Chronic myeloid leukemia - Biology (16)

B1348
BCL-XL EXPRESSION AS A POTENTIAL PROGNOSTIC PARAMETER IN CHRONIC MYELOID LEUKEMIA

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Background: Chronic myeloid leukemia (CML) is characterized by the presence of the Ph chromosome (*BCR/ABL* chimeric gene) in hematopoietic stem cells. Clinically, it is manifested in three distinct phases: chronic, accelerated, and blastic. *BCR-ABL* expression results in constitutive activation of STAT5 which contributes to increased expression of the anti-apoptotic Bcl-2 family member *Bcl-xL*.
Aims: The aim of this work was to investigate the role of *Bcl-xL* expression in CML progression into advanced phases and its possible significance as a prognostic parameter.
Methods: The study was conducted on 32 CML patients including 12 males and 20 females with an age range of 21-79 and a median of 41.5 years. They included 18 in chronic (Group I), 3 in accelerated and 11 in blastic crisis phase (Group II). Hasford score was available for 30 patients. They were divided into 3 risk groups: Low risk group: score 780 (8 patients), Intermediate risk group: score 781-1480 (13 patients) and High risk group: score > 1480 (9 patients). Patients received standard therapy. *Bcl-xL* expression was assessed by RT-PCR; it was studied in relation to various hematological and clinical parameters. The study was approved by the IRB of the NCI, Cairo University and a written informed consent was obtained from all participants.
Results: *Bcl-xL* expression did not differ according to the disease stages. Within group I, TLC and % basophils were significantly higher in patients with *Bcl-xL* positive than those with *Bcl-xL* negative (P=0.004 and 0.02 respectively). Hasford Score was available for 15 cases in group I and 15 in group II; it was significantly higher in group II (1383.16±1259.98 vs.1122.97±474.43, p value=0.01). Within group I, *Bcl-xL* showed a statistically significant higher expression in patients in high risk group according to Hasford score than patients in intermediate or low risk groups The difference was statistically significant in the total cohort (P=0.01) and in group II (P=0.046) but insignificant in group I. A statistically significant better outcome was observed in *Bcl-xL* negative patients as compared to *Bcl-xL* positive ones (P=0.05).
Summary / Conclusion: *Bcl-xL* is not involved in the mechanism(s) underlying the progression into accelerated phase or blastic crisis in CML. However it might serve as a prognostic parameter.

B1349
BCR-ABL KINASE DOMAIN MUTATION FREQUENCY IN CHRONIC MYELOID LEUKEMIA (CML) PATIENTS RESISTANT TO IMATINIB THERAPY

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Background: The major mechanism of resistance to imatinib and another inhibitors of tyrosine kinases of patients with chronic myeloid leukemia (CML) is the mutations in the locus between exon a3 and exon a11 in *ABL* gene, which present in *BCR-ABL* fusion tyrosine kinase and its mRNA. According to recommendations European Leukemia Net (ELN) sequencing of the *BCR-ABL* kinase domain is a necessary analysis for all patients with CML with primary reduced capacity of imatinib to inhibit kinase activity.
Aims: Analysis of incidence mutations frequency in the BCR-ABL kinase domain in patients with chronic myeloid leukemia (CML) with resistance to imatinib therapy.
Methods: Present study involves 846 CML patients with resistance to imatinib therapy in 68 hospitals of 53 cities of Russia during 85 months from January 2006 to February 2013. The patients had different disease stage. Efficiency of imatinib therapy was analyzed in GeneTechnology LLC Molecular Oncology and Hematology Lab in Moscow by RQ-PCR of *BCR-ABL* transcript according IS (International Scale). Identification of point mutations in the locus between exon a3 and exon a11 in mRNA *BCR-ABL* was performed by direct sequencing of the *BCR-ABL* kinase domain.

Fig. 1. Distribution among CML stages and frequency of mutations coursing resistance to 2nd generation ITKs.

