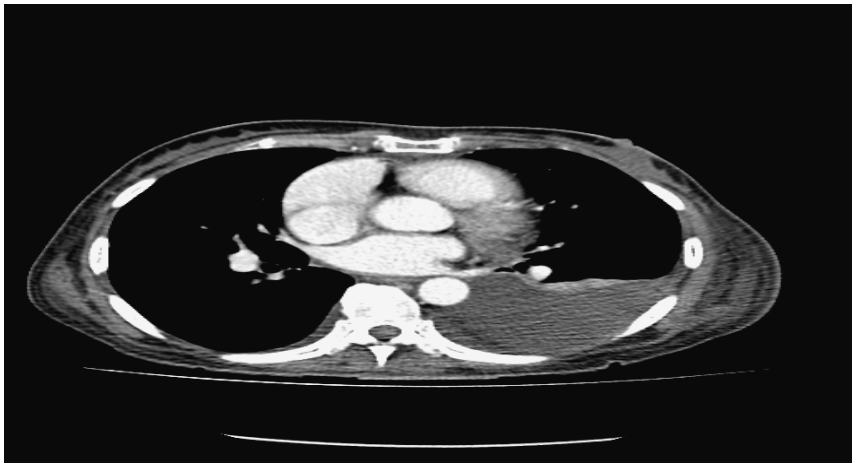
Treatment

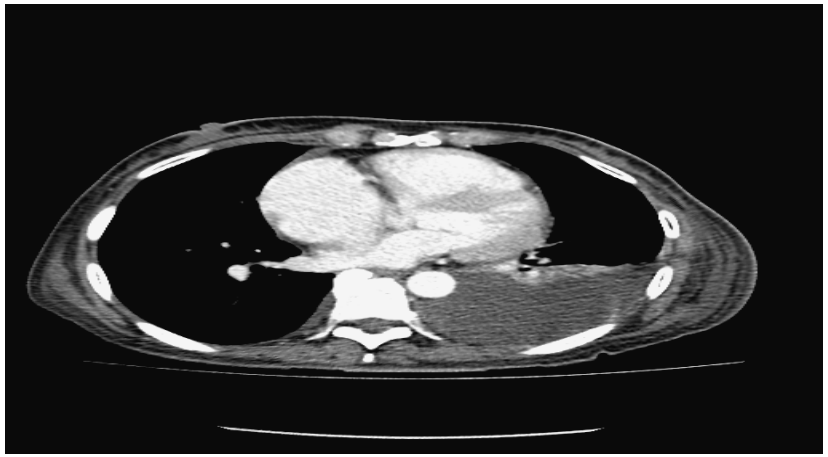
- Admission during Oct 16-Nov 16
- Stop dasatinib
- Drainage and corticos teroid
- DMR(4.0)
- Difficult management of PE and admission on Dec 14 again



