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ASSESSMENT OF EFFICACY OF TYROSINE KINASE INHIBITORS IN TREATMENT OF CHRONIC MYELOID LEUKEMIA

ABSTRACT

This research demonstrated treatment results of 45 patients with chronic myeloid leukemia who were monitored from 2006 to 2015 year. The article is aimed to evaluate a frequency of achievement of hematologic, cytogenetic, molecular responses in patients administered with tyrosine kinase inhibitors, prevalence of resistance to imatinib and its toxicity. It is shown that the treatment of choice for CML is tyrosine kinase inhibitor – imatinib. The use of tyrosine kinase inhibitors allows to reach deep cytogenetic and molecular remission in patients with chronic myeloid leukemia which leads to increased survival. Authors have noted a high prevalence of primary and secondary resistance to first generation tyrosine kinase inhibitor – imatinib. Investigation of results demonstrated that regular hematological, cytogenetic and molecular monitoring is required for effective disease control.

Keywords: chronic myeloid leukemia, tyrosine kinase inhibitors, imatinib.

INTRODUCTION

Chronic myeloid leukemia (CML) is a rare disease new cases of which are approximately 1:100,000 per year. According to data presented in register there are 6466 patients with CML in Russia, 93% of which is alive by 2015 year [5].

Discovery of BCR-ABL tyrosine-kinase inhibitors (TKI) has become one of the most significant achievements in modern oncology. The use of tyrosine kinase inhibitors has led to improvement of patient's outcome and reduction in disease progression to an accelerated stage or blast crisis. The survival rate of CML patients has increased from 3-4 years to 15 years or more, reduction in the frequency of progression to advanced phase [1]. The majority of patients are able to lead a normal daily lifestyle and work.

Imatinib is a generally accepted standard first-line therapy for patients with chronic phase of CML. Numerous studies have found that imatinib blocks binding of BCR-ABL tyrosine kinase with ATP. This leads to suppression of BCR-ABL-dependent signaling pathways and excessive proliferation of myeloid cells. The results of International randomized study IRIS has demonstrated that imatinib has a significant advantage over IFN combination with low-dose cytarabine. Patients with chronic stage CML has shown good tolerability and a high level of complete cytogenetic response (87%) and major molecular response (39%). The subsequent 7-year follow-up and analysis of the results of the study showed a high survival rate among patients receiving imatinib therapy: event-free survival rate was 81%, disease-free survival - 93% and the overall survival – 86% [7].

The article is aimed to evaluate a frequency of achievement of hematologic, cytogenetic, molecular responses in patients administered with tyrosine kinase inhibitors, prevalence of resistance to imatinib and its toxicity.

MATERIALS AND METHODS

The research included 45 patients with verified chronic myeloid leukemia who were monitored from 2006 to 2015 year. A retrospective analysis of medical records was carried out. During investigated period we have found 22 women (49%) and 23 men (51%) with CML. CML most commonly is seen in people aged between 50 and 69 (average age - 44,7 ±15,2). In 42 patients (93,3%) the diagnosis was confirmed with cytogenetic and/or molecular studies. 3 patients (6,7%) doesn't have a results of studies.

At the moment of diagnostic 25 patients (55%) had chronic stage of disease, 20 (45%) – accelerated stage. For risk stratification J.E. Sokal score was used and according to it majority of patient had low risk – 54,2%. Intermediate risk group was established in 37,5%, high risk in 8,3%.

All patients were administered a tyrosine-kinase inhibitor imatinib as first-line therapy. Therapy started with the dose 400 mg/day. In case of no response to treatment or in case of previous complete hematological and/or cytogenetic response loss the dose was increased up to 600-800 mg/day. In case of evidence of disease progression or serious adverse drug effects patients were transferred to other TKI (nilotinib, dazatitnib). Previous therapy with hydroxyurea was found in 12 persons (26.7%), busulfan in 2 (4.4%) and interferon in 1 (2.2%). One patient receives "5 + 2" chemotherapy prior to treatment with imatinib. The median time from the diagnosis of the disease prior to therapy was 4.4 months (range 0 to 48 months). The median duration of imatinib therapy was 49 months (ranging from 6 to 149 months).

Dynamic control of treatment

response was estimated based on complete blood count, morphological and cytogenetic analysis of bone marrow and level of *BCR-ABL* gene expression according to polymerase chain reaction (PCR). Laboratory studies were performed according to federal clinical recommendations on diagnostic and treatment chronic myeloid leukemia [1]. Efficacy of therapy was estimated according to frequency of achieving of hematological, cytogenetic and molecular response, its stability and survival rate. Depending on the depth of clonal neoplastic cells reduction there are different types of response to therapy (table). Rates of overall (OS) survival and progression-free survival (PFS) were calculated with Caplan-Meier method using «Statistica 13.0» software package. In analysis of OS event is implied a death from any cause and loss of patient from monitoring; point of counting is beginning of therapy with first-line TKI. In analysis of PFS event is implied disease progression to accelerated phase or blast crisis.

