

[ CASE REPORT ]

## The Impact of Hemodialysis and Liver Cirrhosis on the Plasma Concentrations of Tyrosine Kinase Inhibitors in a Patient with Chronic Myeloid Leukemia

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### Abstract:

We recently treated a chronic myeloid leukemia (CML) patient with liver and renal dysfunction, who was undergoing hemodialysis (HD). He was treated with 50 mg dasatinib (DAS) once daily just before HD. The maximum plasma concentration of DAS was 227 ng/mL on a non-HD day and 46.9 ng/mL on a HD day. He was subsequently treated with 200 mg bosutinib (BOS) once daily. The plasma concentration of BOS changed from 74.5 ng/mL before HD to 58.8 ng/mL after HD. Our results indicate that close monitoring of the plasma tyrosine kinase inhibitor concentrations should be considered in CML patients with organ impairment.

**Key words:** dasatinib, bosutinib, hemodialysis, liver cirrhosis, plasma concentrations

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### Introduction

Chronic myeloid leukemia (CML) is a cancer of the blood cells, which is characterized by the increased and unregulated proliferation of myeloid cells in the bone marrow. Proliferating myeloid cells, which include mature granulocytes (neutrophils, eosinophils, and basophils) and immature precursors, accumulate in the blood, and their excessive proliferation is largely responsible for the symptoms associated with CML.

CML is a clonal disorder, originating from abnormal stem cells harboring a characteristic chromosomal abnormality called the Philadelphia chromosome, which is created via a translocation between the 9th and 22nd chromosomes. This chromosomal abnormality results in the formation of the

BCR-ABL1 fusion gene, which generates the BCR-ABL protein. The BCR-ABL protein exhibits constitutive tyrosine kinase activity and affects the cell cycle and anti-apoptosis pathway, resulting in the unregulated proliferation that is characteristic of CML.

Most CML patients are diagnosed in the chronic phase (CP) of the condition, which lasts for 4-6 years. If CML-CP patients are not treated or the treatment is ineffective, then CML progresses to the accelerated phase (AP) followed by the blastic phase (BP), in which CML exhibits severe resistance to all treatments. Therefore, the prevention of disease progression is the most important factor affecting the outcomes of CML-CP treatment.

Tyrosine kinase inhibitor (TKI) treatment has greatly improved the prognosis of CML-CP (1). At present, TKI-treated CML patients rarely experience disease progression

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**Table 1. Laboratory Findings in This Case.**

CBC		Chemistry		Coagulation	
RBC	398 ×10 <sup>4</sup> /μL	AST	39 U/L	PT	84.4 %
Hb	11.8 g/dL	ALT	16 U/L	APTT	35.8 s
Hct	37.1 %	ALP	441 U/L		
Plt	34.7 ×10 <sup>4</sup> /μL	LDH	364 U/L		
WBC	28,610 /μL	T-Bil	0.5 mg/dL		
Myeloblasts	0.3 %	TP	7.5 g/dL		
Myelocytes	4.3 %	Alb	3.7 g/dL		
Metamyelocytes	3 %	BUN	26 mg/dL	ICG-R15	17 %
Stab neutrophils	4.7 %	Cre	4.48 mg/dL		
Seg. neutrophils	59.4 %	UA	4.2 mg/dL		
Eosinophils	3.7 %	Glu	91 mg/dL		
Basophils	10 %	CRP	0.95 mg/dL		
Monocytes	6 %				
Lymphocytes	8.3 %				
NAP rate	7 %				

CBC: complete blood count, RBC: red blood cells, Hb: hemoglobin, Hct: hematocrit, Plt: platelets, WBC: white blood cells, Seg. neutrophils: segmented neutrophils, NAP: neutrophil alkaline phosphatase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, T-Bil: total bilirubin, TP: total protein, Alb: albumin, BUN: blood urea nitrogen, Cre: creatinine, UA: uric acid, Glu: glucose, CRP: C-reactive protein, PT: prothrombin time, APTT: activated partial thromboplastin time, ICG-R15: indocyanine green retention rate at 15 min

to AP or BP, and the life expectancy of such patients was found to be almost the same as that of an age-matched control population (2).

