METHODS OF DIAGNOSIS AND TREATMENT

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TREATMENT OF CHRONIC MYELOID THERAPY WITH TYROSINE KINASE INHIBITORS: DRUG TOXICTY AND RESISTANCE TO THERAPY

ABSTRACT

The study was conducted to assess the incidence of tyrosine kinase inhibitors toxicity and resistance to first-line therapy of chronic myeloid leukemia. The results demonstrated that indications to prescription of the second line tyrosine kinase inhibitors are mostly due to significant non-hematologic toxicity. Side effects of mild and moderate degree are represented by general weakness, peripheral edema, headaches, arthralgia. Episodes of hematological toxicity of mild and moderate degree decreased with the prolongation of therapy and don't require treatment withdrawal. Hematological toxicity of the third degree, more often presented by isolated thrombocytopenia, required the drug withdrawal for no longer than 14 days, followed by the resumption of therapy. Study demonstrated cases of development of secondary resistance to imatinib. Optimal response to therapy requires regular clinical and laboratory monitoring for early detection of drug intolerance and resistance to first-line therapy.

Keywords: chronic myeloid leukemia, tyrosine kinase inhibitors, toxicity, resistance.

Introduction

Chronic myelogenous leukemia (CML) is the first oncohematological disease, in which specific changes in chromosomes resulting activation of proto-oncogenes have been described. For many years CML was considered as an incurable and fatal disease with an average life expectancy of about 4 years after diagnosis [6]. Only bone marrow transplantation allowed achieving a long-term remission in 18-20% of patients with chronic phase of CML [8].

Modern understanding of the mechanisms underlying this disease and progress of medical technologies allow using pathogenetical diagnosis and therapy of diseases. The appearance of inhibitors of tyrosine kinase (specific protein) which play a key role in the development of CML, fundamentally changed the tactics of its treatment, making it pathogenetically specific. This allowed to achieve hematological, cytogenetic, molecular remission, increase the overall survival by several times, improve the quality of life and reduce the annual morbidity with the application of the first line tyrosine kinase inhibitor (TKI) – imatinib mesylate (IM)[3].

Currently, three TKI are registered in Russian Federation for treatment of CML: imatinib, nilotinib and dasatinib. IM is the first drug with pathogenetic orientation. It reduces the activation of numerous effector molecules that transmit intracellular stimuli by inhibiting phosphorylation and, thus, prevents subsequent events that induce leukemia transformation. In international randomized IRIS study imatinib demonstrated a significant advantage over a combination of interferon with low doses of cytarabine. Patients with CML in chronic phase showed good tolerability and a high level of complete cytogenetic response (87% of cases) and a major molecular response (39%) [8].

However, subsequently besides high efficacy imatinib demonstrated wide spectrum of side effects, which worsen life quality of patients. Long-term therapy CML with TKI based continuous exposure of drug to the tumor clone, which is not always possible in patients with therapy intolerance (grade III-IV toxicity, long-term grade II toxicity). Involuntary interruptions in drug administration lead to a decrease of effectiveness and may contribute to the disease progression [5]. The development of side effects leads to a decrease in quality of life and compliance, which also affects the efficacy of treatment. According to the literature, the proportion of patients who do not achieve a complete cytogenetic response (CCyR) during 1 year of treatment is 34-35%. In general, the need for a transition from imatinib to second-line TKI therapy is seen in 40-45% of patients with CML [2].

The purpose of the study was to assess the incidence of toxicity and resistance to tyrosine kinase inhibitors.

MATERIALS AND METHODS

The study included 33 patients diagnosed with CML (58,3% women and 41,7% men, mean age 49.6 ± 15.78) receiving therapy with TKI and undergoing regular cytogenetic/molecular monitoring. In 100% of cases, the diagnosis was confirmed by cytogenetic and/or molecular research. The duration of the disease is on the average 7.32 ± 3.64 (from 1 to 18 years).