RESULTS AND DISCUSSION

Complete hematologic response (CHR) is the first reference point of treatment response prognosis. In our study 36 patients (80%) achieved CHR by 3 months of treatment. During the whole therapy time CHR was registered in 43 patients (95,2%), 2 patients (4,8%) has showed primary hematologic resistance.

Cytogenetic study should be performed every 6 months until maintaining complete cytogenetic response (CCyR) then once a year or if loss of CCyR is suspected [1, 6]. Dynamic cytogenetic control of treatment in this study was carried out in 32 patients (71.1%). In 12 patients (26.7%) cytogenetic analysis was aimed only to confirm the diagnosis. Due to the inability to evaluate the cytogenetic response, these patients were excluded from this analysis.

By 6 months of therapy, only 3 (9.3%) patients achieved a CCyR. During the same period 3 patients (9.3%) achieved a partial cytogenetic response (PCyR), 1 (3.1%) - a major cytogenetic response (MCyR) and 1 (3.1%) – minimal cytogenetic response (MinCyR).

By 12 months of therapy 6 patients (18,8%) achieved a CCyR, 3 patients (9.4%) PCyR, 1 patient (3.1%) MCyR, and 1 (3.1 %) - MinCyR. During 18 months of therapy new cases of achieving CCyR observed additionally in 2 patients (6.2%). In any period of therapy CCyR was achieved in 7 people (21.9%).

The total amount of patients who achieved CCyR in imatinib therapy equaled 56,25% cases with median time of achieving CCyR 19,4 month (ranging from 6 to 36 month)

Molecular monitoring the quantitative level of BCR-ABL-transcripts with real-time PCR is commonly used to evaluate response to treatment in patients with CML. This method is particularly important in the era of TKI therapy of CML, when the level of residual leukemia cells are usually below the sensitivity of cytogenetic studies [6]. The level of molecular response is a predictor of disease-free survival, thus molecular analysis is very important.

Regular molecular monitoring is performed in 27 patients (60%). In 15 persons (33.3%) study was conducted in amount that insufficient for response assessment, or not performed at all, and in 3 patients (6.7%), identified in 2014-2015, was excluded from molecular response analysis because of the short duration of treatment. By 12 months of therapy 3 patients (7,4%) achieved major molecular response (MMR), by 18 months additional 5 patients (11,1%). During any time of therapy period MMR was achieved in 17 patients (37,03%). During the whole time of therapy MMR was achieved in 22 patients (48.14%).

Frequency CCyR and MMR according to different authors varies widely depending on the disease stage at the moment of diagnostic, imatinib dose, pretreating and the presence of risk factors [1,3,4,6]. So, with a starting dose of imatinib 400 mg of CCyR rate ranges from 49% to 77%, and the MMR from 18% to 58%. With increasing doses up to 600 or 800 mg improves response to therapy - CCyR up to 49-77% of cases, and the MMR - up to 43-47% [6].

It should be noted that regular hematologic, cytogenetic and molecular control are needed to evaluate treatment response. Unfortunately nowadays the lack of

Types of response to therapy in CML

Type of response	Definition
Hematologic	
Complete hematologic	WBC less than $10x10^9$; basophils less than 5%; no myelocytes, promyelocytes and myeloblasts in the differential, platelets less than $450x10^9/l$
Cytogenetic	
Complete cytogenetic (CCyR)	No Ph+ metaphases
Partial cytogenetic (PCyR)	1-35% Ph+ metaphases
Minor cytogenetic (MCyR)	36-65% Ph+ metaphases
Minimal cytogenetic (MinCyR)	66-95% Ph+ metaphases
None (no CyR)	>95% Ph+ metaphases
Molecular	
Major molecular	Ratio *BCR-ABL/ABL*<0,1% or >0,01 on international scale (IS)

regular cytogenetic and molecular control is a problem as in our region, as in Russian Federation. According to the Russian Register of CML treatment, in 2013, only 41% of patients had regular cytogenetic/molecular (two or more analyzes per year) follow-up, and in 2014 only 20% [5].

Despite the high effectiveness of imatinib some patients develop primary or secondary resistance. Primary resistance is defined as the absence of hematologic response in 3 months, MinorCyR - after 6 months, Major - 12 months, CCyR - after 18 months of therapy. Secondary, or acquired, resistance is the loss of hematologic, cytogenetic or molecular response or progression to the advanced stages. In our study, 20% of patients has demonstrated primary resistance and 17.8% - secondary resistance to imatinib.

