

CLINICAL CASE PRESENTATION 3:

Suboptimal response to imatinib with dose increase rescue

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Man, 55 years old

No relevant comorbidities

January 2005: serotine fever associated with moderate abdominal pain

Peripheral blood count: Hb 9,9 g/dl

WBC 389.000/mmc (N 43%, Ly 8%, M 1%, B 5%, Eo 2%, Pmc 6%, Mc+Mmc 30%, blast cells 5%)

PLTs 299.000/mmc

Physical examination: moderate splenomegaly (5 cm in inspirium), confirmed by ultrasound

Bone marrow biopsy: 25% Pmc, blast cells 8%

Kariotype: no metaphases available

Bcr-abl (bone marrow and peripheral blood): b2a2 fusion transcript detected

**DIAGNOSIS: CML IN CHRONIC PHASE, HIGH SOKAL RISK (1.74)
(WHO 2001 CRITERIA)**

Institute Seràgnoli

- After a cytoreductive therapy with Hydroxiurea, the patient received **Imatinib (400 mg/day)**, obtaining a suboptimal response at sixth months evaluation.
- ?

What would you suggest?

- 1. Continue with the same dosage?
- 2. Increase the dosage?
 - 600 mg BD
 - 800 mg BD
- 3. Check for point mutation and/or additional cytogenetic abnormality?

So.. when to look for ABL KD mutations?

Review article

Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet

Michele Baccarani, Giuseppe Saglio, John Goldman, Andreas Hochhaus, Bengt Simonsson, Frederick Appelbaum, Jane Apperley, Francisco Cervantes, Jorge Cortes, Michael Deininger, Alois Gratwohl, François Guilhot, Mary Horowitz, Timothy Hughes, Hagop Kantarjian, Richard Larson, Dieter Niederwieser, Richard Silver, and Rudiger Hehlmann

Time	Failure	Suboptimal response
Diagnosis	NA	NA
3 mo after diagnosis	No HR (stable disease or disease progression)	Less than CHR
6 mo after diagnosis	Less than CHR, no CgR (Ph ⁺ > 95%)	Less than PCgR (Ph ⁺ > 35%)
12 mo after diagnosis	Less than PCgR (Ph ⁺ > 35%)	Less than CCgR
18 mo after diagnosis	Less than CCgR	Less than MMolR
Anytime	Loss of CHR*, loss of CCgR†, mutation‡	ACA in Ph ⁺ cells§, loss of MMolR§, mutation

-Therefore, the dosage was increased to **800 mg/day**, and the patient reached a Complete Cytogenetic Response

Response to Imatinib (01/2005-08/2007)

Month Response	+1	+3	+6	+12	+18	+24	+30
Hematological	No response	No response	CHR	>	>	>	>
Cytogenetic		No response	Ph+ >35 %	CCyR	CCyR	CCyR	t (9,22)+ ACA
Molecular (ng/RNA K562 GAPDH)				1.9 (BM)	0.13 (BM)	3.285 (BM)	42.87 (BM) 10.05 (PB)

PROGRESSION with Imatinib

Response \ Days	+30	+31
Peripheral blood	Normal counts	Blast cells 14%
Bone marrow	Blast cells < 5%	Blast cells 30%
Karyotype	46,XY, [18] 46, XY, der(3) t (3;?)(q26;?) , del(7q), t(9;22)(q34;q11), add(21q)[6]	
Molecular (ng/RNA K562 GAPDH)	42.87 (bm) 10.05 (pb)	
Mutational analysis	Not evaluable	<u>No mutations</u>

In the presence of ACA what would you suggest?

- 1. Search in any case for point mutation?
- 2. Follow the patient by cytogenetic analysis only
- 3. Both options 1 and 2?

August 2007 (+31 months)

- A progression to Myeloid Blast Crisis was detected
- No BCR-ABL mutations were found
- Treatment with Imatinib was stopped, and the patient started therapy with Dasatinib (70 mgx2/day)
- The patient developed a moderate pleural effusion, recovered with low-dosage steroid therapy

Response to **DASATINIB** (August 07-february 08)

Risposta	Mese	+1	+3	+6
Hematological		CHR	>	>
Bone marrow			<u>Blast cells 9%</u>	<u>Blast cells 9%</u>
Cytogenetic			46,XY, [16] 46, XY, t (3;21) (q26;q22) , del(7q), t(9;22)(q34;q11) [6]	46,XY, [4] 46, XY, t (3;21) (q26;q22) , del(7q), t(9;22)(q34;q11) [18]
Molecular (ng/RNA K562 GAPDH)			10.65 (PB)	
Mutational Analysis				F317I

March-April 2008

March 2008: pancytopenia

- Blast cells 55%
- Karyotype:
46, XY, t (3;21) (q26;q22), del(7q), t(9;22)(q34;q11) [23]

Second Myeloid Blast Crisis

-Mutational analysis: **V299L**

May–October 2008

-The patient received two cycles of standard chemotherapy, obtaining transient a Major Molecular Response (0.0073 BCR-ABL/ABL)

-November 2008: third Myeloid Blast Crisis

- Karyotype :
46,XY [3]
46,XY, t(3;21) (q26;q22), del(7)(q22), t(9;22)(q34;q11) [15]
- Molecular biology:
2.0690 bcr-abl/ABL(%) on peripheral blood

The patient received **Nilotinib** (400 mgx 2/day) for three months, without response.

He has been recently enrolled in clinical trial with **Homocetaxine**