

Analysis of clinical characteristics and efficacy of chronic myeloid leukemia onset with extreme thrombocytosis in the era of tyrosine kinase inhibitors

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Abstract: The aim of this study was to investigate the clinical characteristics and efficacy of chronic myeloid leukemia (CML) onset with extreme thrombocytosis. A total of 121 newly diagnosed and untreated CML patients in chronic phase with complete clinical information from the First Hospital of Jilin University, from January 2010 to December 2014 were retrospectively recruited. Based on the platelet (PLT) count, 22 patients were assigned into CML with thrombocytosis (CML-T) group ($PLT > 1,000 \times 10^9/L$) and 65 patients were classified into CML without extreme thrombocytosis (CML-N) group ($PLT \leq 1,000 \times 10^9/L$). Fifty-four point five percent of patients in the CML-T group were female, which was higher than that in the CML-N group (27.7%) ($P=0.022$). Except for gender, there was no significant difference for clinical information of patients between the two groups. For Sokal and Hasford scoring systems, the percentage of patients at high risk in the CML-T group were higher than those in the CML-N group, 95.5% vs 52.3% ($P=0.000$) and 68.2% vs 41.5% ($P=0.031$), respectively; however, there was no significant difference for European Treatment and Outcome Study (EUTOS) score system between the two groups ($P=0.213$). In terms of major molecular response (MMR) rate, the percent of patients with MMR in CML-T group was lower than that in CML-N group at 36 months after tyrosine kinase inhibitor therapy ($P=0.037$). Up until December 2016, the median of event-free survival was 21 months in the CML-T group, however, that was not reached in the CML-N group ($P=0.027$). The majority of CML patients with extreme thrombocytosis were females, and compared to patients in the CML-N group, the percentage of high risk patients based on the Sokal and Hasford scoring systems was higher in the CML-T group, and the median event-free survival of patients was shorter.

Keywords: BCR/ABL1, MPNs, bone marrow, EFS, chronic phase

Introduction

Chronic myeloid leukemia (CML) is the most common disease in myeloproliferative neoplasms (MPNs) disease spectrum, deriving from the transformation of a multipotent stem cell and characterized by extreme leukocytosis, increased immature granulocytes, basophilia and eosinophilia in peripheral blood (PB). The pathogenesis of CML is closely associated with the translocation of $t(9;22)(q34;q11.2)$, which results in the *BCR/ABL1* fusion gene. At present, the cytogenetic hallmark, Philadelphia chromosome (Ph) and *BCR/ABL1* gene, is often used to distinguish CML from other MPNs.

Thrombocytosis, defined as a platelet (PLT) count $> 450 \times 10^9/L$, is very common in chronic myeloproliferative neoplasms, and it was reported that ~30%–50% of CML patients had thrombocytosis at the time of diagnosis. But, extreme thrombocytosis,

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defined as a PLT count $>1,000 \times 10^9/L$, is rare in CML at initial diagnosis.¹⁻⁸ To date, in addition to some case reports, few articles systematically investigated the clinical characteristics and efficacy of tyrosine kinase inhibitors (TKIs) in CML patients with extreme thrombocytosis. Therefore, in order to fully understand the clinical characteristics and prognosis of those CML patients with extreme thrombocytosis, we retrospectively reviewed and analyzed the clinical information and efficacy of CML patients with extreme thrombocytosis in our hospital.

Materials and methods

Patients

We retrospectively reviewed the clinical information of 121 new and untreated CML patients in the First Hospital of Jilin University in China, from January 2010 to December 2014. In this study, patients who met the following criteria were excluded: 1) accelerated phase and blast phase of CML patients at disease onset; 2) poor patient compliance; and 3) patients did not have complete clinical information and follow-up data in the database. At last, 87 CML patients were successfully recruited in this study. Allele-specific polymerase chain reaction (AS-PCR) was conducted to identify *JAK2 V617F* and *MPL W515K*, and reverse transcription PCR (RT-PCR) was performed to detect *BCR/ABL1* fusion gene. All patients were positive for *BCR/ABL1* and negative for *JAK2 V617F* and *MPL W515K* in this study. This study was performed in accordance with the Declaration of Helsinki, and was approved by the ethics review committee of the First Hospital of Jilin University. Written informed consent was obtained from patients or their legal guardians.

