Philadelphia-Positive B-Acute Lymphoblastic Leukemia: Does it Differ from Philadelphia-Negative One in Egyptian Populations?

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Dear Editor,

In Egypt, the annual incidence of ALL is approximately four cases per 100 000 children per year in the National Cancer Institute (NCI) Cairo University. ALL constitute 30% of all pediatric malignancies and 70% of pediatric leukemias. Cases show a male to female ratio of 2.3:1. The 2-10 years age group constitutes 68.5%.[1] Approximately one-fourth of adult B-ALL expresses the oncogenic protein BCR-ABL1 that reflects a balanced reciprocal translocation between the long arms of chromosome 9 and 22 [t (9;22)(q34;q11)] involving the BCR and ABL genes. At present, detection of BCR/ABL gene rearrangement is mandatory in B-ALL patients at diagnosis for prognostic stratification and treatment decision.[2] Significant advances in treatment of Ph–positive ALL have been made since the discovery of Imatinib which is a selective ABL tyrosine kinase inhibitor. Whereas the outcome with standard chemotherapy was previously poor, incorporation of Imatinib into treatment protocol has improved survival.[3] Little evidence exists regarding the prevalence, clinical outcomes and molecular response of adult patients with Ph+ versus Ph- B-ALL in our country. The aim of our study was to explore the presence of minor BCR-ABL (P190) gene in Egyptian B-ALL patients and correlate it with treatment outcome. Quantitative assessment of minor BCR-ABL gene expression was performed by qRT-PCR in 48 Egyptian B-ALL patients. All patients received classic ALL treatment in addition to TKI (Imatinib) in the minor BCR-ABL +ve patients. Among 48 patients of newly diagnosed B-Acute lymphoblastic leukemia, 21% of all patients possess Ph chromosome. Patients presenting with Ph+ve ALL differed from those with Ph-ve ALL at some aspects as shown in Table 1a and 1b, firstly regarding the clinical data, the present study showed that median age is slightly higher; also the most presenting symptoms in Ph+ve patients were easy fatigability and fever while bleeding, hepatomegaly and seplenomegaly were only 10%. These findings were different from Ph-ve patients although the difference was sometimes not significant. Our data compared to study from Pakistan and Singapore showed similarity regarding incidence, age and presentation.[4-5] Regarding laboratory data, many studies including ours showed that Ph+ve is associated with higher initial leukocyte counts and more blasts in the peripheral blood and bone marrow.[4-5] In respect of immunophenotyping, similar to western data,[6] the present study showed that CD19, CD22 and CD79a % were higher in the Ph+ve, while data from Asian study reported that CD10 expression had significant difference.[7]

Regarding the treatment outcome as shown in Figure 1 and 2, the disease free survival was significantly higher among Ph+ve patients than Ph-ve patients (p= 0.049). This finding compared to older studies prior to use of Imatinib in Ph+ ALL showed that Ph+ patients had poorer outcome.[7-9]

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Table 1a. Clinicopathological parameters according to Ph status

	PH +VE (n= 10)		PH –VE (n= 38)		P value
	N	%	N	%	
Sex					
Male	4	40.0	25	65.8	0.164
Female	6	60.0	13	34.2	
Easy fatigability					
Yes	7	70.0	15	39.5	0.152
No	3	30.0	23	60.5	
Fever					
Yes	7	70.0	20	52.6	0.478
No	3	30.0	18	47.4	
Bleeding tendency					
Yes	4	40.0	9	23.7	0.425
No	6	60.0	29	76.3	
Hepatomegaly					
Yes	1	10.0	9	23.7	0.664
No	9	90.0	29	76.3	
Splenomegaly					
Yes	1	10.0	14	36.8	0.140
No	9	90.0	24	63.2	
Lymphadenopathy					
Yes	3	30.0	15	39.5	0.722
No	7	70.0	23	60.5	