Treatment

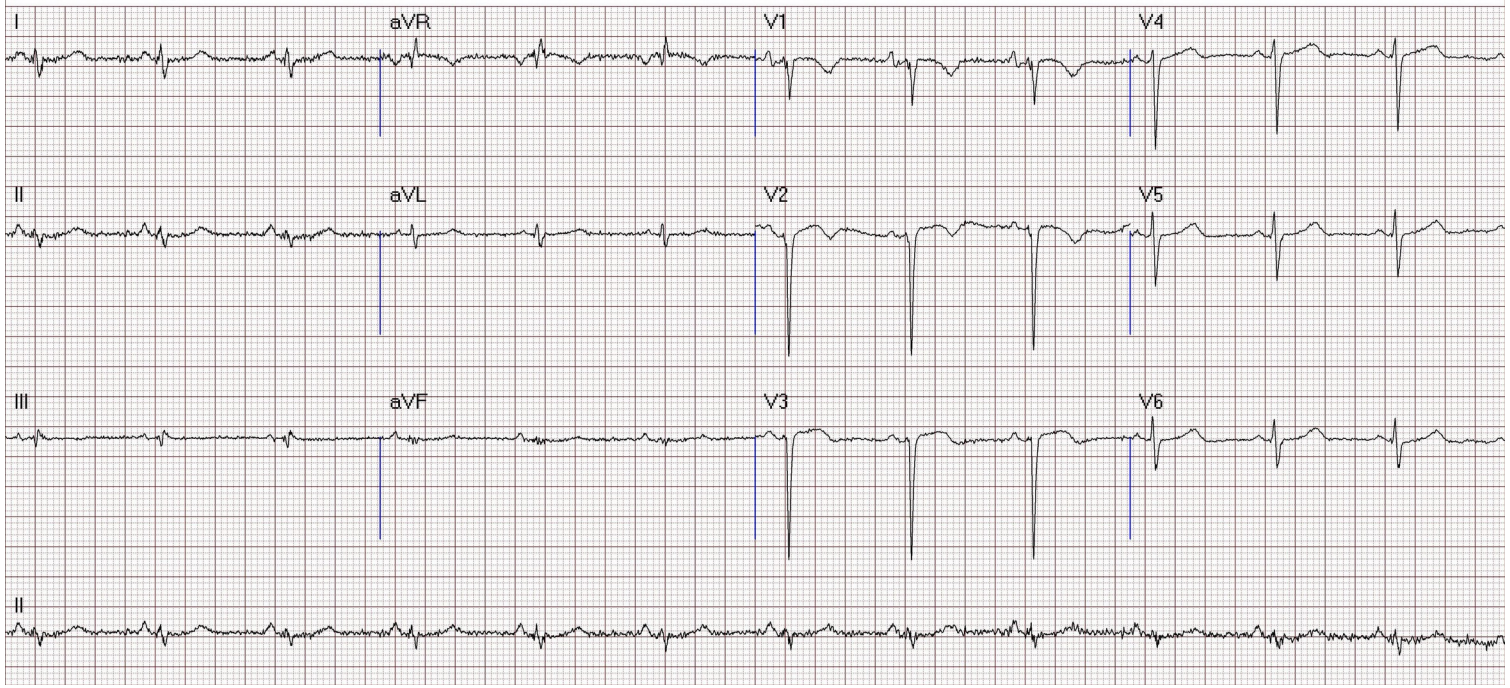






14551247	2018/12/21	9:22:45	
		F	F560

Rate	73
PR	120
QRSd	80
QT	394
QTc	434
– Axes –	
P	33
QRS	
T	17



Echocardiography

- LVEF 56%
- Peak systolic pressure gradient across tric uspid valve 60 mmHg
- Pulmonary artery systolic pressure (PASP) 70 mmHg
- Generalized RV hypokinesia with moderat e RV systolic dysfunction