A retrospective analysis of the patient's medical records for the toxicity and resistance to TKI was carried out. Data taken into account include: patients' complaints, objective examination data, indicators of full blood count, biochemistry, bone marrow examination, instrumental studies and conclusions of specialists consultations. The toxicity of regimens was assessed by the NCI CTCAE scale, proposed by the National Cancer Institute. Imatinib intolerance was defined in patients with chronic CML phase as: non-hematologic toxicity ≥3rd degree, or grade 4 hematologic toxicity lasting more than 7 days, or any non-hematologic toxicity of the 2nd degree, lasting more than 39 days [7].

Dynamics of the response to therapy was assessed based on the data of a clinical blood test, morphological and cytogenetic analysis of the bone marrow and the expression level of the BCR-ABL gene according to polymerase chain reaction (PCR). Laboratory tests were performed according to the terms described in the federal clinical guidelines for the diagnosis and treatment of CML [1].

RESEARCH RESULTS

At the time of investigation, 16 patients (44.4%) are administered with imatinib, 8 patients (22.2%) – nilotinib and 9 patients (25%) - dasatinib. All patients started a ITK therapy with imatinib, in most cases they get therapy in primary care unit. Treatment of patients began with a starting dose of 400-800 mg / day, depending on

the phase in the onset of the disease. In the absence of response to therapy or loss of complete hematologic and / or cytogenetic remission in the process, the dose was increased to 600-800 mg / day. If there were evidence of disease progression or serious side effects, the patients were transferred to other drugs (nilotinib, dasatinib). Pretreatment with hydroxyurea therapy was reported in 7 patients (21.2%), with busulfan in 1 (3.0%). In the onset of the disease, before the treatment with imatinib, two patients underwent chemotherapy according to the protocols for management of blast crisis. The median time from the diagnosis of the disease to the initiation of therapy in patients diagnosed before the era of tyrosine kinases was 7 years (from 4 to 10 years). Since 2005 all patients after diagnosis are included in federal register and receive treatment with imatinib with program «7 high-cost nosologies».

Serious adverse events requiring withdrawal of the drug and transfer to the second-line therapy were detected in 10 patients (30.3%), of which due to non-hematological toxicity in 9 patients (27.3%) and severe hematologic toxicity in 1 (3%). Severe non-hematologic toxicity is manifested by dyspeptic syndrome with prolonged vomiting and diarrhea in 4 (12%) cases, toxic dermatitis - in 2 (6%), significant edema with no response to supportive therapy - in 1 (3%) and cardiotoxicity - in 1 (3%) patients. The most common manifestations of non-hematological toxicity of imatinib are presented in table 1.

Initiation of therapy with imatinib was accompanied by hematologic toxicity of various severity in 13 patients (39.4%). Hematological toxicity of the 1st degree was registered in 5 patients (15.2%), with isolated anemia with a hemoglobin level less than 100 g/l and leukopenia below 3.0 * 109/l being more common. Hematological toxicity of the 2nd degree was registered in 5 (15.2%) patients, including 2-lined cytopenia in 3 (9%) and 1-lined – in 2 (6%). Severe 3rd degree hematological toxicity in 3 patients (9%) manifested by isolated thrombocytopenia (platelet count less than 50 * 10 9/l), in 1 patient by leukopenia (leukocyte level 2 - 1 * 109/L).

During imatinib therapy, 6 patients (18.2%) developed secondary resistance to drug as progression to advanced phases in 5 cases (15.2%) and loss of previously achieved major molecular response (MMR) in 1 (3%). Loss of response in most cases occurred due to irregular intake of the drug. The average duration of therapy with imatinib before the development of secondary resistance was 48.5 ± 19.57 months (from 24 to 72). Progression of the disease has required a course of cytoreductive therapy with hydroxyurea in 1 patient (3%) and a course of chemotherapy with cytarabine in minimal doses in 1 (3%). After loss of the previously achieved response to therapy, 4 patients (12.1%) were transferred to 2nd line TKI, 2 (6.1%) were continued high doses of imatinib.

By 18 months of treatment, 7 patients (21.2%) had not achieved MMR of which 2 (6%) had subsequently lost hematologic, cytogenetic, molecular responses and therefore had been administered with 2nd line of TKI; 3 patients (9%) were transferred to second-line therapy due to drug intolerance; and 2 patients (6%) were continued imatinib therapy with regular cytogenetic / molecular control and dynamics.