Sokal, Hasford and EUTOS scoring systems

At present, Sokal, Hasford and European Treatment and Outcome Study (EUTOS) scoring systems were often used to evaluate the prognosis of CML patients by physicians;⁹⁻¹¹ therefore, all 87 patients underwent the three prognostic assessments mentioned via the website (https://www.leukemia-net.org/content/leukemias/cml/euro_and_sokal_score/index_eng.html). According to the criterion of these prognostic assessments, some patients were diagnosed as low/intermediate-risk subgroup and other patients were evaluated as high-risk subgroup.

PB and bone marrow smear

PB and bone marrow smear tests were performed at the time of initial diagnosis of all patients in this study. In PB smear, up to 200 cells were counted for each patient, while at least

500 nucleated cells need to be calculated for each patient for bone marrow smear.

Treatment and the criterion of clinical efficacy

All patients in this study initially received imatinib (400 mg/day) (Novartis, Basel, Switzerland). Clinical efficacy was verified at the particular treatment time based on the criterion of European LeukemiaNet for CML.¹² It was recommended that those patients with poor treatment response or intolerance during treatment transformed to second-generation TKIs, such as nilotinib and dasatinib.

Statistics

SPSS 20.0 software was used for the statistical analysis. Clinical information and efficacy of patients between CML with thrombocytosis (CML-T) group and CML without extreme thrombocytosis (CML-N) group were compared by Student's *t*-test or the chi-square test. Event-free survival (EFS) was defined as from initial diagnosis to the first event (death from any cause, treatment failure) or last follow-up, and analysis of EFS was performed using Kaplan-Meier method, with differences compared by log-rank test. $P \leq 0.05$ was considered as statistical significance.

Results

Clinical information

In this study, we retrospectively collected the clinical information, such as gender, age, white blood cell (WBC), hemoglobin (HGB), PLTs and below costal margin of patients in CML-T group and CML-N group from the database in our hospital, results showed that there was no significant difference for clinical information between the two groups, except for gender and PLT (Table 1). Compared to patients in CML-N group, the rate of female patients was obviously higher in CML-T group, 54.5% vs 27.7% ($P=0.022$), respectively. In terms of PLT, the median of PLT was $1,398 \times 10^9/L$ in CML-T group; however, the median of PLT in CML-N group was only $326 \times 10^9/L$, and there was statistical difference between CML-T group and CML-N group for PLT ($P=0.000$).

PB and bone marrow smear

The clinical parameters of PB smear, including the percent of eosinophils (EO%), basophils (BA%) and peripheral blast count (PB%), were retrospectively collected in this study, and results showed that there was no significant difference between CML-T group and CML-N group, while the percent of patients with megakaryocytes >100 in bone marrow in

Table 1 Clinical characteristics of patients in CML-T group and CML-N group

	CML-T group (n=22)	CML-N group (n=65)	P-value
Gender			0.022
Male	45.5% (10/22)	72.3% (47/65)	
Female	54.5% (12/22)	27.7% (18/65)	
Age			0.321
>60 y	18.2% (4/22)	7.7% (5/65)	
≤60 y	81.8% (18/22)	92.3% (60/65)	
WBC ($\times 10^9/L$)			0.730
Median	106.0	170.0	
Range	8.9–453.0	2.8–474.0	
HGB (g/L)			0.106
Median	101	105	
Range	59–144	61–166	
PLT ($\times 10^9/L$)			0.000
Median	1,398	326	
Range	1,038–3,649	112–737	
Spleen (cm)			0.745
Median	5.2	5.5	
Range	0–18.0	0–18.0	

Note: Significant differences between the two groups groups for these factors are shown in bold.

Abbreviations: CML, chronic myeloid leukemia; CML-T, CML with thrombocytosis; CML-N, CML without extreme thrombocytosis; y, years; WBC, white blood cell; HGB, hemoglobin; PLT, platelet.