Table 1b. Clinicopathological parameters according to Ph status

	PH +VE (n=10)	PH –VE (n=38)	P value
Age (years)			
Mean ± SD	37.9 ± 12.0	31.2±13.5	0.169
Median	42.5	26.0	
IQR	26.0 - 46.0	20.0 - 43.0	
TLC (x10^3/cm^3)			
Mean ± SD	58.8 ± 72.8	41.0 ± 52.5	0.203
Median	30.0	20.1	
IQR	19.8 - 53.1	2.5 - 72.9	
Hb (g/dL)			
Mean ± SD	7.9 ± 1.8	8.5 ± 2.1	0.458
Median	8.3	8.6	
IQR	7.2 - 9.0	7.3 - 10.0	
PLTs (x10^3/cm^3)			
Mean ± SD	55.2 ± 27.3	58.0 ± 47.6	0.611
Median	55.0	41.0	
IQR	29.0 - 80.0	20.0 - 86.0	
PB blasts %			
Mean ± SD	62.1 ± 22.8	64.1 ± 26.6	0.816
Median	57.0	70.5	
IQR	43.0 - 90.0	45.0 - 89.0	
Bone marrow aspirate (BM blasts %)			
Mean ± SD	94.7 ± 3.7	82.8 ± 23.5	0.483
Median	95.0	95.0	
IQR	90.0 - 99.0	76.0 - 99.0	
CD 19			
Mean ± SD	83.6 ± 17.7	80.3 ± 15.6	0.341
Median	91.2	84.4	
IQR	70.0 - 96.0	72.0 - 93.0	
CD 22			
Mean ± SD	67.5 ± 15.8	61.8 ± 20.8	0.431
Median	68.5	62.5	
IQR	57.0 - 82.0	43.0 - 82.0	
CD 79a			
Mean ± SD	71.6 ± 27.1	68.1 ± 19.2	0.509
Median	77.0	68.2	
IQR	62.0 - 94.4	54.0 - 84.0	
CD 10			
Mean ± SD	54.0 ± 33.1	60.6 ± 29.6	0.594
Median	55.0	64.0	
IQR	18.0 - 88.0	32.0 - 90.0	

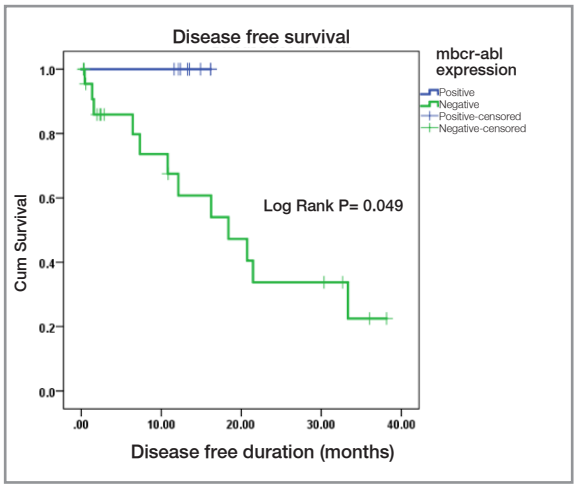

Figure 1. Disease Free Survival according to Ph chromosome status.

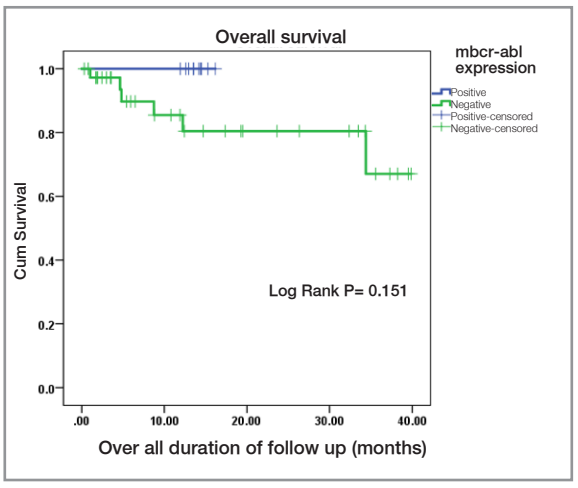

Figure 2. Overall Survival according to Ph chromosome status

Concerning Molecular response (MR), in the present study after receiving chemotherapy accompanied with Imatinib, minor BCR-ABL fusion gene was expressed in mRNA of patient leukocyte (Mean ± SD = 0.006± 0.006), with a 3 log reduction from baseline ratio. This is in accordance with the results previously reported that when Imatinib is added to induction therapy, minor BCR-ABL , mRNA was reduced at least 1 log from baseline after the first induction therapy. In conclusion The TKIs have significantly improved outcomes for adult patients with Ph-positive ALL, with the use of imatinib in combination with intensive chemotherapy early in the treatment course, and continuing through consolidation and maintenance considered as the current standard of care. Over the coming years, the treatment of adult ALL will certainly change from disease-type to molecular-target type and from risk-stratified treatment schedules to more personalised therapies. Determination of cytogenetics, molecular and biological characteristics of the disease would be helpful in identifying high-risk features relevant to local population and in advocating risk adapted therapy. With a potentially enlarging cohort of patients, focus needs to be on molecular targeted therapy along with improvements in upfront therapy and reducing treatment-related morbidity.

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