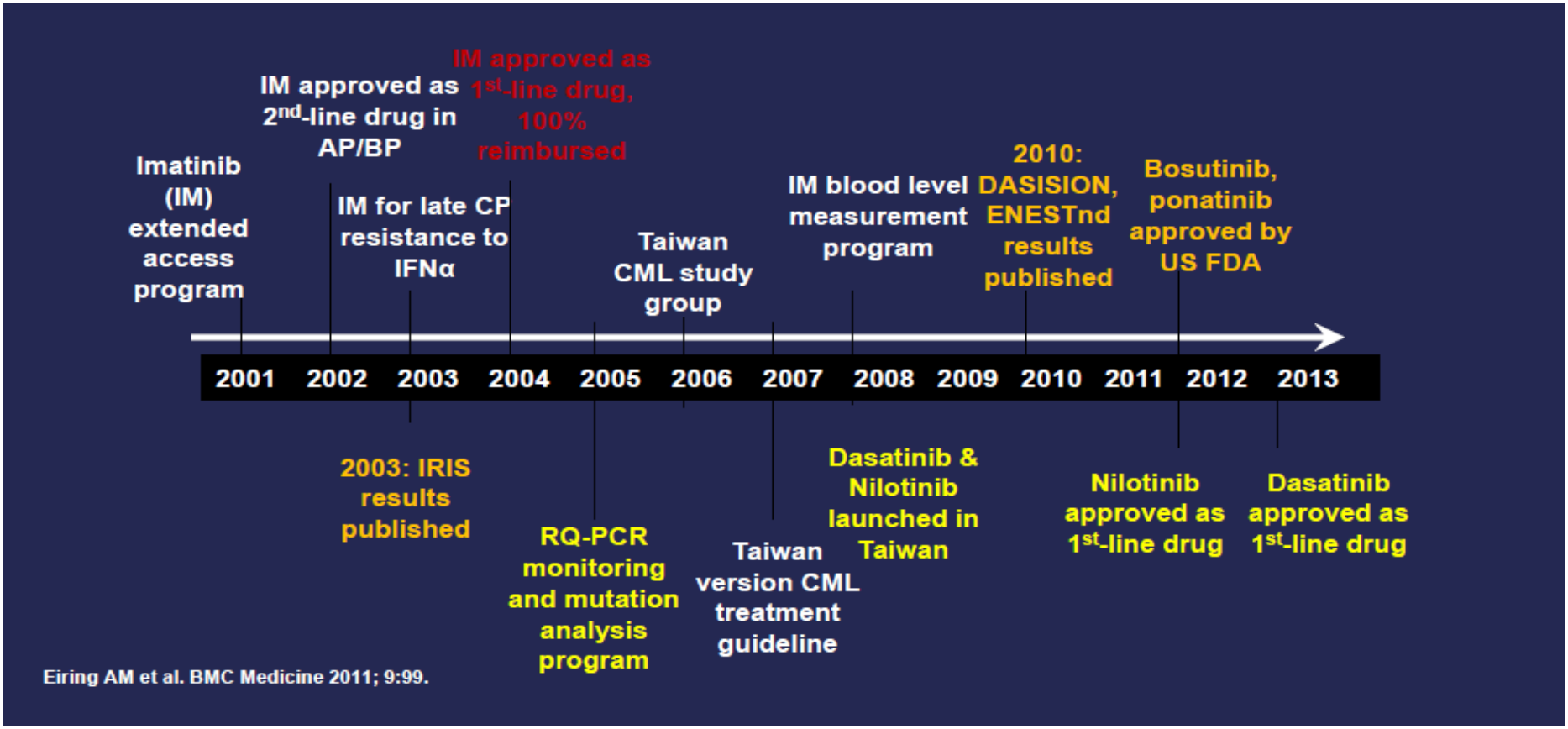
Treatment

- Consult cardiologist
- CAG and endomyocardial biopsy

CAG

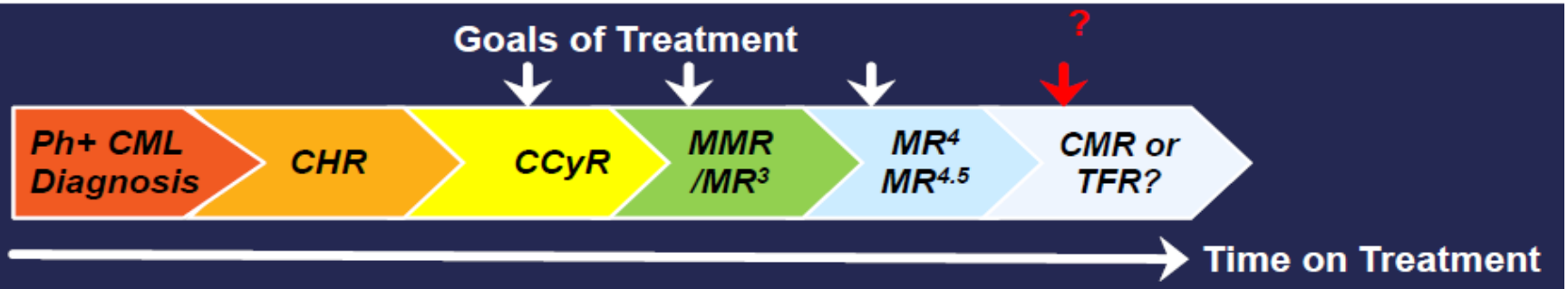
- Pulmonary arterial hypertension, Group I (mPAP 51, C.O 2.8, PVR 12.1 WU)

IMPORTANT CML MILESTONES IN TAIWAN



Eiring AM et al. BMC Medicine 2011; 9:99.