CML-T group was higher than that in CML-N group, 31.8% vs 10.8% ($P=0.047$), respectively (Table 2).

Sokal, Hasford and EUTOS scores

Based on the results of clinical information, we used three prognostic scoring systems generally used for CML to analyze patients in this study, namely, Sokal score, Hasford score and EUTOS scoring system. Results indicated that the percent of patients with high Sokal score in CML-T group was higher than that in CML-N group, 95.5% vs 52.3% ($P=0.000$).

Table 2 The parameters of PB and BM smear

	CML-T group	CML-N group	P-value
EO% in PB			0.100
Median	5.0	3.2	
Range	0–23.0	0–18.0	
BA% in PB			0.779
Median	2.8	2.4	
Range	0–13.0	0–11.0	
Blast% in PB			0.168
Median	1.2	0.7	
Range	0–7.0	0–8.0	
Megakaryocytes in BM			0.047
>100	7	7	
≤100	15	58	

Note: Significant differences between the two groups groups for these factors are shown in bold.

Abbreviations: PB, peripheral blood; BM, bone marrow; CML, chronic myeloid leukemia; CML-T, CML with thrombocytosis; CML-N, CML without extreme thrombocytosis; EO, eosinophils; BA, basophils.

Similar to the Sokal score, the rate of patients with high Hasford score in CML-T group was also higher than that in CML-N group, 68.2% vs 41.5% ($P=0.031$). However, although patients with high risk EUTOS score in CML-T group were more than those in CML-N group, there was no significant difference between the two groups ($P=0.213$) (Table 3).

Second-generation TKI therapy and gene mutation

As of December 2016, 40.9% (9/22) of patients were transforming to second-generation TKIs in CML-T group (six cases due to treatment failure and three cases because of intolerance); however, merely 18.5% (12/65) of patients in CML-N group (nine cases attributed to treatment failure and three cases owing to intolerance) ($P=0.033$). At the same time, ABL kinase domain mutation was examined for those patients with poor treatment response, and results indicated that three patients with T315I were found in CML-T group. However, there were three patients with ABL kinase domain mutation (E255K, M244V and T315I) in CML-N group, although the rate of mutation in CML-T group was higher than that in CML-N group, 13.6% vs 4.6%, respectively. There was no significant difference between CML-T group and CML-N group ($P=0.167$).

Clinical efficacy

With regard to clinical efficacy, we mainly explored the rate of major molecular response (MMR) after TKIs treatment between CML-T group and CML-N group, and the clinical efficacy of all patients were evaluated at 3 months, 6 months, 12 months and 36 months after TKI treatment. Results demonstrated that there was no significant difference at 3 months, 6 months and 12 months after TKI treatment between the

Table 3 Sokal, Hasford and EUTOS score of patients in CML-T group and CML-N group

	CML-T group (n=22)	CML-N group (n=65)	P-value
Sokal score			0.000
Low/intermediate	4.5% (1/22)	47.7% (31/65)	
High	95.5% (21/22)	52.3% (34/65)	
Hasford score			0.031
Low/intermediate	31.8% (7/22)	58.5% (38/65)	
High	68.2% (15/22)	41.5% (27/65)	
EUTOS score			0.213
Low	72.7% (16/22)	84.6% (55/65)	
High	27.3% (6/22)	15.4% (10/65)	

Note: Significant differences between the two groups groups for these factors are shown in bold.

Abbreviations: CML, chronic myeloid leukemia; CML-T, CML with thrombocytosis; CML-N, CML without extreme thrombocytosis; EUTOS, European Treatment and Outcome Study.

Table 4 The percent of MMR in CML-T group and CML-N group

MMR	CML-T group (n=22)	CML-N group (n=65)	P-value
3 months	2 (9.1%)	14 (21.5%)	0.325
6 months	4 (18.2%)	19 (29.2%)	0.310
12 months	6 (27.3%)	25 (38.5%)	0.344
36 months	9 (40.9%)	43 (66.2%)	0.037

Note: Significant differences between the two groups groups for these factors are shown in bold.

