DETERMINANT VALUE OF THE CYTOGENETIC AND MOLECULAR IMATINIB THERAPEUTIC RESPONSE IN CHRONIC MYELOID LEUKEMIA

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Abstract. The hallmark of chronic myeloid leukemia is the existence of the cytogenetic evidence of the Phyladelphia chromosome (reciprocal translocation between chromosome 9 and 22, and is specifically designated t(9;22)(q34;q11). The result of the translocation is the oncogenic BCR-ABL gene fusion, located on the shorter derivative 22 chromosome. This gene encodes the Bcr-abl fusion protein the BCR-ABL tyrosine kinase - a protein that is continuously activated. The result of this unregulated activation is an unregulated neoplastic type cell division - chronic myeloid leukemia. The first targeted molecular treatment operating in cancer- inhibitor of the BCR-ABL tyrosine kinase, Imatinib mesylate, is the standard of care for chronic myeloid leukemia (CML) *Methods*. A retrospective review of patients in one department of hematology with a diagnosis of Ph/BCR-ABL positive CML and received imatinib. *Results*. From 2002 to 2012, 66 patients in CML-CP received imatinib were introduced in the study. 22 (33%) patients received imatinib as upfront therapy, the others as second or third line treatment. The cytogenetic response (CyR) achieved was major in 62% with 56% complete cytogenetic response (CCR), no CyR in 17 patients (25%). The molecular response was complete in 13 (20%) and major in 16 (24%) patients. Better cytogenetic and molecular responses were achieved by those with low and intermediary risk (Sokal) Seven patients developed under imatinib additional cytogenetic anomalies: supplemental chromosome 8 (6), duplication of Ph1 (2), trisomy 17 and 19 (1). The median of follow-up was 69 months (range 18-180) and under imatinib was 52 months (range 3-126). The Sokal score was a better predictor of survival than Hasford's. *Conclusions*. Imatinib remains the best first line treatment, but there are still a significant number of patients who did not achieve a CyR. The responses and survival were not influenced by the previous treatments but the earlier introduction of imatinib is better. The Sokal score seems to have a better prognostic role. The survival of patients with CML is evidently improuved by tyrosin kynase inhibitors.

INTRODUCTION

Chronic myeloid leukemia (CML) is the first human neoplastic pathology associated with a characteristic cytogenetic abnormality - Philadelphia chromosome and fusion gene bcr -abl that could be correlated with leukemogenesis pathogenic events. BCR -ABL protein tyrosine kinase is an aberrant fusion gene transcription resulting from the Philadelphia chromosome. Appearance of tyrosine kinase inhibitor therapy - Imatinib has transformed this leukemia with a life expectancy of about 4-6 years under previous therapies (interferon) into a chronic disease with a true overall survival increasing from year to year. At present, the success of imatinib mesylate therapy in chronic phase chronic myeloid leukemia remains the best example of successful targeted therapy . This statement remains valid despite the associated toxicity and the primary and secondary resistances occurring. However, there are still worries about the long-term tolerability and efficacy of imatinib.

In our study we followed the evolution of patients treated with imatinib mesylate and second generation tyrosine kinase inhibitors for over 10 years and we have identified particularities in terms of therapeutic response, tolerance and survival. In diagnosing and monitoring patients a significant role was played by cytogenetic and molecular exam in accordance with the recommendations of European Leukemia Net.

MATERIALS AND METHODS

We retrospectively analyzed a study group consisting of 66 patients diagnosed with Ph1 positive chronic granulocytic leukemia from February 2002 to August 2012 in Sf. Spiridon Hospital Hematology Department Iasi. All patients were treated with tyrosin kinase inhibitors. Diagnosis was based on morphological and cytogenetic data. The main characteristics of our patients are presented in Table 1.

