

Treatment of patients with primary myelofibrosis using dasatinib

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Abstract. – OBJECTIVE: Primary myelofibrosis (PMF) is a chronic clonal myeloproliferative neoplasm. It is associated with a poor prognosis, with a median survival time of approximately five years. Thus far, there are no specific targeted drugs for PMF. In this study, we evaluated the efficacy and safety of dasatinib, a second-generation tyrosine kinase inhibitor, in six PMF patients.

PATIENTS AND METHODS: From June 1, 2015 to February 29, 2016, six patients with PMF in our department were enrolled into this trial. The efficacy and safety of 100 mg/d (50 mg twice daily) dasatinib were investigated in these patients.

RESULTS: For patients who experienced adverse drug events, the dose was reduced to 70 or 50 mg/d, whereas for those who tolerated the drug well, the dosage was increased to 140 mg/d (70 mg twice a day). Of the six patients, two achieved bone marrow histologic remission, five showed symptomatic improvement, and one reached a stable condition. No severe hematological or non-hematological adverse events were observed thus far.

CONCLUSIONS: Dasatinib treatment may be beneficial to patients with PMF and resulted in significant improvements in splenomegaly, clinical symptoms, physical condition, and quality of life. Therefore, we regard it as an effective therapy for PMF.

Key Words:

Primary myelofibrosis, Dasatinib, Treatment.

Introduction

Primary myelofibrosis (PMF) is a chronic clonal myeloproliferative neoplasm characterized clinically by anemia, splenomegaly, myelofibrosis, bone sclerosis, and the presence of immature granulocytes and teardrop-shaped erythrocytes. Also, it may be accompanied by symptoms such as fever, night sweats, fatigue, and weight loss¹. It has a poor prognosis, with a median survival time

of approximately five years. Deaths from PMF are mainly caused by infection, bleeding, and disease progression to acute myeloid leukemia (AML). Currently, there are no specific targeted drugs for PMF. Available treatments include immune modulators (such as thalidomide, lenalidomide, and interferons), anemia therapies, hydroxyurea, JAK2V617F kinase inhibitors, hematopoietic stem cell transplantation, experimental new drugs, radiation therapy, and splenectomy^{2,3}. Out of these, hematopoietic stem cell transplantation is the only curative treatment for PMF. However, its application is limited by the fact that only a few patients are able to receive the treatment and its high cost.

Dasatinib is a second-generation tyrosine kinase (TK) inhibitor. Tyrosine kinases regulate a wide range of normal cell processes, including metabolism, growth, differentiation, and apoptosis. They are key players in various diseases such as cancer, pulmonary arterial hypertension, and systemic sclerosis⁴. Using a mouse model of pulmonary fibrosis, we showed that dasatinib exerted therapeutic effects in the fibrotic lung. Dasatinib limited myofibroblast activation and collagen-I accumulation by inhibiting PDGFR- α (platelet-derived growth factor receptor- α), Src, and c-Abl activation⁵. Moreover, Cruz et al⁶ reported that dasatinib was effective in inducing macrophage polarization towards the M2 phenotype and in reducing lung inflammation and fibrosis. In this study, we evaluated the efficacy and safety of dasatinib in six PMF patients.

Patients and Methods

Patients

From June 1, 2015 to February 29, 2016, six patients with PMF in our department were

enrolled into this trial. Bone marrow aspiration, bone marrow biopsy, myeloproliferative neoplasm (MPN)-related gene detection, and karyotype analysis was performed. G-banding was used in cytogenetics for karyotype analysis, and the karyotype was named according to the International System for Human Cytogenetic Nomenclature (ISCN2013). Diagnosis criteria were based on the 2008 WHO diagnostic criteria for PMF⁷; the diagnosis met the requirements of three major criteria, as well as two minor criteria. The inclusion criteria were: (1) no severe injuries in major organs such as the heart, liver, and other vital organs; and (2) patients and their families gave their informed consent. The exclusion criteria were: (1) patients with severe concurrent medical conditions and a short predicted survival time, for example, due to another malignancy; (2) women who were pregnant or currently breastfeeding; and (3) patients and their families who chose to withdraw from the clinical trial.