Abbreviations: MMR, major molecular response; CML, chronic myeloid leukemia; CML-T, CML with thrombocytosis; CML-N, CML without extreme thrombocytosis.

two groups; but, at 36 months after TKI therapy, the rate of MMR in CML-T group was worse than that in CML-N group, 40.9% vs 66.2%, respectively, and there were significant differences ($P=0.037$) (Table 4).

Survival

Up to December 2016, all patients were followed-up effectively, and the median follow-up time of all patients was 42 months (24–82 months). Of all patients, one patient died of disease progression in April 2013 in CML-T group; however, in CML-N group, one patient died in October 2016 because of suicide after allogeneic hematopoietic stem cell transplantation, and another patient died in April 2015 as a result of disease progression. The median EFS of patients in CML-T group was 21 months; however, the median EFS of patients in CML-N group was not reached ($P=0.027$) (Figure 1).

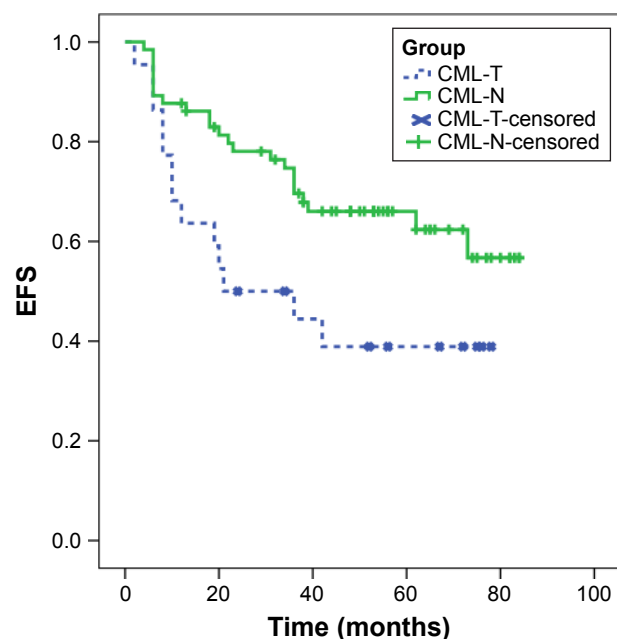


Figure 1 The median EFS of patients in CML-T group and CML-N group.

Notes: The median EFS of patients in CML-T group was 21 months; however, the median EFS of patients in CML-N group was not reached ($P<0.05$).

Abbreviations: EFS, event-free survival; CML, chronic myeloid leukemia; CML-T, CML with thrombocytosis; CML-N, CML without extreme thrombocytosis.

Discussion

In this study, unlike patients in CML-N group, the majority of patients in CML-T group were female, and the phenomenon in this study was consistent with those results previously reported. In China, there are almost 25 CML patients with thrombocytosis reported to date; of 25 patients, 64% were female, and the median age of disease onset was 36 years.⁷ Stoll et al¹³ and Michiels et al¹⁴ found that all CML patients with thrombocytosis were female. Morris et al¹⁵ investigated the clinical characteristics of CML patients with thrombocytosis, and results displayed that ~83.3% of patients were female; therefore, we may draw a conclusion from these data previously reported, that the majority of CML patients with thrombocytosis are female.

The results of three scoring systems, Sokal, Hasford and EUTOS, were completely evaluated, and results demonstrated that there were significant differences for patients with high risk according to Sokal and Hasford scoring systems between CML-T group and CML-N group, however, there was no statistical difference between the two groups for EUTOS scoring system. It was known that Sokal and Hasford scoring systems were associated with six factors, age, spleen below costal margin, PLT count in PB, and the percent of basophils, eosinophils and myeloblasts in PB; however, EUTOS scoring system only included two factors (spleen below costal margin and basophils in PB). Therefore, we retrospectively reviewed these factors for patients in this study, and results showed that there was no significant difference for those parameters between the two groups, except for PLT count in PB. Consequently, we considered that significant differences in Sokal and Hasford scoring systems may be closely involved in extreme thrombocytosis between the two groups, and there was no doubt for no difference in EUTOS scoring system, because there was no significant difference for these two factors mentioned earlier between the two groups.