The hematologic, cytogenetic were evaluated. The molecular response was investigated in bone marrow and/or peripheral blood samples by quantitative and qualitative PCR [Mihăşan et al., 2012]. Cytogenetic exam was performed in Molecular Biology Laboratory of Hospital "Sf. Spiridon" Iasi. Cytogenetic response was defined: complete cytogenetic response

(CCyR) metaphases Ph1 positive 0%; partial cytogenetic response (PCyR) metaphases Ph1 positive 1-35%; minor cytogenetic response (mCyR) metaphases Ph1 positive > 35%; no cytogenetic response metaphases Ph1 positive >95%; major cytogenetic response: response partial and complete .

Molecular response performed in the same laboratory by real time -PCR was defined: major molecular response reduction > 3 log BCR-ABL <0,1%; complete molecular response BCR-ABL transcript undetectable.

The statistic significance of variate parameters was evaluated by SPSS 14 software

Table 1. Caractheristics of study group

Parameter	Frequences
Sex (Men/Women)	34/32
Medium age at diagnosis	41 (13-79 years)
White Blood Cells (mediane x10^9/L)	145 (10-465)
Hemoglobin value at diagnosis (mediana g/L)	9,8 (5,4-15,5)
Basophils (%)	2 (0-14)
Bone marrow blasts cells(%)	5 (1-30)
Peripheral blood blasts cells (%)	2 (1-19)
Sokal prognostic score (high/intermediate/low)	30/25/11
Hasford [b] prognostic score (high/intermediate/low)	14/30/22

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RESULTS AND DISCUSSION

In our group of patients Imatinib was introduced at variable intervals in relation to diagnosis and previous treatment lines. In 22 patients (33%) Imatinib was the first line treatment, in 24 patients was second line therapy and 20 patients received imatinib as third line therapy. Time from diagnosis to initiation of Imatinib therapy ranged 0-104 months with a median of 6.5 months. Therapeutic response to Imatinib varied. Complete hematologic response was achieved in 91% of patients, complete cytogenetic response was obtained in 56% of patients (65 % of patients achieved a major cytogenetic response - partial and complete). Complete molecular response was present in 20% of patients and major molecular response in 24% of patients. Maximum cytogenetic response was achieved on average of 20 months (median 12 months) and the maximum molecular response after 19 months (median 18 months).

It was assessed the impact of different clinical and biological parameters on therapeutic response
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Statistically significant impact of Sokal score was observed (p = 0.001) both on cytogenetic response (fig.1) to Imatinib, and on the molecular response (p = 0.025). Patient with low and intermediate risk calculated by Sokal score respond better at Imatinib therapy. Hasford prognostic score influenced less cytogenetic response (p = 0.358), but instead had a statistically significant influence on molecular response.

The line of therapy when administered Imatinib significantly influenced both cytogenetic response (p = 0.005) and the molecular response (p = 0.015) - those who received therapy in line I or II responded better than those who received treatment in the third line. Time until initiation of treatment - those receiving imatinib in less then 24 months after diagnosis responded significantly better than those who received therapy later (p = 0.026). Interestingly, no significant difference for those receiving Imatinib in the first 12 months from diagnosis.

Imatinib cytogenetic response accordind to Sokal prognostic score

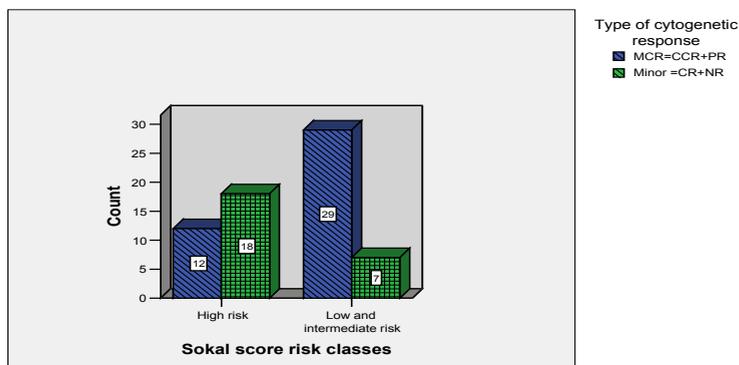
Fig.1 Imatinib cytogentic response according to Sokal prognostic score.