Dasatinib Treatment

All patients signed the informed consent forms and voluntarily participated in this clinical trial. The study protocol was approved by our institution's Ethics Committee (approval number: ChiE-CRCT-20150071). Patients were administered 100 mg/d (50 mg twice a day) dasatinib. Prognostic stratification of patients was based on DIPSS Plus before the commencement of treatment⁸. The Myeloproliferative Neoplasm Symptom Assessment Form (MPN10) was used to assess the symptoms⁹, which included fatigue, inactivity, concentration, early satiety, abdominal discomfort, itching, night sweats, bone pain (diffuse, non-arthritis or joint pain), unintentional weight loss in the past six months, and fever ($> 37.8^{\circ}\text{C}$). Symptom severity was rated on a 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be) scale. Patients received the treatment until the appearance of intolerable side effects or until they chose to withdraw from the trial. The follow-up period ended on February 29, 2016. During the treatment period, dosage adjustments or transient suspension of treatment was allowed based on drug tolerability or occurrence of adverse events. The dosage for patients who developed adverse drug reactions was reduced to 70 or 50 mg/d, whereas for those who tolerated the drug well, the dosage was increased to 140 mg/d (70 mg twice a day). The dasatinib tablets (20 and 50 mg) used in this study were manufactured by ChiaTai Tian Qing

Pharmaceutical Group Co, Ltd. (CTTQ: Yinishu, produced in Jiangsu Province, China).

Evaluation of drug efficacy was based on criteria proposed by the European Myelofibrosis Network (EUMNET) in 2005. The definition of the response to treatment in patients was based on hematological, histological, and cytogenetic parameters¹⁰. The International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) proposed new efficacy evaluation criteria in 2006¹¹.

Safety evaluations included assessments of adverse events such as hepatic, renal, and cardiac toxicity, monitoring of lung disease, pleural effusion, gastrointestinal symptoms, vital signs, weight, and behavioral status, as well as blood, metabolic, and urine analyses. Classification of adverse events was based on the NCI/NIH common toxicity criteria.

Results

Patients' Details

Details of the six enrolled patients are shown in Tables I and II. One patient discontinued dasatinib treatment for personal reasons. Subsequently, the disease progressed and the patient died from cachexia, severe diarrhea, and pleural effusions. The other five patients continued with the treatment.

Efficacy Assessment

At the end of the treatment period, dasatinib markedly reduced spleen volume in all six patients (100%) who received the treatment, but did not induce a significant increase in the peripheral blood count. The reduction in spleen volume is shown in Figure 1, where the splenomegaly measurement is represented by line "1". One patient tested positive for JAK2V617F mutation before the treatment, which persisted two months after dasatinib treatment. Before the treatment, another patient tested positive for JAK2V617F mutation and 20q-; the patient had grade 3 bone marrow fibrosis and erythroid hypoplasia. Ten weeks after dasatinib treatment, the patient still tested positive for the JAK2V617F mutation and 20q-, but a bone marrow biopsy showed that the fibrosis had reduced to grade 1, and that the bone marrow showed erythroid hyperplasia with primary cells $< 5\%$. Another patient also tested positive for the JAK2V617F mutation before treatment

Table I. Basic clinical information of patients with PMF.

No.	Sex	Age (year)	ECOG score	Sokal score	MPN score	Prognostic stratification	Genetic mutation	Treatment duration (week)
1	Female	55	3	1.54	50	Intermediate-2	JAK2V617F	16
2	Male	58	2	1.08	28	Intermediate-2	JAK2V617F	10
3	Female	64	2	0.66	38	Intermediate-2	JAK2V617F	10
4	Male	60	2	1.38	39	Intermediate-2	JAK2V617F	10
5	Female	69	3	1.64	31	High risk	JAK2V617F	11
6	Female	60	2	1.39	32	Intermediate-2	ASXL1, MPLW515	8

and had grade 3 bone marrow fibrosis; the patient tested positive for JAK2V617F mutation 11 weeks after treatment with dasatinib, but the fibrosis had reduced to grade 1 and the primary cell count was < 5%. One patient tested positive for ASXL1 and MPLW515 mutations even eight weeks after the treatment; further, bone marrow biopsy showed that the myelofibrosis grade was MF3 as before. Thus far, the histological and cytogenetic efficacy of dasatinib treatment in the other patients has not been evaluated.

