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CHRONIC MYELOGENOUS LEUKEMIA PROGNOSIS AND EVOLUTION

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Abstract: *Chronic myelogenous leukemia (CML), a clonal myeloproliferative disorder, is characterized by a biphasic or triphasic course. The disease is diagnosed in chronic phase in over 80% of patients, 10% in accelerated phase and, another10% of patients in blast crisis.Tthe median survival in chronic phase with conventional chemotherapy is 35 to 65 months, being improved by the tyrosine kinase inhibitors-88% of patients at 72 months. The clonal evolution and genetic instability are the main causes of the progression of the disease in accelerated phase or blast crisis, in these conditions the survival rate being significantly lower.*

Key words: *Chronic Myeloid Leukemia, chronic phase, accelerated phase, blast crisis, karyotypic/molecular evolution.*

1. Introduction

The chronic myelogenous leukemia (CML) is a clonal myeloproliferative disorder resulting from the neoplasic transformation of the hematopoietic stem cell [8]. The marker of the disease is the reciprocal translocation between the long arms of chromosomes 9 and 22 – t(9;22) (q34.1;q11.21)- named the Philadelphia chromosome, and present at 95% of the newly diagnosed patients [20]. The presence of the Philadelphia chromosome in the cells of the patients diagnosed with CML was for many years the single specific cytogenetic anomaly associated with a neoplastic disease. The result of the translocation t (9;22) is the hybrid gene BCR-ABL which codifies the p210 protein with high level increase of tyrosine kinase activity compared to the normal homologue p145, determining an uncontrolled cellular proliferation, inhibiting the adherence of cellular hematopoteic progenitors to the medullar stroma and blocking the apoptosis [8].

2. Epidemiology

The disease has an incidence of 1-2 cases at 100000 inhabitants per year in the Western countries, representing approximately 15% of the leukemia incidences at adults. In Romania, there is estimated to be around 200 new diagnosed cases per year [4], [19], [20].

The average age at diagnosis is 55-60 years, less than 10% of cases being at patients under 20 years, CML at children representing under 2-3% from total leukemia cases. A slight increase in the number of the diagnosed patients with ages

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over 60 years has been observed lately. The sex ratio male-female is of 1,3-1,4, without noticing a difference in evolution according to sex [8], [19], [20].

3. Diagnosis Evaluation

In order to confirm the diagnosis of chronic myelogenous leukemia, to stage and estimate the prognosis, a series of investigations are essential :full blood count and peripheral film examination, bone marrow aspirate and bone marrow trephine biopsy, cytogenetic test (in order to observe the Philadelphia cr. and the possible additional chromosomal abnormalities) and the qualitative and quantitative real time PCR molecular test made in order to detect the presence and the level of the BCR-ABL transcript. The Fish testing is optional, if it is made presents the advantage that it detects the BCR-ABL gene by examining a large number of cells from the peripheral blood, but as a monitoring method for the therapeutic response it is indicated only if the RQ-PCR test cannot be performed [1], [9], [19].

Over 40% of CML cases are diagnosed on the occasional routine check ups, the patients being asymptomatic. The most frequent manifestation in case of symptomatic patients are: fatigability, weight loss, nocturnal sweating, sensation of gastric fullness, anorexia, pain in the left hypochondrium determined by the splenomegaly, purpura [8], [19], [23]. The typical blood tests modifications in the first stages of the disease are: leucocytosis with leukocyte formula deviated up to the stadium of myeloblast, anemia and thrombosis [3], [8], [19].

4. Prognosis Factors

Some clinical factors (age, spleen size) and laboratory factors (number of platelets and leucocytes, percentage of blasts, basophiles and eosinophils) have been included in two prognosis systems for calculating the relative risk (RR) from the debut of the disease - RR Sokal (American prognostic score) and RR Hasford (European prognostic score). According to the risk classification – low, intermediate, high – the cases with unfavorable evolution may be identified from the debut [10], [25].

Variables with prognostic significance in CML - After J. Corte, modified Table 1

Clinical Factors	**Factors Sssociated with the Treatement**
Symptoms at diagnosis	Cytogenetic response
Age	Molecular response
Race	Time to achieve the response
Spleen size	Mielosupresion
Liver size	
Hemoglobin level	
White blood cell count	
Platelet count	
% nucleted red blood cells in peripheral blood	
% Blasts in peripheral blood or bone marrow	
%basophils in peripheral blood or bone marrow	
% promyelocytes + % myelocytes in peripheral blood	
% eosinophils in peripheral blood	
Time from diagnosis	
Variant Ph chromosome	
Deletion of der(9)	
Breakpoint site in the BCR gene	
Expression of the BCR/ABL gene	

5. Evolution of the Disease

Chronic myelogenous leukemia is characterized by a biphasic course, initially a chronic phase and then a blast crisis, passing from the initial stage to the final one by an intermediate stage, the accelerated phase.