On the other hand, the prognosis of CML patients with high Charlson comorbidity indices (CCI) was significantly worse than the prognosis of CML patients with low CCI (3). However, the efficacy of TKIs did not differ among these cohorts, suggesting that it is important to appropriately manage pre-existing complications and the toxicities of TKIs in CML patients. Therefore, appropriate dose adjustment of TKIs should be considered according to the patients' backgrounds (including their comorbidities).

Both the efficacy and toxicity of TKIs are dependent on the plasma concentrations of the drugs (4-7). However, the plasma concentrations of TKIs are affected by concomitantly administered drugs and the functions of the liver and kidneys, which are involved in drug absorption, metabolism, and excretion. Thus, special attention should be paid to patients who are taking multiple drugs or that have organ dysfunction when prescribing TKIs.

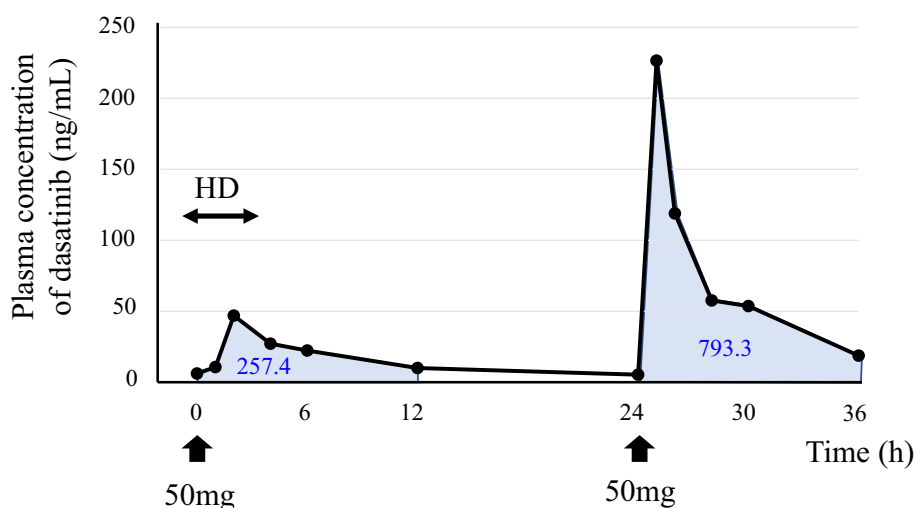
We recently experienced a case involving a CML-CP patient with liver cirrhosis, who was undergoing hemodialysis (HD).

Little is known about the influence of HD on the plasma concentrations of TKIs in CML patients with renal insufficiency. We herein report on the changes in the plasma concentrations of dasatinib (DAS) and bosutinib (BOS) that occurred in the abovementioned patient and review the effects of HD on the plasma concentrations of TKIs.

## Case Report

A 64-year-old man was referred to Kindai University Hospital with leukocytosis. He had chronic kidney disease (CKD) due to chronic glomerulonephritis, and had been undergoing HD three times a week since 1985. In addition, he had liver cirrhosis (Child-Pugh classification: class A), and his indocyanine green retention rate at 15 minutes was 17%. He had a history of acute hepatitis B, and serological tests produced the following results: HBsAg (-), HBsAb (+), and HBV-DNA (-). At his first visit, he was free from splenomegaly, ascites, fever, night sweats, and general fatigue. His laboratory data are shown in Table 1. A bone marrow aspirate specimen revealed marked hypercellularity with myeloid hyperplasia, but no dysplasia or increase in the blast ratio was seen. Karyotyping of his bone marrow cells produced the following result: t(9;22)(q34;q11.2). No other cytogenetic abnormalities were detected. The patient was diagnosed with CML-CP, and DAS treatment was started at a dose of 50 mg once a day.