The median EFS of patients in CML-T group was much worse than those in CML-N group. In this study, there was as high as 95.5% of patients in high-risk group (Sokal scoring system) and 68.2% of patients in high-risk group (Hasford scoring system) in CML-T group, and these patients all received imatinib therapy after definite diagnosis, according to the criterion of Chinese guidelines for CML.¹⁶ At present, it was reported that the Sokal and Hasford scoring systems were significantly associated with the overall survival of CML-chronic phase patients treated with imatinib ($P=0.014$ and 0.016 , respectively).¹⁷ Yahng et al¹⁸ also reported that all three high-risk groups (Sokal,

Hasford and EUTOS) showed significantly lower incidence of both Complete Cytogenetic Response (CCyR) and MMR compared to low-risk groups; therefore, we considered that the poor EFS of patients in CML-T group may be involved with a higher proportion of patients with high risk in Sokal and Hasford scoring systems. For those patients with high risk in Sokal and Hasford scoring systems, it is gratifying that they could achieve better results if initially receiving second-generation TKIs therapy, rather than imatinib,^{19,20} but, nilotinib was not used as first-line therapy for CML-chronic phase patients until 2016 in China.²¹ Based on those facts mentioned earlier, we considered that clinical efficacy and survival of patients in CML-T group may be improved if they regarded nilotinib as first-line therapy after diagnosis, but the conclusion should be verified by multi-center clinical study.

Hemorrhagic and thrombotic complications are rare in CML patients; even with marked thrombocytosis, it is reported that the incidence of hemorrhagic and thrombotic events is 3% and 1%, respectively.²² Sorà et al² reviewed the behavior of CML with extreme thrombocytosis at their center, and of 100 CML patients, only one patient developed thrombosis at diagnosis, while no patients reported a history of bleeding. Rice and Popat²³ reported two cases of females who initially presented with only severe thrombocytosis and vascular events (stroke and myocardial infarction) and later developed typical features of CML. In this study, we also investigated the episodes of hemorrhagic and thrombotic events, and merely one of 85 CML patients was detected with thrombosis at diagnosis, while no case with bleeding; therefore, we thought that elevated thrombocytosis in CML patients had no close relationship with hemorrhagic and thrombotic events.

To date, the molecular mechanisms resulting in the extreme thrombocytosis seen in CML-chronic phase patients have not been clarified. Recently, Turakhia et al²⁴ not only reviewed the blood and bone marrow morphological findings of seven CML-T, four otherwise typical CML and one CML in blast phase but also explored the incidence of *JAK2 V617F*, *CALR* mutation and p-STAT5 expression of those patients by RT-PCR and immunohistochemistry (IHC), and results displayed that p-STAT5 was activated in 85.7% (6/7) of CML-T patients. Raised thrombopoietin (TPO) and cmpl (TPO receptor) levels were observed by Karakuş et al²⁵ in CML with thrombocytosis. Balatzenko et al⁵ published a case report in 2008, and results revealed that the enhanced megakaryocytopoiesis and thrombopoiesis could be due in part to the aberrant expression of the *EVII* gene. It was

acknowledged that PLTs were derived from megakaryocytes in bone marrow, and interestingly, the percent of patients with megakaryocytes >100 in CML-T group was remarkably higher than those in CML-N group in this study. We speculate that increased megakaryocytes in CML-T group may be closely associated with the activation of certain proteins, such as STAT5 protein and *EVII* gene abnormality.

Conclusion

The vast percentage of patients in CML-T group were female, and compared to patients in CML-N group, the percentage of patients at high risk according to Sokal and Hasford scoring system was higher, and the median EFS of patients with extreme thrombocytosis was lower. We consider that patients in CML-T group might obtain better treatment response if they receive second-generation TKIs as first-line therapy.

Disclosure

The authors report no conflicts of interest in this work.

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