TRABAJOS ORIGINALES

Study of patients diagnosed with Chronic Myelogenous Leukemia treated with STI 571 (Gleevec) in Ecuador

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RESUMEN. Se considera como principal marcador de la Leucemia Mieloide Crónica (LMC) la translocación t(9;22) o cromosoma Ph que ocurre en un 90 - 95% de pacientes con LMC.

Uno de los tratamientos más efectivos es el Gleevec cuyo blanco son las células Ph positivo. Una ventaja de esta nueva droga es la discriminación entre células normales y anormales, y la inducción de apoptosis. Se estudiaron 31 pacientes: 13 en fase crónica, 12 en fase acelerada y 6 en crisis blástica a lo largo de 1 año. Se obtuvo remisión hematológica en todos los casos de fase crónica, pero en los pacientes en fase acelerada y crisis blástica respondieron aproximadamente el 50%. La remisión citogenética ocurrió en un 79% de fase crónica y varía de un 17 a 32 % en fase acelerada y crisis blástica. No existió remisión molecular en ningún paciente. El análisis genético es una buena herramienta para determinar la efectividad del tratamiento y seguimiento de los casos de leucemia.

PALABRAS CLAVE. STI 571, leucemia mieloide crónica, *BCR/ABL*, kinasas, fase crónica, fase acelerada, crisis blastica.

The Philadelphia chromosome is the first cytogenetic marker present in Chronic Myeloid leukemia (1-3) which is the result of the reciprocal translocation t(9;22)(q34:q11) occurring in 90 to 95% of CML patients (3). The molecular consequence of the translocation is the fusion of the proto-oncogen *abl* and the bcr gene (4, 5). It produces a fusion protein of 210 kD (p210) or 190kD (p190) (4) that functions as a tyrosine kinase which is essential to the pathogenic roll of CML (2, 6-7). Currently, a derived compound

of 2-phenylaminopyrimidine called STI571, which is a potent and selective inhibitor for *abl* tyrosine kinases (8).

In order to evaluate the effect of therapy in CML Ecuadorian patients treated with STI 571 a monthly hematological evaluation was performed during one year. To determine the presence of the BCR/ABL junction, RNA was extracted from bone marrow using a RNAesy mini kit (QIAGEN, Md, USA); followed by RT-PCR (M-MLV and random primers) using primers described (8). The cytogenetic study was carried out with RPMI-1640 medium (enriched with: L-glutamine, calf serum and antibiotic-antimicotic) in which the bone marrow was cultured for 24 and 48 hours. Thirty one CML patients were positive for the Philadelphia chromosome, and only one was Ph-/BCR-ABL+, 8 females, 23 males, age range 19-60 years were divided into three groups: chronic phase group (13), accelerated phase group (12) and blastic phase group (6) (see table 1). The treatment with STI 571 was initiated after 1 month of the termination of previous treatment. All patients were Interferon α resistant after receiving 6 million units INFα three times a week, which means that within 6 months there was no cytogenetic remission. Complete blood cell counts were done once a week in the first month and once a month thereafter. Assessments using bone marrow were performed every 3 months. Hematological response tests show that each patient had in the bone marrow a blast count below 5%. The patients in chronic phase group (N=13) were treated with daily $\geq$400mg of STI 571 and hematological response occurred in 100% of cases. Accelerated and blastic phase groups were treated with daily 600mg that were escalated to 800mg/day if the blast count increased. In 50% (6/12) of patients in the accelerated phase group, and 33% of the blastic phase group had an hematological response (4) but 50% (6/12) of the accelerated phase group and 67% (4/6) of the blastic phase group did not respond to the treatment; 8 patients died and 2 progressed to the blastic phase. Other reports show that the hematological response usually occurred within two weeks of the start of the therapy (4). This study shows a similar response that occurred one to three weeks after therapy was initiated in all cases. The term cytogenetic response, which refers to the partial or complete absence of Philadelphia (Ph) chromosome, occurred in 79% of patients (9/13) in the chronic phase group, in 32% (4/12) of patients in the accelerated phase group, and in 17% (1/6) patients of the blastic phase group. Cytogenetic responses occurred approximately 6 to 12 months after the initiation of treatment. Both, complete and partial responses lasted until the end of

the year long treatment. During treatment, blood cell counts gradually decrease indicating the apoptotic effect of the drug, which is not as fast as chemotherapy (nor as painful), but seems to have a good hematological response in spite of not showing cytogenetic responses [4]. Also two accelerated phase patients showed a b3a2 rearrangement that became b2a2, but did not have any significance in the response to treatment or in the prognosis; there were also two accelerated phase and two blastic phase patients with two different transcripts (b2a2/b3a2), and one blastic phase patient Ph-/ BRC-ABL + who did not respond in any way to the treatment. In the accelerated phase and the blastic phase groups, most individuals did not respond to the treatment. This could be due to the presence of other aberrations involved in the pathogenesis of leukemia in addition to the BCR-ABL gene, which are not detectable at the cytogenetic level. Unexpectedly, almost all patients had a normal kariotype, and only one patient from the accelerated phase group had an additional cytogenetic change (47, XX, +8). This person had an astounding response until the end of the treatment a year later.

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Table 1. Characteristics of studied patients

Characteristic	Value		
	Chronic phase	Accelerated phase	Blastic phase
Sex M/ F	9/4	8/4	6/0
Age (years)			
Median	45	41	53
Range	63-28	19-62	23-82
Duration of disease (years)			
Median	3.4	2.9	2.8
Range	1-6	50.5-6	0.5-5
White blood cell count			
median	57350	156991	64791
Hemoglobin			
median	13.30	9.98	9.85
Platelets			
median	268868	302750	156666