One week after the start of the DAS treatment, we had the drug's plasma concentration measured by MASIS (Food and Drug Nano Analysis, MASIS, Aomori, Japan) on two consecutive days (the patient was on HD on the 1st day and off HD on the 2nd day). DAS was given to the patient just before HD, and its maximum plasma concentration (C<sub>max</sub>) was 46.9 ng/mL at 2 hours. In contrast, its C<sub>max</sub> was elevated (227 ng/mL) on the non-HD day. The area under the time-concentration curve over the first 12 hours [AUC (0-12)] was 257 ng·h/mL on the HD day and 793 ng·h/mL on



**Figure.** The plasma concentrations of dasatinib (DAS) before and after hemodialysis (HD) in our patient. The DAS concentration did not increase on the day of HD. The DAS concentration was markedly elevated on the non-HD day.

the non-HD day (Figure). However, 2 weeks after the start of the DAS treatment, mild bilateral pleural effusion and pulmonary hypertension (PH) (45 mmHg) were detected on an X-ray examination and cardiac ultrasonography. Although we considered that the PH had been caused by chronic heart failure, rather than the DAS treatment, because DAS had only been administered for a short period, we were worried about the possibility that DAS might further worsen the PH. Thus, we replaced the DAS with 200 mg BOS once a day.

After the start of the BOS treatment, we measured the plasma concentration of BOS at Akita University (Akita, Japan). BOS was administered just before HD, and its plasma concentration at 2 hours was 273 ng/mL, whereas its plasma concentration on the non-HD day was 180 ng/mL. The AUC (0-12) of BOS was 912 ng·h/mL on the HD day and 851 ng·h/mL on the non-HD day. However, the plasma concentration of BOS fluctuated markedly from 85.5 to 273 ng/mL during the HD. Therefore, we next examined whether HD removes BOS by examining its plasma concentrations before and after HD without administering BOS. As a result, it was found that the plasma concentration of BOS was 74.5 ng/mL before the HD and 58.8 ng/mL after the HD. Thus, we considered that BOS was only partially removed by HD and that the dosage of BOS was appropriate for this patient. He continued receiving BOS at the same dosage and achieved a BCR-ABL international scale value of <10% at 3 months [the optimal response according to the European LeukemiaNet (ELN) 2013 (8)] after the start of the BOS treatment.

## Discussion

The liver plays a central role in the pharmacokinetics of most drugs by regulating not only their metabolism and elimination, but also their absorption and distribution. DAS is mainly metabolized by CYP3A4 in the liver. Most (85%)

of its metabolites are excreted in feces, and only 4% are excreted in urine (9). Therefore, it is assumed that the plasma concentration of DAS is increased by hepatic dysfunction. However, according to the packaging data for DAS submitted to the US Food and Drug Administration (FDA), the mean C<sub>max</sub> and AUC values of DAS are lower in patients with hepatic dysfunction. As a result, dose adjustment, especially dose reduction, is not necessary to consider during DAS treatment, even for patients with hepatic dysfunction (9). In contrast, in Japan it is recommended that DAS should be prescribed with caution to patients with hepatic dysfunction due to the risk of overprescription (10). Our patient had mild liver cirrhosis (Child-Pugh class A). In addition, he was being treated with carvedilol for heart failure, which is also metabolized by CYP3A4, and it was assumed that it would increase the serum concentration of DAS through competitive metabolism. Therefore, we prescribed DAS at a daily dose of 50 mg. However, even though only a half-dose was administered, the C<sub>max</sub> of DAS was elevated (227 ng/mL), and its AUC was 793 ng·h/mL on the non-HD day. When DAS was given to Japanese patients with solid tumors at a daily dose of 100 mg, its C<sub>max</sub> was 140 ng/mL, and its AUC was 538 ng·h/mL (10). Although we have to consider the effects of carvedilol, these results suggest that dose reduction is required for CML patients with liver dysfunction who are treated with DAS.

BOS is also primarily metabolized by CYP3A4 in the liver, and its plasma concentration is elevated by liver dysfunction (11). When BOS was taken at a daily dose of 200 mg, its mean C<sub>max</sub> in Western healthy controls was 34.0 ng/mL, whereas its mean C<sub>max</sub> in Child-Pugh A, B, and C patients was 86.7 ng/mL, 68.4 ng/mL, and 58.8 ng/mL, respectively (11). In our patient, the C<sub>max</sub> of BOS was 273 ng/mL on the HD day and 180 ng/mL on the non-HD day, which were much higher than the levels seen in the healthy controls and Child-Pugh A patients. Thus, we considered