The criteria of diagnosis in CML [3], [20] Table 2

CHRONIC PHASE	ACCELERATED PHASE	BLAST CRISIS
1. Leucocytosis with leukocyte formula deviated to the left 2. Absolute basophily ≤ 20% 3. Monocites ≤ 3% 4. Normal no. of thrombocytes 5. Minimal or absent dysplastic modifications ***COMPULSORY CRITERIA*** 1. Blasts ≤ 15% * 2. Blasts + Promyelocytes ≤ 30%* * in peripheral blood and/or in bone marrow	1. Non-infectious fever 1. Progressive splenomegaly 2. Anemia and ***thrombocytopenia*** 3. Recurrent ***thrombocytopenia*** 4. Dysplastic modifications 5. Myelofibrosis grades I/II ***COMPULSORY CRITERIA*** 1. Blasts 15-29%* 2. Blasts + Promyelocytes ≥ 30%* 3. Basophiles ≥ 20% * in peripheral blood and/or in bone marrow	1. Fever > 38 C for 7 days 2. Loss of weight > 10% 3. Increase in the size of the spleen > 25% 4. Anemia <10g/dl 5. ***Thrombocytopenia*** <100000/l 6. Leucocytes >50000/l 7. Reticulinic fibrosis in bone marrow ***COMPULSORY CRITERIA*** 1. Blasts ≥ 30% * 2. Extramedullary blastic tumors 3. Additional cytogenetic anomalies * in peripheral blood or in bone marrow

CML is diagnosed in chronic phase in over than 80% of cases, 10% representing patients on accelerated phase at the moment of diagnosis, while other 10% in blastic crisis [4], [19], [20].

Survival with CML is determined by phase of the disease, but especially by the risk and therapy factors. After the progresses achieved in therapy (interferon, allogeneic hematopoietic stem cell transplantation, tyrosine-kinase inhibitors) the evolution of CML has been modified, and as a consequence must be analyzed according to treatment.

5. Evolution in Chronic Phase

Under traditional treatment with hydroxyurea, busulfan and/or cytosar, the survival in chronic phase is of 35-65 months [4], [8]. On the basis of prognostic score, the three relative risk groups – low, intermediate and high – at 48 months with classic chemotherapy have survival rates of 62%, 43%, and respectively 33% [11]. Besides the fact that the survival of patients treated with classic chemotherapy proved to be similar to the patients that were not treated or were subject only to radiation therapy, with these therapies the evolution of the disease cannot be kept under control.

Introduction in the 1980s of the treatment with interferon alpha, by its antiviral, immunomodulator, antiproliferative and antiangiogenetic effects, has provoked the suppression of the Ph positive clone. The long term survival under treatment with interferon has been observed in cases with normal values of hemoglobin, normal number of platelets, low percentage of basophiles and blastic cells in peripheral blood, normal spleen size, these parameters being detected at the moment of diagnosis. Reported to the 3 relative risks groups according to Hasford – low, intermediate and high – the survival rate after 5 years is of 76%, 55%, and respectively 25% [4], [16]. Associated to the relative risk group, the most important predictive factors for the evolution and survival are the cytogenetic type and molecular response, as well as the time interval necessary to attain these responses. Thus, from the 20-25% of patients with complete cytogenetic response (CCR), 78% have survived after 10 years [17]. The synchronism between cytogenetic response – molecular response allows an objective appreciation of the evolution of the disease. 48% of patients with CCR but with a level of BCR-ABL/ABL $\geq$ 0,05% (less than major molecular response) had a relapse risk after 48 months [5].

Definition of cytogenetic and molecular responses [6] Table 3

CYTOGENETIC RESPONSE	**MOLECULAR RESPONSE**
MINIMAL CYTOGENETIC RESPONSE → 66-95% Ph positive metaphase	MAJOR MOLECULAR RESPONSE (MMR): Decrease with > 3 log in BCR-ABL level The BCR-ABL/ABL level < 0,05%
MINOR CYTOGENETIC RESPONSE (mCR) → 36-65% Ph positive metaphase	
PARTIAL CYTOGENETIC RESPONSE (PCR) → 1-35% Ph positive metaphase	COMPLETE MOLECULAR RESPONSE (CMR) Negative RT-PCR
MAJOR CYTOGENETIC RESPONSE (MCR) → 0-35% Ph positive metaphase	
COMPLETE CYTOGENETIC RESPONSE (CCR) → 0% Ph positive metaphase	

The evolution of the CML diagnosed in chronic phase was significantly modified once with the discovery of tyrosine-kinase inhibitors. Imatinib, first tyrosine-kinase inhibitor used, connects to the inactive form of ABL gene and acts by a competitive antagonism of the ATP binding site located in the tyrosine-kinase P-loop of BCR-ABL gene, blocking the transduction signal of cell increase.