Hematologic Adverse Events

Most of the hematologic adverse events induced by dasatinib treatment were classified as grades 1/2, and occasionally as grades 3/4. Grades 3/4 hematologic adverse events occurred in one patient (ID no. 1), whose blood profile showed the lowest hemoglobin (Hb) concentration (50 g/L) before treatment; treatment with dasatinib did not result in significant difference in the patient's Hb concentration. Furthermore, there was a significant decrease in white blood cell (WBC) count, absolute neutrophil count (ANC), and platelet count. Patients recovered quickly from adverse drug reactions after a dose adjustment or treatment discontinuation, but some required red blood cell transfusion, platelet transfusion, and recombinant human granulocyte colony-stimulating factor injection (Table III).

Non-hematologic adverse events

The most common non-hematologic adverse events of dasatinib administration included edema, pleural effusion, fatigue, headache, joint and muscle pain, rash, gastrointestinal reactions, elevated levels of total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase, hypokalemia, hypocalcemia, hypophosphatemia, and hypomagnesemia (Tables V and VI). During dasatinib treatment, patients received regular supplements of calci-

um, potassium, and magnesium tablets, as well as hepatoprotective agents. In the event of edema, pleural effusion, gastrointestinal reactions, and other adverse reactions, symptomatic treatment with diuretic, digestive, and antidiarrheal agents can help alleviate these conditions. One patient discontinued dasatinib treatment for personal reasons. Thereafter, the disease progressed and the patient experienced severe diarrhea, effusions, hypoproteinemia, and intestinal flora imbalance. However, symptomatic treatment failed to significantly alleviate these adverse drug reactions. After discontinuation of dasatinib, the patient's spleen became enlarged again and the patient died because of cachexia.

Discussion

PMF is a chronic clonal myeloproliferative neoplasm, characterized clinically by anemia, splenomegaly, myelofibrosis, bone sclerosis, and the presence of immature granulocytes and tear-drop-shaped erythrocytes. It may be accompanied by constitutional symptoms such as fever, night sweats, fatigue, and weight loss. PMF has a poor prognosis, and so far, there are no specific targeted drugs. Hematopoietic stem cell transplantation is currently the only curative treatment for primary myelofibrosis, which is suitable for patients with a poor prognosis when a matched donor is available.

Imatinib is a first-generation TK inhibitor and the first-line treatment for chronic myeloid leukemia (CML). Besides BCR-ABL tyrosine kinase, imatinib can also inhibit the activity of other kinases such as PDGFR and c-KIT¹². Myeloproliferative disorders are most often associated with JAK2V617F and c-KIT mutations. Imatinib has been evaluated in clinical trials to treat PMF patients. However, the outcomes were mostly unfavorable. Recently, imatinib was used by Robibaro

Table II. Basic clinical information of patients with PMF (con't).

No.	WBC ($\times 10^9/L$)	ANC ($\times 10^9/L$)	Hb (g/L)	PLT ($\times 10^9/L$)	Blasts and immature cells (%)	Liver	Spleen	Line I (cm)	Lymph node	Myelofibrosis
1	3.4	2.52	50	103	0	Hepatomegaly	Splenomegaly	24.5	No	+++
2	4.1	2.8	101	58	0	No	Splenomegaly	18	No	+++
3	1.0	0.62	45	78	0	No	Splenomegaly	10	No	+++
4	46.6	35.88	116	100	1	No	Splenomegaly	19.5	No	+++
5	3.4	2.21	85	159	0	Yes	Splenomegaly	21.5	No	+++
6	2.20	1.0	57	116	0	Yes	Splenomegaly	20	Yes	+++

et al¹³ in the treatment of a PMF patient; however, the expected hematologic reaction was not observed, and the therapy had to be terminated owing to serious interstitial lung disease. Only one previous work has shown that splenomegaly was resolved in four PMF patients (29%) after treatment with imatinib¹⁴.

Systemic mastocytosis (SM) is a rare chronic myeloproliferative neoplasm which is characterized by abnormal mast cell proliferation. The only therapeutic option for the specific cutaneous symptoms is symptomatic therapy: leukotriene antagonists, commonly antihistamines, local immunosuppressants or local UV radiation, glucocorticoids, and in selected special cases tyrosine kinase inhibitors (TKIs). However, the role of imatinib mesylate therapy has not been well established. I. MARTO used imatinib as treatment for a female ISM patient with recurrent cutaneous symptoms that impaired her quality of life, even though neither FIP1L1-PDGFR α gene rearrangement nor a KIT D816V mutation nor any imatinib-sensitive KIT mutation was present¹⁵. He found that shortly after the imatinib the patient's skin symptoms improved.