Mutation	CML (CP), N=129	CML (AP), N=78	CML (BC),N=55	Resistance
T315I	5,4%	16%	27%	Imatinib, Nilotinib, Dasatinib
E255K/V F359V/C Y253H	6,2% 9,3% 5,4% } 20,9%	12,8% 7,7% 8,9% } 29,4%	16,4% 2,7% 7,3% } 26,4%	Imatinib, Nilotinib
F317L/I	4,6%	12,8%	16,4%	Imatinib, Dasatinib

Results: 31% (n=262) patients with CML and resistance to imatinib therapy had mutations in the *BCR-ABL* kinase domain, among them 59,9% men (n=157) and 40,1% women (n=105), median age – 50 (from 15 to 74). As well as5,7% patients (n=16) had two mutations, we were detected 278 mutations from 262 patients with CML. Total amount of mutations comprise 40 variations sorting by decrease: T315I or G250E (35/262 – 12%); T317L (33/262 –7,9%); M244V (21/262 –7,5%); F359V, H396R or Y253H (18/262 –5,6%); E255K (16/262 –5,7%); E255V, L248V or M315T (11/262 –3,9%); E355G (8/262 –2,8%); F359C (7/262 –2,5%); del ex7, Q252H or L387F (5/262 –1,8%); S348L (4/262 –1,4%); Ins 98-72 bp, F317I or E255D (3/262 –1,1%); E275K, E279A, K247R, L387M or V299A (2/262 – 0,7%); E292V, E334G, E450K, E459A, E459K, F359I, F486S, L383F, P441L, Q252M, Q491L, T305I, T345I, Y312C, T520S or G425Stop (1/262 – 0,3%). Double mutationswere associatedwith the variations in the P-loop domain. The median of detecting mutations was 27 months (from 3 to 83 months). Part of the mutations (include T315I) with resistance to nilotinib comprised 40,3%, to dasatinib – 21% (Table). 69% (n=584) patients with CML and resistance to imatinib therapy had not mutations in the *BCR-ABL* kinase domain, among them 46% men (n=268) and 54% women (n=316), median age – 51 (from 24 to 74).
Summary / Conclusion: Present study confirmed essential influence mutations in *BCR-ABL* kinase domain on resistance to imatinib therapy (for 31% patients). But in 2/3 cases resistance to inhibition of the tyrosine kinases associated with no *BCR-ABL* mutations. We also indicated that besides well know point substitutions took place another mutations that lead to essential alteration in protein structure and cause resistance. Patients during imatinib therapy had significant count mutations in *BCR-ABL* domain of leading to resistance to second-line inhibitors of tyrosine kinase. As the result it is necessary to identify *BCR-ABL* mutations for changing therapy to using dasatinib and nilotinib. Similar structure of imatinib and nilotinib explained that common sets of mutations of resistance to nilotinib therapy are prevailed over mutations of resistance for dasatinib. If dasatinib and nilotinib will move to first-line therapy the change of this situation is expected.

B1350
LOWER INCIDENCE OF CML IN O BLOOD GROUP AND SECRETOR INDIVIDUALS

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Background: ABO blood groups have been associated with many bacterial, fungal infections, and malignancies.
Aims: To examine such association and the possibility of explaining it, through studying (591) patients with hematological malignancies (HM); AML, ALL, CML, CLL, HL, NHL, and MM, compared to (196) blood donor controls
Methods: Standard conventional techniques were used for ABO; Rh grouping. Secretor status was determined by Lewis blood grouping and haem-agglutination inhibition test.Informed consents were obtained from both patients and controls according to medical ethics regulation.
Results: ABO & Rh blood groups and secretor status results showed no significant difference from controls, except in CML patients; where blood group A incidence was significantly (*P: 0.0007*) higher (55.0 %) than normal control (32.1%) and than other (HM) (31.3%) (*P: 0.0001*). Blood group O was significantly (*P: 0.0074*) lower in CML (21.7%) than normal (38.3%) and than other (HM) (41.4%) (*P: 0.0015*). No significant difference in the secretor status was found between different (HM) but a significant lower incidence was found in CML (60%) as compared to controls (74.0%)(*P: 0.0187*), and to other (HM) (73.6%)(*P: 0.0127*). Also there was a lower incidence of secretor status in CML patients with O blood group (45.5%) as compared to controls and to other (HM) patients (*P: 0.0197)(P: 0.0198*) respectively.
Summary / Conclusion: A significant lower frequency of O blood group was found in patients with CML. This means blood group O individual are protected from CML. This can be explained at least partially, by the higher frequency