Progression to advanced stages is extremely negative outcome of disease. During the whole time of treatment disease progression was noted in 13 patients (28,9%), of which 4,4% (2 cases) - to blast crisis, and 24.5% (11 cases) – to the accelerated stage. During imatinib therapy progression was observed in 10 patient (71,4%), another 4 (28,6%) gets progression during 2 generation of TKI administration. Investigation of treatment results demonstrated that 5-year PFS of patients with CML in chronic stage is 77.64%, 10-year – 58,48% (fig. 1).

In general 12 (26,7%) of the patients died during the follow-up period. Progression of disease occurred in 13,3% of cases, death from comorbid disease was noted in 6.7%. In 4.4% patients the cause of death has not been registered. The 5-year OS rate in patients with chronic stage of CML treated with TKI is 91.57% and 10-year-survival - 80.12% (fig. 2). Review of literature showed demonstrated that our results correspond with survival data from other regions of RF, where 5-year OS is 92,9 and 90,6% [3,4].

Clinical studies have shown that imatinib is well tolerated drug with acceptable ratio of the expected benefits and potential side effects for patients in all stages and lower risk of serious side effects. The frequency and severity of adverse drug effects depend on the drug dose and CML stage.

Common side effects include fluid retention, myelosuppression, nausea, vomiting, fatigue, cramps, headaches, joint pain, rash, and increased activity of the enzymes alanine and aspartate transaminase [4]. Myelosuppression of 3-4-th degree is noted more frequently in CML patients with advanced stages.

Adverse side effects of wide spectrum were observed in 30 patients (66.7%). Periorbital edema, headache, arthralgia, dyspepsia were observed in 18 patients (60%). Side effects associated with imatinib, were mostly mild or moderate (1st and 2nd degree). Serious adverse events that required drug withdrawal were found in 33.3% of patients (10 of 30). Imatinib withdrawal mainly was caused by cardiotoxicity manifested by arrhythmias and toxic cardiomiopathy, severe toxic dermatitis and long-lasting dyspeptic syndrome with nausea and vomiting. In 66.7% of patients (20 of 30) adverse drug effects managed with dose reduction, temporary cancellation of the drug and supportive care. Hematologic toxicity of grade 3-4 was noted in 15,5% of patients (7 of 45). It required drug withdrawal for not more than 14 days, followed by resumption of the previous dose. One patient demonstrated persisting anemia, leukopenia and thrombocytopenia, so she was started therapy with 2 generation TKI.

CONCLUSION

Currently, imatinib is still the drug of choice in the treatment of patients with chronic myeloid leukemia. Analysis of the treatment of chronic myeloid leukemia in the Republic of Sakha (Yakutia) during last 10 years has shown that imatinib allows to achieve clinical remission in 95.2% of cases, complete cytogenetic response in 56.25%, and major molecular response in 48.14%. 10-year progression-free survival rate was 58,48%, and the overall 10-year survival rate of 80,12%.

Despite the effectiveness of imatinib, we found high prevalence of primary and secondary resistance, which requires administration of 2 generation TKI.

