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Persistent splenomegaly during imatinib therapy and the definition of complete hematological response in chronic myelogenous leukemia

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Splenomegaly belongs among typical findings on physical examination in patients with newly diagnosed chronic myelogenous leukemia (CML) (1). Its disappearance is a part of achieving complete hematological response (CHR), that is nowadays (when second generation of tyrosine kinase inhibitors are available) of particular interest during imatinib treatment. However, the kinetics of the disappearance of splenomegaly in patients with CML has still never been studied. We have analyzed 20 out of 245 patients with newly diagnosed chronic phase CML that had a still palpable spleen at the 3rd month of imatinib therapy in terms of treatment response at 18 months from the start of therapy. Our analysis have showed that eight (40%) of these 20 patients had achieved a treatment response at these time points. Moreover 11 patients had still a palpable splenomegaly at the 6th month after the start of imatinib therapy and 6 (54%) of them had a therapeutic response at the 18th month, suggesting that slower spleen shrinkage in patients with newly diagnosed chronic phase CML does not necessarily mean the failure of the therapy in the future.

Very recently Baccarani et al. (2) postulated the new European LeukemiaNet (ELN) criteria for the treatment response in patients with newly diagnosed chronic myelogenous leukemia in the early chronic phase. Compared to previous recommendations (3) from 2006 prepared by the same group, there is (among others) one important change: the non achievement of complete hematological response at the third month of treatment is now defined as a 'failure of therapy'. In the 2006 criteria (3), the absence of CHR at the 3rd month was defined as a suboptimal response and failure of therapy was considered only when the CHR was not present at the 6th month. In some patients even this 2006 criterion could be very strict to define failure. CHR definition namely includes the complete disappearance of initial splenomegaly. However, to our best knowledge there are no clear data about the kinetics of the shrinkage of an enlarged spleen in patients with CML during different types of therapy,

including tyrosine kinase inhibitors; namely imatinib. We would therefore like to point out that while the achievement of CHR within the meaning of blood count parameters is undoubted, splenomegaly may persist for several months even after the normalization of blood count and may not be a clear criterion for failure of this therapy in the future.

We have analyzed data from 245 patients with newly diagnosed chronic phase CML treated between 2005-2008. We have focused on the presence of palpable splenomegaly during physical examination at the third month of imatinib treatment and its further disappearance as a prognostic marker for imatinib treatment response.

One hundred and one (41%) out of 245 patients had a palpable spleen at the time of diagnosis and the start of imatinib treatment.

At the third month after the start of imatinib therapy - the time point when CHR should have been achieved according to 2009 ELN criteria (2) - 20 patients (8% from total number of our patients and 20% from the group of patients with initial splenomegaly) still had a palpable spleen. These patients were further analyzed in terms of treatment response at 18 months from the start of therapy, as well as at the last available follow up. Baseline clinical characteristics of these 20 patients are in Table 1. The median length of imatinib treatment at the time of evaluation or at the moment of treatment change in this group of patients was 19.5 months (range 3-36 months).

At 18 months from the start of imatinib treatment, 10 (50%) out of these 20 patients with persistent splenomegaly at the 3rd month had been classified (according to ELN criteria (2, 3)) as 'imatinib failure' (including 9 patients with change of treatment within the 3rd to 18th month). However, 8 (40%) had achieved a treatment response (5 optimal, 3 suboptimal) according to these criteria and 2 were not evaluable (cytogenetic data are missing). At the last follow up (median 30 months; range 16-42 months) of these 20 patients with splenomegaly at the 3rd month, 10 had still been on standard dose of imatinib and eight (40%) had achieved a

treatment response (5 optimal, 2 suboptimal and one suboptimal with very recently detected increase in *BCR-ABL* transcript levels).

There weren't any significant differences among spleen sizes below the left costal margin at the time of diagnosis in patients with persisting splenomegaly at the 3^{rd} month that had failed (median 13 cm; range 3-19 cm) or hadn't failed (median 12 cm; range 1-18 cm) the imatinib treatment at 18 months (p = 0.360; Mann-Whitney test). A high Sokal score index at the time of diagnosis was more frequent among patients with splenomegaly at 3 months that were classified as failure at 18 months (90%) compared to patients that did not fail (40%) at this point of time (p = 0.043; Fisher exact test).

Between the 3rd and the 6th months splenomegaly had disappeared in 9 of the 20 presented patients, but was still palpable in 11 of them and thus these patients fulfilled the criterion of "failure" according to the 2006 ELN criteria (3). However, when these patients were followed up at 18 months, 6 (54%) had a therapeutic response to imatinib according to the ELN criteria(2, 3), 3 (27%) had failed and 2 were not evaluable (cytogenetic data are missing). Finally, one patient out of 20 with splenomegaly at the 3rd month had a palpable spleen at 12 months. This patient had an optimal response at 18 months (Table 2.).

