MOLECULAR CYTOGENETICS AND CLINICAL DATA OF A CHRONIC MYELOID LEUKEMIA PATIENT WITH A NEW THREE-WAY T(5;9;22) ASSOCIATED TO A POOR OUTCOME

Rocha MM[1], Monteso K[1,2], Pinto ILS[3], Lima LBA[3], Matos RRC[1,2], Otero L[1], Ferreira E[1], Gonzaga YBM[3], Silva MLM[1,2], Abdelhay E[1,4]

[1]Cytogenetics Department, Bone Marrow Transplantation Unit, Instituto Nacional de Câncer (INCA-RJ), Rio de Janeiro, Brazil

[2]Post-Graduate Program in Oncology, Instituto Nacional de Câncer (INCA-RJ), Rio de Janeiro, Brazil

[3]Hematology Department, Instituto Nacional de Câncer (INCA-RJ), Rio de Janeiro, Brazil

[4]Stem Cells Department, Bone Marrow Transplantation Unit, Unit, Instituto Nacional de Câncer (INCA-RJ), Rio de Janeiro, Brazil

OBJECTIVE

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disease characterized by the translocation t(9;22)(q34;q11) which juxtaposes *ABL1* and *BCR* genes, forming the *BCR-ABL1* fusion gene. This rearrangement is identified by the presence of the Philadelphia chromosome (Ph) in the leukemic cells.

Cytogenetic analysis of bone marrow and/or peripheral blood allows the identification of the Ph translocation and other chromosome abnormalities that are associated with this leukemic process. Here we present a new Ph variant three-way translocation t(5;9;22)(q13;q34;q11), detected by G-banded karyotyping and FISH technique during patient treatment with tyrosine kinase inhibitors, associated to trisomy 21 (+21) and a second Ph (+Ph).

MATERIAL AND METHODS

A 56-year-old woman was admitted to the Cancer National Institute (INCA) with leukostasis symptoms and weight loss. At admission, her white blood cell count was 525 x 10^9/l, platelet count was 132 x 10^9/l, hemoglobin was 9,4 g/dl, and DLH was 2.184UI/l. Physical examination revealed splenomegaly (2cm). Bone marrow aspirates were processed in 24 hours cell cultures (Cytogenetics Laboratory, INCA, RJ).

Cytogenetic and molecular analyses were performed according to standard protocols. The karyotypes were described according to the International System for Human Cytogenetic Nomenclature. The patient was classified as low risk and was treated with Imatinib 400mg/dl. Treatment had to be stopped twice (hepatotoxicity CTC level 3 and skin rash CTC level 3).

RESULTS

At diagnosis, an FISH assay revealed a *BCR-ABL1* fusion gene. At the sixth month of treatment, the cytogenetic analysis (Figure 1) showed the complex karyotype 48,XX,t(5;9;22)(q13;q34;q11), associated to +der(22)t(9;22)(q34;q11),+21,+Ph, further confirmed by FISH (Figure 2 and 3). At that moment, the patient was in hematological response.

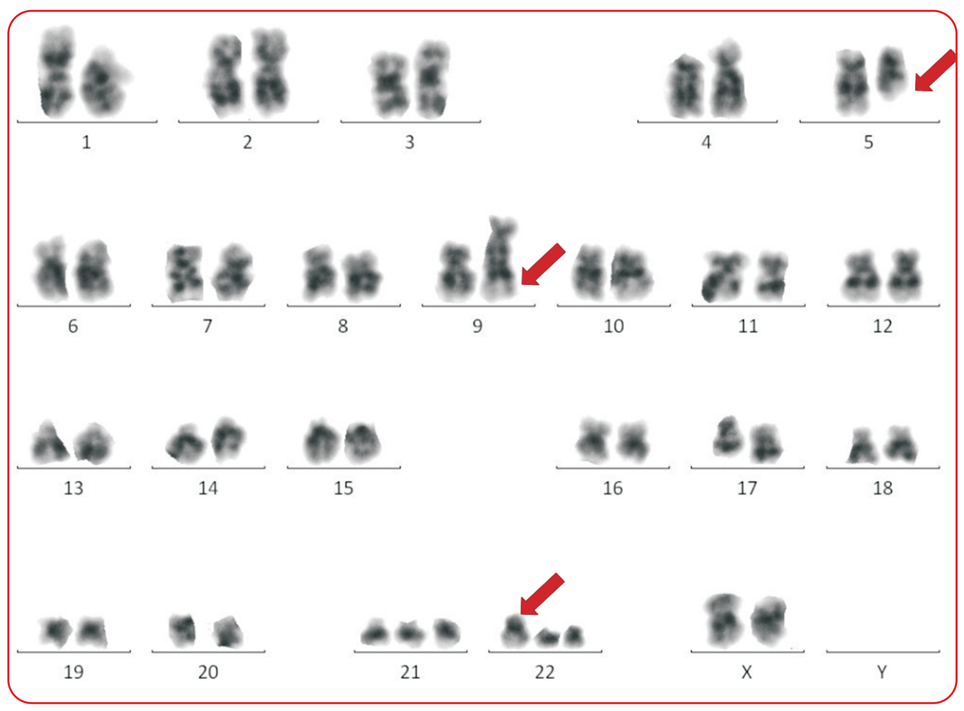

Figure 1: G-banded karyotype showing 48,XX,t(5;9;22)(q13;q34;q11),associated to +der(22)t(9;22)(q34;q11),+21,+Ph

