Секция «Тезисы на английском языке»

The genetic analysis of BCR-ABL+ clone with del. c.1086-1270 (p.R362fs*21) in Russian patients with chronic myeloid leukemia

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Background

One of the most controversial causes of the resistance to tyrosine kinase inhibitors (TKI) in patients with CML is the pathogenic significance of the transcript BCR-ABL del. c.1086-1270. This mutation was first described by Curvo et al. (2008) and was thought to confer TKI resistance. Then it was suggested that the exon 7 deletion (del. c.1086-1270) can cause the TKI-resistance.

Transcript BCR-ABL del. c.1086-1270 encodes truncated fusion protein BCR-ABL p.R362fs*21 and it can appear as the result of alternative splicing. Previously, computer modeling have shown that such truncated protein has no chance to have tyrosine kinase activity because of the damage in the ATP-binding site. However, we suggest that the expression of pathogenic effect of BCR-ABL p.R362fs*21 can be attained by the dimerization with a typical protein BCR-ABL p210. Such mechanism has already been proved for the splice variant of serine-threonine kinase BRAF.

Aims

Assessment of the impact BCR-ABL-del. c.1086-1270 (p.R362fs*21) in the TKI-resistance in Russian CML patients.

Methods

33 male and 49 female CML patients (age 24-80) with BCR-ABL transcript level $> 0.1\%$ were included in the study. BCR-ABL del. c.1086-1270 was estimated by nested PCR followed by Sanger sequencing. Initial screening for deletions was performed by means of fragment analysis (Applied Biosystems 3130).

Results

92 DNA specimens isolated from 82 CML patients were tested. BCR-ABL del. c.1086-1270 (p.R362fs*21) was found in 32 patients (39%). 15 out of 32 (47%) patients with deletion were TKI sensitive while 17 (55%) were TKI resistant. In one TKI resistant case BCR-ABL del. c.1086-1270 was accompanied by BCR-ABL c.844G[U+02C3]C p.E282Q point mutation not described so far. This mutation was found in BCR-ABL del. c.1086-1270 transcript only and was absent in «wild type» Bcr-Abl p21 transcript.

Direct sequencing has showed that in all TKI-resistant patients the tumor clone which contains the BCR-ABL1 del.c.1086-1270, always paired with a normal clone of BCR-ABL p210. This fact could be verified by the results of electrophoresis on agarose gel. This is the indirect evidence of the dimerization of the protein BCR-ABL del. c.1086-1270 with chimeric protein Bcr-Abl p210.

Furthermore, the deletion clone in each TKI-resistant patient always goes together with a point mutation (F317V, F317L, E282Q, M351T, T315I), which is unlikely for the normal. This fact contradicts with the theory of alternative splicing. Moreover a new point mutation c.844G[U+02C3]C p.E282Q was detected in one of the clones of BCR-ABL1 del.c.1086-1270.

Summary/Conclusions

The results of the study of Russian CML-patients show a definite correlation between the presence of the deletion and TKI-resistance. The deletion is likely to play a trigger-role in the formation of TKI-resistance: clones with the exon 7 deletion is very tends to the accumulation of combined point mutations, which in many times increase the TKI-resistance.