

# Comparison of the Efficacy of Nilotinib and Imatinib in the Treatment of Chronic Myeloid Leukemia

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## ABSTRACT

**Objective:** To compare the efficacy of nilotinib and imatinib in the treatment of chronic myeloid leukemia (CML).

**Study Design:** Analytical study.

**Place and Duration of Study:** Department of Hematology, Chongqing Three Gorges Central Hospital, China, from January 2016 to January 2018.

**Methodology:** Eighty patients with CML were randomly divided into the nilotinib group (treated with nilotinib) and the imatinib group (treated with imatinib), 40 patients in each group. The therapeutic effects of the two groups of patients were compared.

**Results:** After months of treatment, the neutrophilic granulocytes and neutrophilic metamyelocyte, serum interleukin (IL)-6 and IL-8 and  $\alpha$ 1-acid glycoprotein (AGP) levels in nilotinib group were lower than those in imatinib group ( $p=0.002$ ,  $p<0.001$ ,  $p=0.027$ ,  $p<0.001$  and  $p=0.001$ , respectively); the proportion of patients with BCR-ABLIS  $\leq 10\%$  in nilotinib group and the proportion of patients with BCR-ABLIS  $\leq 0.0032\%$  were higher than those in imatinib group ( $p=0.032$  and  $0.043$ , respectively). During treatment period, there was no significant difference in the incidence of adverse reactions such as mild liver damage, nausea and vomiting, rash, musculoskeletal pain and edema between two groups ( $p = 0.556$ ,  $0.396$ ,  $0.576$ ,  $0.775$  and  $0.390$ , respectively).

**Conclusion:** Nilotinib is superior to imatinib in the treatment of CML. There is no significant difference in the safety of the two drugs, and the adverse reactions can be tolerated.

**Key Words:** Nilotinib, Imatinib, Chronic myeloid leukemia (CML), Interleukin-6 (IL-6), Interleukin-8 (IL-8).

## INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal hematopoietic disorder. This disease caused by the fusion gene between breakpoint cluster region (BCR) and C-ABL proto-oncogene.<sup>1,2</sup> Activated tyrosine kinase triggers multiple signalling pathways downstream of RAS, STAT5, MAPK, etc., which in turn leads to the proliferation of hematopoietic cells.<sup>3</sup> Bone marrow transplantation is currently recognised as the most ideal treatment for CML.<sup>4</sup> However, most patients cannot receive bone marrow transplant due to economic conditions, transplant donors, and age of transplant recipients. The main purpose of CML treatment is to improve health and quality of life, and prolong survival as much as possible.

At present, the main therapeutic agents for the treatment of CML are hydroxyurea, interferon, imatinib, nilotinib, etc.<sup>5,6</sup> Studies have shown that hydroxyurea treatment does not improve the cytological and molecular effects of CML patients, but only can temporarily relieve symptoms, failure to achieve the purpose of delaying disease progression.<sup>7</sup> Interferon can reduce hematological

and cytogenetic remission in a small number of patients, but it cannot eliminate the BCR/ABL fusion gene of CML, and has large side effects.<sup>8</sup>

Imatinib is a first-generation tyrosine kinase inhibitor (TKI) that specifically inhibits tyrosine kinases. Its mechanism of action is to selectively inhibit the proliferation of BCR/ABL fusion genes.<sup>9</sup> Research has confirmed imatinib treatment of CML is significantly better than traditional treatment, but about 20% of patients treated with imatinib are still not ideal.<sup>10</sup> Nilotinib is a second-generation tyrosine kinase inhibitor (TKI).<sup>11</sup> *In vitro* experiments revealed that nilotinib binds to the BCR/ABL domain with higher affinity than imatinib.<sup>12</sup> However, there are few studies which compare the clinical efficacy of nilotinib with imatinib in the treatment of CML.

The objective of this study was to compare the early efficacy and safety of nilotinib and imatinib in the treatment of CML.

## METHODOLOGY

This analytical study was conducted at Hematology Department, Chongqing Three Gorges Central Hospital, China, from January 2016 to January 2018 after approval by the Hospital Ethics and Research Committee. Inclusion criteria included patients who met the diagnostic criteria for CML; had only received tyrosine kinase inhibitor (TKI) treatment; and their liver

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function, kidney function and heart function were normal. Exclusion criteria included patients who were unable to tolerate treatment with severe cardiovascular disease, and had been treated with tyrosine kinase inhibitor (TKI), pregnant or lactating women, and patients who had contraindications for the use of agents in this study.