DISCUSSION

It is possible to observe a different rearrangement involving 22q11, 9q34 and one or more additional chromosomal regions generating the *BCR-ABL1* fusion in 5–10% of CML cases. Variant translocations may have a negative impact on prognosis if they occurred in the setting of advanced phases.

Besides, additional cytogenetic alterations in Ph-positive cells can be found in 5% of patients at diagnosis, but are more commonly observed in advanced disease phases, being about 30% in accelerated phase and up to 80% in blast phase. These abnormalities can be represented by trisomy 8 (+8), isochromosome (17q), trisomy 19 (+19) and a second Ph (+Ph), and minor route represented by monosomy 7 (-7), monosomy 17 (-17), trisomy 21 (+21), loss of Y chromosome (-Y) and t(3;21) (q26; q22).

In this work, we describe for the first time a new three-way translocation involving chromosomes 5, 9 and 22, associated with additional abnormalities, +21 and +Ph, detected six months after initial diagnosis. Such cytogenetic abnormalities, commonly observed in the blast phase, are usual when the patient is not responsive to treatment. Interestingly, these abnormalities were found during treatment, when our patient was in hematological response but with no molecular response. Soon after, she presented a blast phase (24% myeloid blasts). She started Dasatinibe 140mg/dia, but developed pulmonary hypertension, so the medication had been discontinued, and she was treated with 7+3 protocol. At D14 she was aplasized. At D19 she died due to fungal infection.

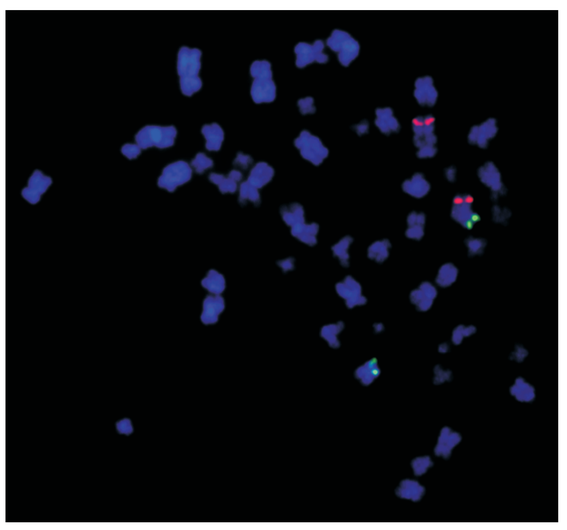

Figure 2: Vysis LSI EGR1/D5S23, D5S721 Dual Color Probe Set confirmed the t(5;9). The sole red signal shows the derivative chromosome 9 and the sole green signal shows the derivative chromosome 5.

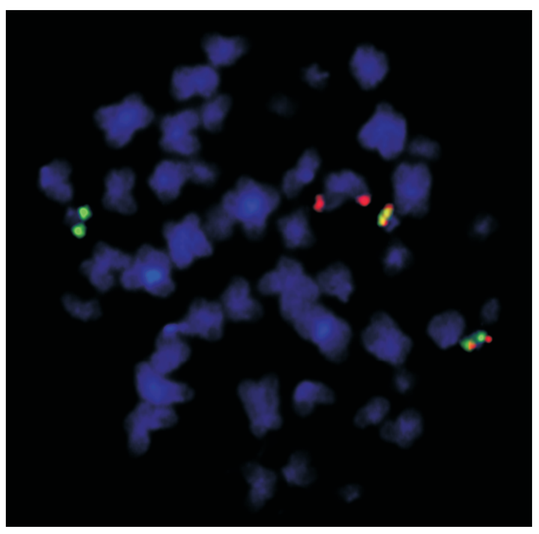

Figure 3: LSI BCR-ABL1 Dual color, dual fusion probe confirmed the gene fusion.

CONCLUSION

Thus, it is important to highlight that despite the advent of molecular assessment, banding cytogenetics and FISH still have a significant role in diagnostic and prognostic approaches to CML.

Projeto Gráfico: Setor de Edição e Informação Técnico-Científica / INCA