CML TREATMENT GOALS HAVE BECOME MORE AMBITIOUS OVER TIME



1st or 2nd L pivotal Trial	Treatment	Primary endpoint	Secondary endpoint
IRIS[1]	Imatinib vs IFN/AraC	Progression to AP/BP, Loss of **CHR/MCyR**	CHR, MCyR
CA 180-034[2]	Dasatinib low vs Dasatiinib high	**MCyR** at 6 month	CHR, MCyR by 24 month
DASISION[3]	Dasatinib vs Imatinib	**CCyR** at 12 month	MMR at 12 month, PFS, OS
ENESTnd[4]	Nilotinib vs Imatinib	**MMR** at 12 month	Durable MMR by 24 month CCyR by 12 month
EPIC[5]	Ponatinib vs Imatinib	**MMR** at 12 month	MMR at 5 yrs, CCyR at 12 month, PFS, OS
$ENEST_{1st}$[6]	Nilotinib	**MR4** at 18 month	CCyR, MMR, MR4, MR4.5 at 12/24 month, PFS, OS

3. Kantarjian H et al. N Engl J Med 2010; 362:2260-70.
4. Saglio G et al. N Engl J Med 2010; 362:2251-9.
5. Lipton JH et al. Lancet Oncol 2016; 17:612-21.

Frequency of Key Drug-Related AEs

AE[b]	Patients[a] with an event, n (% of total patients)	
	Grade 1/2 (n = 23)	Grade 3/4 (n = 11)
Headache	12 (30.8)	1 (2.6)
Pleural effusion	10 (25.6)	0
Rash	9 (23.1)	0
Fatigue	8 (20.5)	1 (2.6)
Dyspnea	7 (17.9)	1 (2.6)
Diarrhea	6 (15.4)	2 (5.1)
Nausea	6 (15.4)	0
Dizziness	4 (10.3)	0
Arthralgia	3 (7.7)	0
Pericardial effusion	3 (7.7)	0
Pruritus	3 (7.7)	0
Anemia	1 (2.6)	3 (7.7)

[a]Individual patients can fall into more than one AE category.
[b]AEs with ≥3 reported incidents are shown.

Pleural Effusion Was Grade 1/2, Manageable, And Did Not Affect Efficacy

Pleural effusion, n (%)	Dasatinib 100 mg QD N=258
All grades	26 (10)
Grade 1	5 (2)
Grade 2	21 (8)
Grade 3 or above	0

- **24/26 patients (92%) with pleural effusion achieved CCyR by 12 months**

Pleural effusion management, n	Pleural effusion on dasatinib N=26
Dasatinib dose interruption	19
Diuretics	12
Dasatinib dose reduction	8
Corticosteroids	7
Therapeutic thoracentesis	1

Pulmonary Arterial Hypertension in Patients Treated by Dasatinib

David Montani, MD, PhD; Emmanuel Bergot, MD; Sven Günther, MD; Laurent Savale, MD, PhD; Anne Bergeron, MD, PhD; Arnaud Bourdin, MD, PhD; Helene Bouvaist, MD; Matthieu Canuet, MD; Christophe Pison, MD, PhD; Margareth Macro, MD; Patrice Poubeau, MD; Barbara Girerd, PhD; Delphine Natali, MD; Christophe Guignabert, PhD; Frédéric Perros, PhD; Dermot S. O'Callaghan, MD; Xavier Jaïs, MD; Pascale Tubert-Bitter, PhD; Gérard Zalcman, MD, PhD; Olivier Sitbon, MD, PhD; Gérald Simonneau, MD; Marc Humbert, MD, PhD

Background—The French pulmonary hypertension (PH) registry allows the survey of epidemiological trends. Isolated cases of precapillary PH have been reported in patients who have chronic myelogenous leukemia treated with the tyrosine kinase inhibitor dasatinib.