During the natural course of CML, the spleen is infiltrated by Philadelphia-chromosome (Ph) positive cells, causing its enlargement. Interestingly, the spleen may be more important than the bone marrow for futher karyotypic evaluation of Ph positive cells that announce the transformation to advanced phases of the disease (4, 5).

We know from the work of Kamada et al. and other researchers, that spleen enlargement correlates with the grade of leukocytosis as a marker of disease burden, as well as with the progression of CML to advanced stages and thus with the prognosis of patients with this malignancy (6, 7). However, data showing that slower treatment response in splenomegaly corresponds with imatinib failure are missing.

Our data, from patients with chronic phase CML that were treated with front-line imatinib with persistent splenomegaly at the third month, denotes that even though the frequency of imatinib failure at the 18th month seems to be higher than in the general population of patients with chronic phase CML, solely its presence at the third month does not necessarily mean failure of imatinib therapy in the future in each individual patient.

In the view of published recommendations of Baccarani et al.(2) all 20 presented patients that do not reach the complete hematological response due to persistent splenomegaly at the third month would have been classified as 'failure of imatinib therapy' and should have been switched to the second generation of tyrosine kinase inhibitors or allogeneic stem cell transplantation should be offered to them. However, as showed, 40% of them did not need this change in therapy during all the observed period and might not need it in the future. Thus, in our opinion and based on our data mentioned above, previous recommendations from European LeukemiaNet (3) where not achieving complete hematological response at the third month of imatinib treatment was only the 'suboptimal response' were probably more appropriate for routine clinical practice.

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Tables

Table 1. Patients characteristics.

Table 2. Response of patients with persistent splenomegaly at the 3rd, 6th and 12th months assessed at 18 months after the start of imatinib treatment according to European LeukemiaNet criteria (2).

Table 3. Patients with splenomegaly at the 3rd month – baseline characteristics, white blood cell count, white blood cell differential count, cytogenetic response, molecular response and treatment of chronic myelogenous leukemia at the 3rd, 6th, 12th, 18th months and at the last follow up. Gray fields - not performed. Black fields - not applicable. (* - spleen size in cm bellow costal margin; ^a - patient refused bone marrow examination after the 3rd month; WBC - white blood cells; WBC diff. - white blood cell differential count; eos. - eosinophiles; baso. - basophiles; myeloc. - myelocytes; minim. CgR - minimal cytogenetic response; PCgR - partial cytogenetic response; CCgR - complete cytogenetic response;

59 60

Table 1. Patients characteristics

7		
8	Characteristics	No. (%) or median [range]
10	Total No. of pts.	245
13	No. of pts. with splenomegaly at diagnosis	101 (41%)
15 16		
17	No. of patients with splenomegaly at the 3 rd month	20 (8% of total No. of pts. and 20% of
19 20 21 22 23 24 25 26 27 28 29 30 31		pts. with splenomegaly at diagnosis)
23	Male/ female	8/12
25 26	Sokal index low/intermediate/high	2 (10%)/ 5 (25%)/ 13 (65%)
27 28	Additional cytogenetic abnormalities in Ph+ clone	2 (10%)*
30	Median hemoglobin level at the time of diagnosis (g/l)	93 [60-158]
32	Median leukocyte count at the time of diagnosis (10 ⁹ /l)	110 [42-612]
35	Median thrombocyte count at the time of diagnosis (10 ⁹ /l)	394 [95-1695]
32 33 34 35 36 37 38 39	Median spleen size at the time of diagnosis (cm)	13 [1-19]
40	Median spleen size at the 3 rd month of imatinib treatment (cm)	4,5 [1-15]
41 42 43		
44 45	No. of patients with splenomegaly at the 6 th month	11 (4.5% of total No. of pts. and 11% of
45 46 47 48		pts. with splenomegaly at diagnosis)
49	Median spleen size at the 6 th month of imatinib treatment (cm)	1 [1-6]
51		
53 54	No. of patients with splenomegaly at the 12 th month	1 (0.4% of total No. of pts. and 1% of
52 53 54 55 57 58		pts. with splenomegaly at diagnosis)
58		

^{*} only 19 patients were evaluable for this analysis

Table 2. Response of patients with persistent splenomegaly at the 3rd, 6th and 12th months assessed at 18 months after the start of imatinib treatment according to European LeukemiaNet criteria(2)

Response at 18 months	Optimal	Suboptimal	Failure	Not
				evaluable
Presence of splenomegaly	5 (25%)	3 (15%)	10 (50%)	2 (10%)
at the 3 rd month (n=20)				
Presence of splenomegaly	4 (36%)	2 (18%)	3 (27%)	2 (18%)
at the 6 th month (n=11)				
Presence of splenomegaly	1 (100%)	-	-	-
at the 12 th month (n=1)				