Dasatinib is a second-generation TK inhibitor. In addition to targeted inhibition of the BCR-ABL1 gene, which could block signaling pathways activated by BCR-ABL, dasatinib also targets PDGFR, c-Kit, ephrin receptor kinase, and the Src and Src-related family of kinases. Recently, Mohamed et al¹⁶ reported an incidence of CML masquerading as PMF in a patient, and after four months of dasatinib therapy, bone marrow biopsy revealed a change in the grade of fibrosis from M3 at initial diagnosis to M1. It was also demonstrated that there was a marked regression of myelofibrosis upon reduced-dose dasatinib treatment for chronic myelogenous leukemia in the accelerated phase¹⁷. Dasatinib has not been used for the treatment of PMF in China, and there has been little such research elsewhere. Only one open-label, single-center study was conducted in 2008, in which the efficacy of dasatinib (140 mg/d) was investigated in 67 patients with various myeloid disorders. Among these patients, there were 11 with PMF. No objective clinical responses were observed in 10 patients, and dasatinib was discontinued in one patient due to toxicity. One patient with systemic mastocytosis-PMF {KIT-D816V negative, FIP1L1-PDGFR α negative, JAK2V617F positive; complex abnormalities on cytogenetic analysis [47, XY, +1, der (1;7) (q10;p10), +9]} achieved complete response that lasted for five

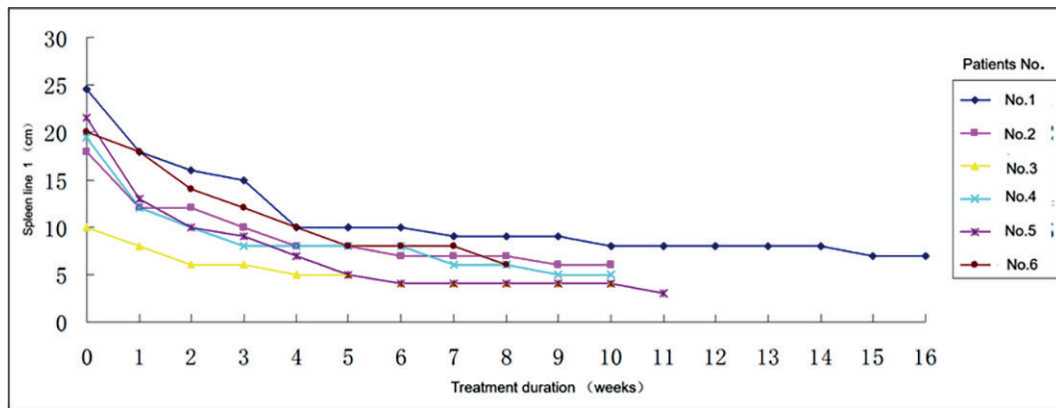


Figure 1. Reduction in spleen volume after dasatinib treatment.

months. However, the patient then progressed to AML after eight months of dasatinib therapy and died¹⁸.

Ruxolitinib is an oral Janus kinase 1/2 (JAK1/2) inhibitor. Several researchers have investigated its efficacy against myeloproliferative disorders, including PMF, polycythemia vera, and essential thrombocythemia, and found that it exerts significant therapeutic effects in PMF patients¹⁹. In a study by Harrison et al²⁰, 219 patients with PMF, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis were assigned to receive either oral ruxolitinib (146 patients) or the best available therapy (73 patients). Among the patients in the ruxolitinib group, 28% showed at least a 35% reduction in spleen volume at week 48, compared with 0% in the group receiving the best available therapy; the corresponding percentages at week 24 were 32% and 0%. The results of the study demonstrated that continuous ruxolitinib therapy was associated with marked and long-lasting reductions in splenomegaly and other disease-related symptoms, improvements in quality of life, and modest toxic effects.