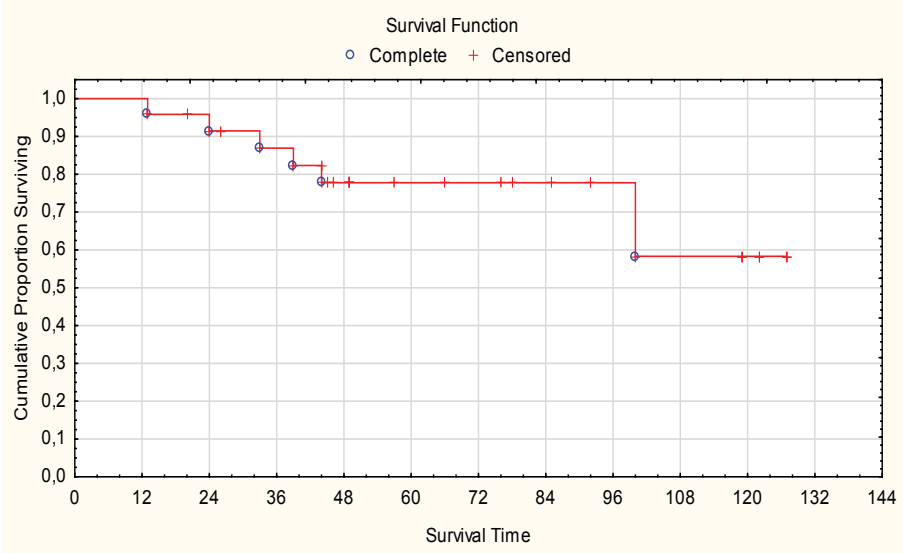

Fig.1. Progression-free survival of patients with CML treated with TKI

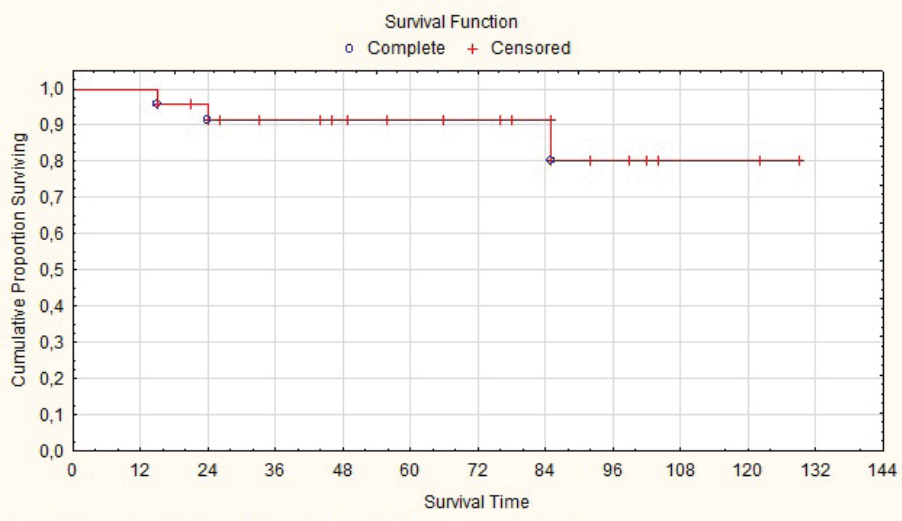

Fig.2. Overall survival of patients with CML treated with TKI

REFERENCES

1. Abdulkadyrov K.M., Abdullaev A.O., Avdeeva L.B. [et al.] Federal’nye klinicheskie rekomendatsii po terapii khronicheskogo mieloleykoza [Federal clinical recommendations for diagnosis and treatment of chronic myeloid leukemia] Vestnik gematologii [The bulletin of hematology]. 2013, №3, V.9, P.4-43.

2. Davydkin I.L., Syrotko I.I., Egorova G.A. [et al.] Opyt primeneniya ingibitorov tirozinkinazy u bol’nykh khronicheskim mieloleykozom v Samarskoy oblasti [Experience of tyrosine kinase inhibitors using in patients with chronic myeloid leukemia in Samara region] Effektivnaya farmakoterapiya [Effective pharmacotherapy]. 2013, №4, Vol.46, P.14-19.

3. Kusnetsova E.Y., Ol’khovik T.I., Shulmin A.V. [et al.] Opyt primeneniya ingibitora tirozinkinazy pervogo pokoleniya (glivek) u bol’nykh khronicheskim mieloleykozom v khronicheskoy faze zabolevaniya po dannym gorodskogo gematologicheskogo otdeleniya Krasnoyarska [Five-year results of imatinib (gleevec) in patients with chronic myeloid leukemia in chronic phase] Fundamental’nye issledovaniya [Fundamental research]. 2011, №10, P.95-98.

4. Savelyeva M.I., Samoylova O.S., Samarina I.N. [et al.] Otsenka nezhelatel’nykh lekarstvennykh reaktsiy targetnoy terapii u patsientov s khronicheskim mieloleykozom [Assessment of adverse drug effects of targeted therapy in patients with chronic myeloid leukemia] Klinicheskiy vestnik [The clinical bulletin]. 2012, №2, P.52-55.

5. Turkina A.G., Golenkov A.K., Napso L.I. [et al.] Rossiyskiy registr po lecheniyu khronicheskogo mieloidnogo leykoza v rutinnoy klinicheskoy praktike: itogi mnogoletney raboty [Russian register for treatment of chronic myeloid leukemia in routine clinical practice: outcome of long-term work] Effektivnaya farmakoterapiya [Effective pharmacotherapy]. 2015, №10, P.8-13.

6. Shukhov O.A. Molekulyarnaya i tsitogeneticheskaya kharakteristika Ph-pozitivnogo klona u bol’nykh khronicheskim mieloleykozom pri dlitel’nom vozdeystvii ingibitorov tirozinkinaz [Molecular and cytogenetic characteristic of Ph-positive clone in patients with chronic myeloid leukemia under a long exposure of tirosyne kinase inhibitors]: diss. cand. of med. sciences: 14.01.21. Moscow, 2015, P.113.

7. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia / S.G. O’Brien, F. Guilhot, R. Larson R [et al.] // N Engl J Med. – 2003. – Vol. 348. – P.994-1004.

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