Imatinib dose was increased in 26 patients, 17 patients achieved an improvement in therapeutic response. In 7 patients treatment with Imatinib was changed with second generation tyrosine kinase inhibitor: in 6 patients with Dasatinib and with Nilotinib in 1 patient. Treatment was discontinued in 17 patients due to severe cytopenias, evolution of the disease to acceleration and acute phase, lack of response or loss of response.Seven patients developed under imatinib additional chromosomal abnormalities : extra chromosome 8 (6), Ph1 duplication (2), trisomy 17 and 19 (1).During our study 13 patients progressed to accelerated phase of the disease, 6 patients to blast phase, 3 patients had second neoplasia.10 patients died in our study, the most important cause of death was acute phase of the diasease. Survival under Imatinib therapy was on average 56 months (3-126 months). The duration of overall survival was on average 76 months (18-180 months).It was evaluated the statistic influence, by Kaplan Meyer survival curves, of different parameters at diagnosis.

The only parameters that influenced survival of patients under Imatinib therapy were Sokal score (fig.2) at diagnosis ($p = 0.043$), therapeutic line receiving imatinib . Imatinib therapy in line I + II – has a positive impact on survival ($p = 0.004$), time to initiation of treatment with Imatinib less than 12 months (fig.3) or less than 24 months after diagnosis had a positive prognostic impact on survival ($p = 0.000$; $p=0.005$) . As expected cytogenetic and molecular response had a positive impact on survival under treatment in ourstudy. .
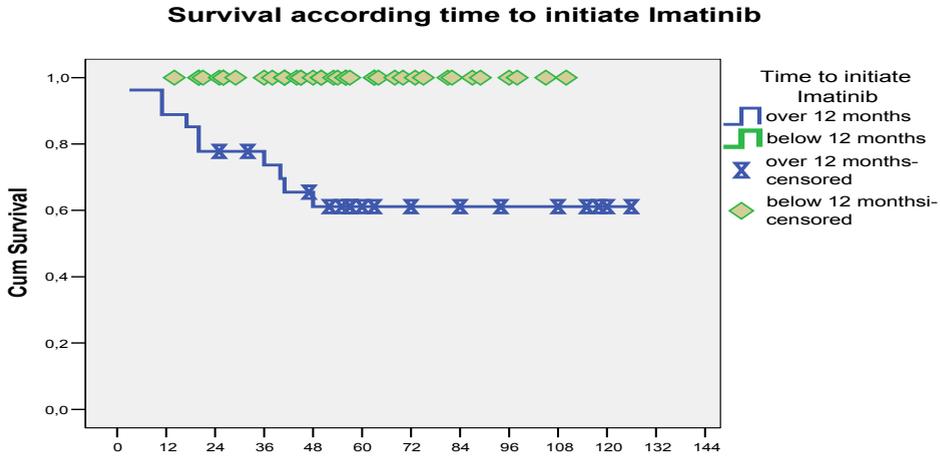
Survival according time to initiate Imatinib

Fig. 2. Influence on survival of Sokal score.

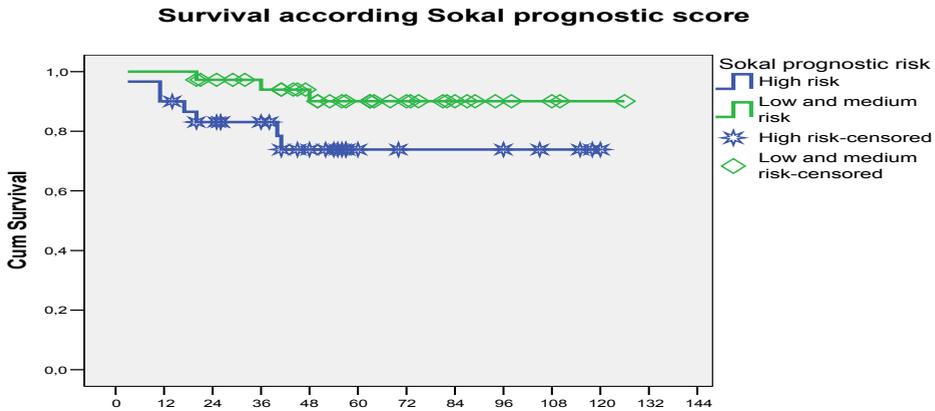**Survival according Sokal prognostic score**

