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.\(^1,2\) Activated tyrosine kinase triggers multiple signalling pathways downstream of RAS, STAT5, MAPK, etc., which in turn leads to the proliferation of hematopoietic cells.\(^3\) Bone marrow transplantation is currently recognised as the most ideal treatment for CML.\(^4\) 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.\(^5,6\) 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.\(^7\) 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.\(^8\)

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.\(^9\) 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.\(^10\) Nilotinib is a second-generation tyrosine kinase inhibitor (TKI).\(^11\) In vitro experiments revealed that nilotinib binds to the BCR/ABL domain with higher affinity than imatinib.\(^12\) 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
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 α1-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) <10% and BCR-ABLIS <0.0032% were observed. The BCR-ABLIS detection was used a quantitative Taqman real-time PCR (QT-PCR) method, using ABL as a housekeeper gene. The patient's adverse reactions were monitored during the treatment.

Data was analysed in SPSS version 21. Mean value ±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 ±3.93 years. The duration of disease was 1-10 (5.16 ±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 ≤10% in nilotinib group was 87.50% (35 cases), and the proportion of patients with BCR-ABLIS ≤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 ≤0.0032% in nilotinib group was 55.00% (22 cases), and the proportion of patients with BCR-ABLIS ≤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.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Time</th>
<th>Nilotinib group (n=40)</th>
<th>Imatinib group (n=40)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophilic granulocytes (%)</td>
<td>Before treatment</td>
<td>27.43 ±3.55</td>
<td>27.36 ±4.07</td>
<td>0.935</td>
</tr>
<tr>
<td></td>
<td>After 3 months of treatment</td>
<td>4.57 ±1.78</td>
<td>6.03 ±2.21</td>
<td>0.002</td>
</tr>
<tr>
<td>Neutrophilic metamyelocyte (%)</td>
<td>Before treatment</td>
<td>29.62 ±4.99</td>
<td>29.74 ±5.38</td>
<td>0.918</td>
</tr>
<tr>
<td></td>
<td>After 3 months of treatment</td>
<td>3.91 ±1.39</td>
<td>5.71 ±2.47</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Time</th>
<th>Nilotinib group (n=40)</th>
<th>Imatinib group (n=40)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6 (pg/mL)</td>
<td>Before treatment</td>
<td>46.83 ±4.78</td>
<td>46.79 ±5.10</td>
<td>0.971</td>
</tr>
<tr>
<td></td>
<td>After 3 months of treatment</td>
<td>33.25 ±5.07</td>
<td>35.66 ±4.49</td>
<td>0.027</td>
</tr>
<tr>
<td>IL-8 (pg/mL)</td>
<td>Before treatment</td>
<td>28.26 ±3.78</td>
<td>28.18 ±4.10</td>
<td>0.928</td>
</tr>
<tr>
<td></td>
<td>After 3 months of treatment</td>
<td>13.24 ±2.89</td>
<td>15.91 ±3.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AGP (g/L)</td>
<td>Before treatment</td>
<td>1.23 ±0.34</td>
<td>1.21 ±0.28</td>
<td>0.777</td>
</tr>
<tr>
<td></td>
<td>After 3 months of treatment</td>
<td>0.62 ±0.12</td>
<td>0.75 ±0.19</td>
<td>0.001</td>
</tr>
</tbody>
</table>
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.\(^1^3\) Second-generation TKI nilotinib inhibit 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.\(^1^4\) α1-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.\(^1^5\) 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%.\(^1^6\) Detection of BRC-ABL levels by quantitative RT-PCR can more accurately reflect patient remission. The use of peripheral blood specimens to detect BRC-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.\(^1^7\) 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 ≤10%) at the 3rd and 6th 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 ≤10% and BCR-ABLIS ≤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.\(^1^8\)

Drug treatment tolerance is one of the important factors affecting the relief of CML treatment.\(^1^9\) 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.\(^2^0\)

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.

**REFERENCES**

3. Wang Y, Cheng Q, Liu J, Dong M. Leukemia stem cell-released microvesicles promote the survival and migration of myeloid leukemia cells and these effects can be inhibited by microRNA34a overexpression. Stem Cells Int 2016; 9:9313425.


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