In this paper, all six patients exhibited a reduction of about 2/3 in spleen volume compared to the baseline value within a week of dasatinib treatment. Before the treatment, all patients experienced early satiety, abdominal discomfort, inactivity, and other symptoms due to splenomegaly. After an average of 5-7 days of dasatinib treatment, the volume of the spleen began to decrease, and continued medication helped to maintain its normal size. Further, the Eastern Cooperative Oncology Group (ECOG) score decreased, patients' quality of life improved significantly, and the disease no longer affected the patients' daily lives. However, no significant improvement was observed in WBC count, Hb level, or platelet count in conventional blood tests. To better understand the effects of dasatinib, bone marrow biopsy was performed in two patients, and the results indicated histological remission of the bone marrow. Cytogenetic abnormalities remained in four patients after treatment, and they did not achieve a complete cytogenetic response, probably due to the short treatment period. Of the six patients, five showed symptomatic improvement, and one was

Table III. Bone marrow suppression in PMF patients caused by dasatinib treatment.

No.	Lowest WBC count ($\times 10^9/L$)	Lowest ANC count ($\times 10^9/L$)	Lowest Hb (g/L)	Lowest PLT count ($\times 10^9/L$)
1	III	III	IV	III
2	II	II	II	II
3	II	I	II	I
4	0	0	IV	II
5	III	II	II	0
6	III	III	III	0

Table IV. Adverse events in PMF patients treated with dasatinib.

No.	Fluid retention	Diarrhea	Headache	Nausea	Rash	Breathing difficulty	Bleeding	Fatigue	Pain	Infection	Vomit	Cough	Abdominal pain	Fever
1	IV	IV	I	III	0	II	II	IV	0	III	II	III	0	II
2	II	II	I	I	0	I	0	0	0	II	I	0	0	II
3	0	0	0	I	0	0	0	I	0	II	II	0	0	0
4	II	III	0	I	0	II	0	0	0	II	0	0	0	0
5	II	III	0	0	I	0	0	0	0	II	0	I	0	II
6	II	0	II	I	0	III	0	I	0	0	0	I	I	0

in a stable condition. Based on our observations, we believe that the treatment duration was too short, and recommend evaluating the efficacy after every three months of treatment.

So far, no severe hematological toxicity was observed. Hematologic toxicities included WBC grade 0 (one case), II (two cases), and III (three cases), and ANC grade 0 (one case), I (one case), II (two cases), and III (two cases). The Hb grades were II (three cases), III (one case), and IV (two cases). The lowest Hb levels for patients in stages N1 and N3 were 45 g/L and 41 g/L, respectively. However, these two patients had severe anemia before the start of the treatment, so it should not be regarded as a dasatinib-induced hematologic toxicity. The platelet grades were grade 0 (two cases), I (one case), II (two cases), and III (one case).

Similarly, no severe non-hematologic adverse reaction was observed during treatment. Side effects observed in the six patients included edema, rash, nausea, diarrhea, elevated levels of total bilirubin, ALT, AST, and alkaline phosphatase, hypokalemia, hypocalcemia, hyperphosphatemia, and hypomagnesemia. These adverse events may be alleviated or ameliorated by treating patients with diuretics, glucocorticoids, hepatoprotective agents, and other therapies, or by correcting the electrolyte imbalance.

In this study, dasatinib therapy was associated with a marked reduction in spleen volume and improvement in the quality of life, similar to that induced by the JAK1/2 inhibitor, ruxolitinib. However, the underlying mechanism of its action is not clearly understood. It is not known whether dasatinib targets PDGFR, c-Kit, ephrin kinase, Src family of kinases, or other kinase pathways to significantly reduce the spleen volume. It is also not understood whether the present findings are specific to this study or if dasatinib has beneficial effects in other PMF patients. This needs to be further clarified using appropriate study designs and clinical trials with a large sample size to properly evaluate the drug efficacy and safety.

Conclusions

We suggest that dasatinib therapy may benefit PMF patients based on the significant improvements in splenomegaly, clinical symptoms, physical condition, and quality of life, and that it is an effective treatment before hematopoietic stem cell transplantation.

Table V. Adverse events in PMF patients treated with dasatinib (Con't).

No.	Elevated transaminase	Elevated bilirubin	Hypocalcemia	Hypokalemia	Hypophosphatemia	Abnormal creatinase
1	0	0	II	0	II	0
2	I	I	I	0	0	0
3	I	0	I	0	0	0
4	I	0	II	0	0	0
5	I	II	I	0	0	0
6	0	0	0	0	0	0

Conflict of Interest

All authors declare that they have no conflict of interests in this paper.

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