Fig. 3. Influence on survival of time to initiation of Imatinib therapy less than 12 months

We conducted a retrospective study and this type of study shows some disadvantages in data analysis. However we consider it important experience of a single center in our country in evaluation of prognostic impact of Imatinib therapy on the evolution of patients with chronic granulocytic leukemia.

Technique for diagnosis and follow-up are modern equipment required in current specialty literature - cytogenetic and molecular examinations.

The therapeutic response rate both cytogenetic and molecular in patients of our study is lower than reported in the Phase III IRIS in newly diagnosed chronic myeloid leukemia -chronic phase patients receiving Imatinib compared with interferon alfa. Cytogenetic response rate comparative with rate described in this landmark study that included 1106 patients (Deininger M et al, 2009) and 8 years of follow-up was 83 %, compared to only 56 % in our study patients.

This finding can be explained by the fact that our group of patients was not homogeneous, only 22 patients (33 %) received first-line therapy with imatinib and only 38 patients started treatment within 12 months of diagnosis. Approximately 30% of patients in our study treatment was treated with Imatnib in third line.

If compare our results with those of the phase I trial (Druker BJ et al, 2001) study with patients recruited after resistance of alfa Interferon therapy we notice that our response rate were superior - complete cytogenetic response rate was 13% in this study compared to 56 % in the our study.

Our results are comparable to those of the phase II trial (Kantarjian H et al, 2002) who were recruited 454 patients in chronic phase and complete cytogenetic response rate was 41 %.

Complete hematologic response rate of 91 % obtained in our study afost comparable with both hematologic response rate obtained in the IRIS 98 % (Deininger M et al, 2009) and with the 95 % response rate obtained in Phase II trial (Kantarjian H et al, 2002).

Persistence of influence of prognostic Sokal score on therapeutic response and survival of patients with chronic myeloid leukemia after appearance of Imatinib has been discussed in several studies. (Uz B et al, 2013; Trask PC et al, 2012). Sokal score maintained impact and prognostic value on therapeutic response and on survival even Imatinib era. In our study between all analyzed parameters Sokal score at diagnosis was the one with the greatest statistics impact on the cytogenetic response, molecular response and on survival.

Time to initiation of imatinib therapy less than 12 months from diagnosis or between 12-36 months was considered with no prognostic significance in a study published by Kantarjian H et al in 2012, 368 patients with CML treated with Imatinib after failure of alfa Interferon therapy . However our study showed a statistically significant impact of these parameters on survival and on therapeutic response, possibly becuase in our study was included younger patients and 33% of patient was treated with Imatinib in first line.

Obtaining the cytogenetic and molecular response was prognostic factors with evident impact on survival in our study and in study described prevously (Kantarjian H et al, 2012).

CONCLUSIONS

This study retrospectively analyzed the evolution under treatment with Imatinib of a relatively homogeneous group of patients followed in a single center. Chronic myeloid leukemia is a model of proliferation expressing a unique cytogenetic and molecular hallmark.

Given the great therapeutic impact of tyrosine kinase inhibitors in this form of cancer and because chronic myelogenous leukemia is a disease diagnosed at younger ages we need to evaluate prognostic at diagnosis and rigorously monitoring cytogenetic and molecular response to imatinib, in the light of their impact on survival. Analysis of the diagnostic parameters showed that , in our study, the response to Imatinib therapy seems to be influenced by Sokal score and the precocity of initiating therapy.

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