According to IRIS trial, administered as a first line therapy in precocious chronic phase of CML (first 6 months), an overall survival of 88% was determined after 72

months of follow up [7]. In late chronic phase, defined by resistance or intolerance to rIFN α, the use of imatinib determined a disease-free survival of 69% after 60 months. A particular aspect observed during the studies was that in spite of the CCR was not attained, the use of imatinib increases the survival rate, even if introduced in the late phase of the disease [2]. Despite the efficiency of imatinib, 20-30% of cases do not respond to this therapy, the cause being either the primary resistance to imatinib, or secondary. According to the mechanism of resistance – primary, secondary, BCR-ABL dependent or BCR-ABL independent, the use of the second line of tyrosine-kinase inhibitors (dasatinib, nilotinib, bosutinib, etc.) can stabilize the disease and increase survival. The presence of T315I mutation, resistance to the currently used therapies, influences negatively the evolution of the disease.

Allogeneic hematopoietic stem cell transplantation, the only curative therapy, determined according to EBMT data (European Bone Marrow Transplantation Association) a survival rate of 34% after 20 years of surveillance [2].

6. Evolution of the Disease in Accelerated Phase and Blast Crisis

Following a normal evolution of 2-4 years in chronic phase, CML progresses either slowly in accelerated phase, with the occurrence of medullar failure manifested through anemia and thrombocytopenia, or suddenly blast crisis [20]. Two thirds of cases of blastic crisis are of myeloid type, while one third is of lymphoid type.

With all the therapeutic progresses made in the previous years, the advanced phase of CML is characterized in most of the cases by a significantly reduced survival rate, of only 1-2 years in accelerated phase and of only 3-12 months in blastic crisis [4], [8]. There has been noted a survival of 51% after 5 years in those cases where alpha interferon has suppressed the evolution of the disease [5]. The survival rate is slightly increased when imatinib in a dose of 600mg/day induces an early major cytogenetic response [26].

The evolution of the disease is determined by the clonal evolution, gene amplification and the occurrence of new mutations.

Clonal evolution is present at 20-40% of patients passing from the chronic phase in the accelerated phase [4]. Although in most of the cases, in the chronic phase of CML the only chromosomal anomaly is t (9;22), there are 5-10% cases that associate variants of t(9;22). All the same, derived deletions of 9 chromosome – der (9) – are met in 10-15% of patients with CML in chronic phase and represent modifications at the level of the long left arm of 9 chromosome, adjacent to the break point occurred in the t(9;22) translocation. These anomalies, as well as the persistence and reoccurrence of the t(9;22) under the treatment with tyrosine kinase inhibitor, induce a chromosomal instability correlated with an increased risk of the disease transformation and a reduced survival rate [18]. Most frequent chromosomal anomalies associated to the clonal evolution are: trisomy 8 (30-40% of cases), occurrence of the second Ph chromosome (20-30% of cases), isochromosome 17 and other anomalies of 17 chromosome (15-20% of cases) [4], [18].

The gene amplification and the occurrence of new punctiform mutations in

different regions of the tyrosine kinase domain of BCR-ABL gene are the main factors which determine the progression of the disease, the genetic instability contributing to the increased speed of the disease transformation [20]. The expression of the BCR-ABL gene fusion determines the activation of multiple signal paths inside the cell, as Ras, Rac, p42 and p38 MAPK, JNK/SAPK, PI3K(phosphatidilinositol-3 kinase), Akt, NF-kB and JAK/STAT [12], [13], [27].

The inactivation of p53, p16 (codified by CDKN 2A gene, with regulatory role for the cellular progression) and Rb genes, as well as the over expression of EVI gene, Ikaros and PAX5 deletions are correlated with the progression of CML in accelerated phase [22]. Modifications in p53 were observed in 5% of cases, N-Ras and Ki-ras mutations observed in other 5% of cases that evolved to the acute phase of CML [24]. Ikaros deletions are frequently met in 60%, in the Ph+ cells at patients with progression of disease [20].

The inadequate secretion of growth factors as IL-1b, IL-6, stimulation factor for the granulo-monocyte colonies, also contributes to the unfavorable progression of CML, determining a decrease in the adherence of progenitors to medullar stroma.

7. Conclusions

The progression of chronic myelogenous leukemia has registered modifications once with the introduction of the therapy with tyrosine kinase inhibitors. Thus, from a survival of maximum 65 months in the past, at the moment the IRIS trial shows a survival of 88% after 72 months. The prognosis is still reserved in the advanced phases of the disease, the progression leading inexorably to death. The precocious diagnosis in chronic phase, as well as identification of risk factors from the debut of the disease allows an improvement in the progression and global survival.

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