Methods and Results—This study was designed to describe incident cases of dasatinib-associated PH reported in the French PH registry. From the approval of dasatinib (November 2006) to September 30, 2010, 9 incident cases treated by dasatinib at the time of PH diagnosis were identified. At diagnosis, patients had moderate to severe precapillary PH with functional and hemodynamic impairment. No other incident PH cases were exposed to other tyrosine kinase inhibitors at the time of PH diagnosis. Clinical, functional, or hemodynamic improvements were observed within 4 months of dasatinib discontinuation in all but 1 patient. Three patients required PH treatment with endothelin receptor antagonist (n=2) or calcium channel blocker (n=1). After a median follow-up of 9 months (min-max 3–36), the majority of patients did not demonstrate complete clinical and hemodynamic recovery, and no patients reached a normal value of mean pulmonary artery pressure (≤20 mm Hg). Two patients (22%) died at follow-up (1 of unexplained sudden death and 1 of cardiac failure in the context of septicemia, respectively, 8 and 12 months after dasatinib withdrawal). The lowest estimate of incident PH occurring in patients exposed to dasatinib in France was 0.45%.

Conclusions—Dasatinib may induce severe precapillary PH fulfilling the criteria of pulmonary arterial hypertension, thus suggesting a direct and specific effect of dasatinib on pulmonary vessels. Improvement is usually observed after withdrawal of dasatinib. (***Circulation*. 2012;125:2128-2137.**)

Six-Year Follow-Up Of Dasatinib-Related Pulmonary Arterial Hypertension (PAH) For Chronic Myeloid Leukemia In Single Center

Young-Woo Jeon, Sung-Eun Lee, Soo-Hyun Kim, Soo-Young Choi, Jin-Eok Park, Hye-Rim Jeon, Eun-Jung Jang and Dong-Wook Kim

Blood 2013 122:4017

8 of 66 patients, 12.1% in Korea.
we suggest that the long-term dasatinib treatment for CML requires careful attention to cardiopulmonary adverse effects. and routine cardiovascular an d pulmonary evaluation on regular basis is strongly recommended before a nd during treatment with dasatinib.

British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2018) **84** 835–845 835

REVIEW

Dasatinib-induced pulmonary arterial hypertension

Drug-induced (group 1) pulmonary hypertension (PH) is an important subgroup of PH involving dasatinib as a likely related agent, which is a second-generation tyrosine kinase inhibitor (TKI) used in the treatment of chronic myeloid leukaemia (CML). The mechanism of dasatinib-induced pulmonary arterial hypertension (PAH) is unclear. However, the occurrence of PAH with late onset in CML patients suggests a chronic pathological mechanism with an insidious onset rather than an acute inflammatory or cardiac aetiology. Dasatinib has a broader effect than other TKIs; the major known difference between dasatinib and other TKIs is the additional inhibition of Src family kinases. Therefore, Src inhibition was thought to play a role in the development of dasatinib-induced PAH. However, recently, it was also speculated that chronic dasatinib therapy may cause pulmonary endothelial damage, attenuate hypoxic pulmonary vasoconstriction responses and increase susceptibility to PAH independently of the Src family kinase-induced mechanism. Dasatinib-induced PAH usually seems to be reversible with the cessation of the drug, and sometimes with PAH-specific treatment strategies. Transthoracic echocardiography can be recommended as a routine screening prior to dasatinib initiation, and this non-invasive procedure can be utilized in patients having signs and symptoms attributable to PAH during dasatinib treatment.

Dasatinib induced Pulmonary Artery Hypertension

- 0.45%-12% in different series
- Clinical , functional and hemodynamic improvement within 4-5 months after discontinuation drugs
- Mechanism unknown
- *SRC* kinase family inhibition ?
- Pulmonary endothelial damage ?
- Immunomodulating effect of dasatinib

Echocardiography

- LVEF 60%
- Peak systolic pressure gradient across tricuspid valve 52 mmHg
- Pulmonary artery systolic pressure (PASP) 62 mmHg