	At diagnosis At the 3rd month							At the 6th month						At the 12th month							At the 18th month					At the last follow up						
Patient No.	Gender	Age	Sokalindex	Spleen size⁺	WBC x 10.9/I	Aditional cytogenetic abnormality	WBC x 10.9/I	WBC diff.	Spleen size*	Cytogenetic response	Molecular response	Chnage of therapy from IMA 400 mg/day	WBC x 10.9/I	WВС diff.	Spleen size*	Cytogenetic response	Molecular response	Chnage of therapy from IMA 400 mg/day	WBC x 10.9/I	WBC diff.	Spleen size*	Cytogenetic response	Molecular response	Chnage of therapy from IMA 400 mg/day	WBC x 10.9/I	WBC diff.	Spleen size*	Cytogenetic response	Molecular response	Chnage of therapy from IMA 400 mg/day	Therapy with IMA 400 mg/day	The best achieved response at this timepoint
1	М	40	Н	14	187	no	6	normal	8		none	no	5	normal	0	PCgR	none	no	10	normal	0	PCgR	none	no	7	normal	0		MMoR	no	yes	MMoR
2	F	61	Н	18	58	no	8	normal	15		none	no	10	baso. 5%; other normal	6	CCgR	none	no	10	normal	2	CCgR	MMoR	no	10	normal	0	CCgR	MMoR	no	yes	CMoR
3	М	30	L	11	398	no	6	normal	5		none	no	6	normal	1		none	no	6	normal	0	CCgR	MMoR	no	5	normal	0	CCgR	none	no	yes	CCgR and recently detected increase in BCR- ABL transcript
4	F	36	L	1	55	no	10	eos. 10%; other normal	1		none	no	9	normal	0	PCgR	none	no	13	normal	0		none	no	9	normal	0	CCgR	none	no	yes	CCgR
5	М	36	Int.	14	5	no	6	normal	5		none	no	5	normal	1	CCgR	none	no	5	normal	0	CCgR	MMoR	no	5	normal	0	CCgR	MMoR	no	yes	MMoR
6	М	32	Int.	12	612	no	6	normal	7		none	no	6	normal	2	PCgR	none	no	7	normal	0	CCgR	none	no	8	normal	0	CCgR	none	no	yes	CCgR
7º	М	33	Н	14	457	trisomy 8	5	normal	8	minim. CgR	none	no	6	metamyelo. 1%; myelo. 1%; other normal	1		none	no	9	normal	0		none	no	6	normal	0		none	no	yes	NA
8	F	38	Int.	12	91	no	4	normal	5	none	none	no	5	normal	1		none	no	5	normal	0	PCgR	MMoR	no	4	normal	0	CCgR	MMoR	no	yes	MMoR
9	F	60	Н	1	31	no	3	normal	4		none	no	4	normal	1	CCgR	none	no	4	normal	0	CCgR	MMoR	no	3	normal	0	CCgR	MMoR	no	yes	CMoR
10	F	57	Int.	2	49	no	2	normal	1		none	no	3	normal	1	PCgR	none	no	3	normal	0	minor CgR	none	no	2	normal	0		none	no	yes	minim. CgR
11	М	49	Н	13	429	no	8	normal	6		none	no	6	myeloc. 1%; other normal	2		none	no	5	normal	0	none	none	no	3	normal	0	minim. CgR	none	no	no - dasatinib	
12	F	36	Н	3	92	no	4	normal	1		none	no	4	normal	0	none	none	no	5	normal	0	CCgR	none	no	4	normal	0	PCgR	none	yes - imatinib 600 mg/day		
13	F	55	Н	13	252	no	1	normal	8		none	no	2	normal	0	PCgR	none	no	2	normal	0	minim. CgR	none	yes - dasatinib								
14	F	53	П	19	127	no	3	normal	1	none	none	no	5	normal	0	PCgR	none	no	7	baso. 12%; metamyelo. 2%; other normal	2	non + addit. abnorm.	none	yes-allo HSCT								
15	F	24	Int.	13	84	no	2	eos. 9%; other normal	3		none	no	3	normal	0	minim. CgR	none	no	4	normal	0	minim. CgR	none	yes - dasatinib								
16	F	54	Н	12	72	no	5	normal	8		none	no	3	baso. 6% and other normal	5	minor CgR	none	no	6	normal	0	minim. CgR		yes - dasatinib								
17	F	61	н	8	340	no	6	baso. 8%; eos. 6%; other normal	3		none	no	6	baso. 8%, metamyelo. 8%; other normal	0	none	none	no	17	baso. 11%; metamyelo. 4%; myelo. 2%; blasts1%	0	minim. CgR	none	yes - dasatinib								
18	М	34	Н	14	350	no	4	normal	2		none	no	4	myeloc. 1%	2	minor CgR	none	yes - allo HSCT														
19	М	68	Н	15	372	no	16	normal	3	minor CgR	none	no	7	myeloc. 1%	0	none	none	yes - dasatinib														
20	F	30	Н	15	32	del 9q	2	blasts 5%; other normal	3		none	yes - allo HSCT																				