The results of this study has established that the most frequent cause of imatinib withdrawal and prescribing 2nd line TKI was drug intolerance due to the development of severe non-hematological toxicity.

As a second-line therapy, 11 patients (33.3%) received nilotinib, 5 patients (15%) received dasatinib. Therapy with 2nd line TKI was accompanied with nonhematoligal toxicity presented with general weakness, periorbital edema, arthralgia as well as imatinib therapy. Nilotinib therapy was complicated by dermatitis in 3 (27%) patients, dyspeptic disorders in 4 (36%), with diarrhea in 1 (9%) and severe abdominal pain in 1 (9%), cardiotoxicity in 1 (9%). Secondary resistance to nilotinib was developed in 3 (6%) patients, including progression of the disease in 1 (3%) and MMR loss in 2 (6%). During follow-up 4 patients (36%) were transferred to 3rd line therapy - dasatinib, due to non-hematologic toxicity (27.3%) and secondary resistance (8.7%).

DISCUSSION

All side effects noted during TKI therapy are reflected in the drugs instructions. The side effects of imatinib were mostly mild or moderate (grade 1 and grade 2) and include fluid retention, nausea, vomiting, fatigue, headaches, joint pain, rash. Particular importance of these side effects is acquired due to the need for a constant intake of drugs ITK. Even mild side effects persistent for a long time can lead to a decrease in adherence to treatment (compliance) – irregular admission, or a decrease in the dose of the drug by patients, which leads to worsening of treatment efficacy. According to the literature, imatinib intolerance is established in 32% of cases, which is an indication for prescribing another TKI, as the profile of non-hematological toxicity of drugs is different and the cross-over intolerance is minimal. In our study, intolerance to imatinib therapy was found in 27.3% of cases, which coincides with the literature data. As the analysis showed, at translating into 2nd line TKI the severity of symptoms decreases. Intolerance to both imatinib and nilotinib was noted in only two patients (6%), who were subsequently transferred to dasatinib with satisfactory tolerability.

Hematological toxicity of the 3rd degree required temporary discontinuation of the drug, for no more than 14 days, with the subsequent resumption of therapy in the previous dose. The manifestations of hematological toxicity decreased with the prolongation of therapy. In one case, prolonged thrombocytopenia with hemorrhagic syndrome required the transition to dasatinib.

Another problem of TKI therapy is the presence of primary and secondary resistance to imatinib. A study of the causes of resistance to imatinib showed that a significant (up to 10 times) increase in the expression of the BCR-ABL gene appears in a number of patients, and the amplification of the gene is found in some cells. In addition, resistance may occur as a result of an irregular intake of the drug. In our study the most patients who developed secondary resistance to imatinib reported irregular drug intake. In some cases adverse drug events can

The most common manifestations of nonhematological toxicity of imatinib

Non-hematological toxicity	Prevalence, % (absolute)
General weakness	63,0 (21)
Peripheral edema	51,5 (17)
Headaches	39,4 (13)
Arthralgia	33,3 (11)
Dyspepsia	24,0 (8)
with vomiting and diarrhea	15,0 (5)
Dermatitis	12,1 (4)
Dysphagia	9,0 (3)

lead to irregular drug intake.

CONCLUSION

The study showed that the need for switching from imatinib to the 2nd line therapy is required in 51.5% of patients. In most cases this requirement is caused by significant non-hematologic toxicity. However, the side effects due to imatinib decreased after administration of the 2nd generation TKI. Cases of cross-over intolerance to all drugs have not been reported. 21.2% of patients had not achieved MMR during recommended time. Careful monitoring of therapy efficacy and safety will help for early detection of drug intolerance and the timely appointment of the second-line therapy, which allows achieving optimal response to treatment, improving the quality of life of patients. Transfer of patients to the 2nd line TKI is complicated by the high cost of drugs and requires the inclusion of nilotinib, dasatinib in the federal program of «7 high-cost diseases».

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