All patients were randomly single-blind divided into nilotinib group and imatinib group, 40 cases in each group. Patients in nilotinib group were received oral monotherapy with nilotinib, 600-800 mg/d, taken 2 hours after meals, 2 times/day. Patients in the imatinib group received a single-agent imatinib 300-400 mg/day, taken at mealtimes, 2 times/day. Both groups were treated for 3 months.

Before treatment and 3 months after treatment, venous blood was taken for 3 mL without anticoagulation. The upper serum was separated by centrifugation for 15 minutes under the conventional 3000 r/min condition. The samples were stored at -20°C for uniform detection.

Determination of neutrophils and neutrophils in peripheral blood of patients was done by flow cytometry. Serum interleukin (IL)-6 and IL-8 levels were measured by double antibody sandwich enzyme-linked immunosorbent assay (ELISA). The level of  $\alpha$ 1-acid glycoprotein (AGP) was determined by immunoturbidimetry.

Three months after treatment, the proportion of patients with early molecular reactions (EMR) of BCR-ABL fusion gene international standard value (BCR-ABLIS)  $\leq 10\%$  and BCR-ABLIS  $\leq 0.0032\%$  were observed. The BCR-ABLIS detection was used a quantitative Taqman real-time PCR (QT-PCR) method, using ABL as a house-keeper gene. The patient's adverse reactions were monitored during the treatment.

Data was analysed in SPSS version 21. Mean value  $\pm$ SD was calculated for numerical variables, examined by independent sample t-test. Frequencies and percentages were calculated for categorical variables, examined by Chi-square test. The p-values less than 0.05 were regarded as significant.

## RESULTS

Among the 80 subjects, 46 (57.50%) were males and 34 (42.50%) were females. Age ranged from 24-70 years, the average age was  $47.35 \pm 3.93$  years. The duration of disease was 1-10 ( $5.16 \pm 1.37$ ) months. According to the Sokal score, 33 patients were at low risk (41.25%); 30 patients at intermediate risk (37.50%), and 17 patients at high risk (21.25%).

There were no significant differences in levels of neutrophilic granulocytes and neutrophilic metamyelocyte between two groups before treatment ( $p=0.935$  and  $0.918$ , respectively); after 3 months of treatment, the neutrophilic granulocyte and neutrophilic metamyelocyte in nilotinib group were lower than those of imatinib group ( $p=0.002$  and  $p<0.001$ , respectively, Table I).

Before treatment, there were no significant differences in serum IL-6, IL-8 and AGP levels between two groups ( $p=0.971$ ,  $0.928$  and  $0.777$ , respectively); after 3 months of treatment, serum IL-6, IL-8 and AGP levels were lower in nilotinib group than those of imatinib group ( $p=0.027$ ,  $p<0.001$  and  $p=0.001$ , respectively, Table II).

After 3 months of treatment, the proportion of patients with BCR-ABLIS  $\leq 10\%$  in nilotinib group was 87.50% (35 cases), and the proportion of patients with BCR-ABLIS  $\leq 10\%$  in imatinib group was 67.50% (27 cases). There was significant difference between the two groups ( $p=0.032$ ). The proportion of patients with BCR-ABLIS  $\leq 0.0032\%$  in nilotinib group was 55.00% (22 cases), and the proportion of patients with BCR-ABLIS  $\leq 0.0032\%$  in imatinib group was 32.50% (13 cases). There was significant difference between the two groups ( $p = 0.043$ ).

During treatment period, there was no significant difference in the incidence of adverse reactions such as mild liver damage, nausea and vomiting, rash, musculoskeletal pain and edema between the two groups ( $p= 0.556$ ,  $0.396$ ,  $0.576$ ,  $0.775$  and  $0.390$ , respectively, Table III).

**Table I:** Comparison of neutrophilic granulocytes and neutrophilic metamyelocyte in peripheral blood.

Parameters	Time	Nilotinib group (n=40)	Imatinib group (n=40)	p-value
Neutrophilic granulocytes (%)	Before treatment	27.43 $\pm$ 3.55	27.36 $\pm$ 4.07	0.935
	After 3 months of treatment	4.57 $\pm$ 1.78	6.03 $\pm$ 2.21	0.002
Neutrophilic metamyelocyte (%)	Before treatment	29.62 $\pm$ 4.99	29.74 $\pm$ 5.38	0.918
	After 3 months of treatment	3.91 $\pm$ 1.39	5.71 $\pm$ 2.47	<0.001

**Table II:** Comparison of serum IL-6, IL-8 and AGP levels between two groups.

Parameters	Time	Nilotinib group (n=40)	Imatinib group (n=40)	p-value
IL-6 (pg/mL)	Before treatment	46.83 $\pm$ 4.78	46.79 $\pm$ 5.10	0.971
	After 3 months of treatment	33.25 $\pm$ 5.07	35.66 $\pm$ 4.49	0.027
IL-8 (pg/mL)	Before treatment	28.26 $\pm$ 3.78	28.18 $\pm$ 4.10	0.928
	After 3 months of treatment	13.24 $\pm$ 2.89	15.91 $\pm$ 3.20	<0.001
AGP (g/L)	Before treatment	1.23 $\pm$ 0.34	1.21 $\pm$ 0.28	0.777
	After 3 months of treatment	0.62 $\pm$ 0.12	0.75 $\pm$ 0.19	0.001

**Table III:** Comparison of the incidence of adverse reactions during treatment between two groups..

Parameters	Nilotinib group (n=40)	Imatinib group (n=40)	p-value
Mild liver damage [n(%)]	8 (20.00)	6 (15.00)	0.556
Nausea and vomiting [n(%)]	2 (5.00)	4 (2.00)	0.396
Rash [n(%)]	7 (17.50)	9 (22.50)	0.576
Musculoskeletal pain [n(%)]	8 (20.00)	7 (17.50)	0.775
Edema [n(%)]	6 (15.00)	9 (22.50)	0.390

Liver function damage was mild in both groups, and liver function returned to normal after liver protection treatment; nausea, vomiting and musculoskeletal pain usually appeared within one month of taking the drug, then gradually reduced and disappeared; edema was basically tolerable.

## DISCUSSION

The first-generation TKI imatinib improves survival in patients with CML, but about 20% of patients are intolerant to the drug.<sup>13</sup> Second-generation TKI nilotinib is approved for the treatment of newly diagnosed or imatinib-resistant or intolerant CML patients.

Serum IL-6 and IL-8 levels can be used as a reference indicator for the observation of leukemia.<sup>14</sup>  $\alpha$ 1-acid glycoprotein (AGP) is an acute phase response protein in humans and its concentration increases with the progression of malignant tumors. One study showed AGP could be used for clinical treatment monitoring of leukemia patients.<sup>15</sup> This study found that serum levels of IL-6, IL-8 and AGP in the nilotinib group were lower than those in imatinib group. It indicated that nilotinib can effectively reduce serum IL-6, IL-8 and AGP levels. In addition, the authors also found that nilotinib improved peripheral blood neutrophils and neutral late granulocyte counts in patients with more obvious than imatinib.

Hematologic remission, cytogenetic remission, and molecular biological remission are important indicators for evaluating the efficacy of CML patients. The cytogenetic remission mainly uses the karyotype analysis of bone marrow. Some patients may not have metaphase cells for analysis. Fluorescence *in situ* hybridisation (FISH) analysis is required, but the FISH false positive rate is 1%-10%.<sup>16</sup> Detection of BCR-ABL levels by quantitative RT-PCR can more accurately reflect patient remission. The use of peripheral blood specimens to detect BCR-ABL after hematologic remission can reduce the pain of bone penetration examination. The National Comprehensive Cancer Network (NCCN) guidelines state that FISH is not recommended for treatment response monitoring, if quantitative PCR is available.<sup>17</sup> The NCCN guidelines state that treatment adjustments in patients with CML are primarily adjusted for molecular biology relief, patients who did not achieve early molecular biological remission (BCR-ABLIS  $\leq$ 10%) at the 3<sup>rd</sup> and 6<sup>th</sup> months of treatment need to consider

replacing the TKI drug or increasing the dose. Thus, early molecular biological remission is closely related to the prognosis of patients. The results of this study showed that after 3 months of treatment, the proportion of patients with BCR-ABLIS  $\leq$ 10% and BCR-ABLIS  $\leq$ 0.0032% in nilotinib group was higher than those in imatinib group. It is suggested that the rate of early molecular biological response in patients with CML treated with nilotinib is higher than that of imatinib. The conclusion of this study is basically consistent with previous research reports.<sup>18</sup>

Drug treatment tolerance is one of the important factors affecting the relief of CML treatment.<sup>19</sup> Maintaining good adherence during treatment and avoiding withdrawal are key to ensuring clinical outcomes in patients with CML. The study found that during the treatment period, there was no significant difference in the incidence of adverse reactions such as mild liver damage, nausea and vomiting, rash, musculoskeletal pain, edema, and adverse reactions were tolerated. This suggests that nilotinib is safe for the treatment of CML. This conclusion is consistent with previous reports.<sup>20</sup>

The sample size of this study is small, the follow-up time is short, and the long-term efficacy needs to be extended by the follow-up time and the number of patients is confirmed.

## CONCLUSION

Nilotinib is superior to imatinib in the treatment of CML. There is no significant difference in the safety of the two drugs, and the adverse reactions can be tolerated. Nilotinib is worthy of further clinical research and application.

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