**Table 2. Case Reports of TKI Treatment in Patients on HD.**

Reference	Age	Sex	Diagnosis	TKI	Dosage	Concentration change with HD	Response
16	44	Female	GISTs	IM	400 mg QD	None	PR
17	54	Female	CML-CP	IM	400 mg QD	N/A	MR
18	69	Male	EGISTs	IM	400 mg QD	N/A	CR
19	75	Male	GISTs	IM	400 mg QD	N/A	N/A
20	46	Female	CML-CP	IM	300 mg QD	N/A	MMR not achieved
20	46	Female	CML-CP	NIL	200 mg BID	None	MMR
20	61	Male	CML-CP	IM	200 mg QD	N/A	CCyR
20	61	Male	CML-CP	NIL	200 mg QD	None	MMR
20	78	Female	CML-CP	IM	400 mg QD	N/A	N/A
20	78	Female	CML-CP	NIL	200 mg BID	None	MMR
21	58	Female	CML-BP	DAS	70 mg BID	N/A	PCyR
22	87	Male	CML-CP	DAS	50 mg QD/dialysis day	N/A	N/A
23	73	Male	CML-CP	DAS	100 mg QD	None	DMR

TKIs: tyrosine kinase inhibitors, HD: hemodialysis, GISTs: gastrointestinal stromal tumors, CML-CP: chronic myeloid leukemia in chronic phase, EGISTs: extra-gastrointestinal stromal tumors, CML-BP: chronic myeloid leukemia in blastic phase, IM: imatinib, NIL: nilotinib, DAS: dasatinib, QD: quaque die, BID: bis in die, N/A: not available, PR: partial response, MR: molecular response, CR: complete response, MMR: major molecular response, CCyR: complete cytogenetic response, PCyR: partial cytogenetic response, DMR: deep molecular response

that the concomitant use of carvedilol was also responsible for the high C<sub>max</sub> of BOS observed in our patient.

The AUC of BOS increased by 35% in patients with mild renal dysfunction and by 60% in patients with severe dysfunction (12). As for the mechanism responsible for this, a previous study showed that the activity of cytochrome P450, including CYP3A4, in the liver (13) and intestines (14) was low in animals with CKD. Also, CYP3A4 activity was reported to be low in patients with renal dysfunction (15). These findings suggest that the reduced CYP3A4 activity seen in patients with renal dysfunction might result in excessive increases in the plasma concentration of BOS.

In addition to liver dysfunction, our patient was undergoing HD, which might have removed the administered TKIs from his plasma. At present, there are few reports about TKI treatment in HD patients. In previous cases, imatinib was given to 7 HD patients (16-20): in only one case, the plasma concentration of imatinib was measured, and there was no difference between before and after HD (16). Moreover, apparent toxicities of the imatinib for the HD patients have been rarely reported so far (Table 2), which suggests that it is not necessary to modify the dose of imatinib given to CML patients on HD. In addition, there have been 3 reports about the treatment of CML with nilotinib (NIL) in 3 HD patients (20). There were no significant differences between the plasma NIL concentrations observed before and after HD. This suggests that NIL is not eliminated by HD, and dose reduction of NIL is not necessary for patients on HD. As for DAS, we could only find three reports about its use in HD patients (21-23). In the first case, the patient exhibited a partial cytogenetic response without any marked tox-

icities (21). In the second case, although only 50 mg DAS was administered on the HD days, the DAS treatment was stopped immediately because it exacerbated the patient's pleural effusion (22). In these two cases, the effects of HD on the plasma DAS concentration were not evaluated. In the third case, the plasma concentration of DAS was not affected by HD (23). On the other hand, in the present case the C<sub>max</sub> of DAS was 46.9 ng/mL on the HD day, and it increased to 227 ng/mL on the following (non-HD) day, suggesting that DAS was markedly eliminated by HD. We administered DAS just before HD, and its C<sub>max</sub> was recorded during the HD. In contrast, the DAS concentration was recorded at its trough level in the previously reported case (23), which might have masked the impact of HD on the plasma concentration of DAS. In contrast, the C<sub>max</sub> of BOS was 273 ng/mL on the HD day and 180 ng/mL on the non-HD day. In addition, we confirmed that the plasma concentration of BOS only partially decreased from 74.5 ng/mL to 58.8 ng/mL after HD. These results imply that BOS was only partially removed by HD.

### Conclusion

We measured the plasma concentrations of DAS and BOS in a CML patient with renal failure requiring HD and liver cirrhosis. The concentrations of DAS and BOS are affected by liver function. In addition, we found that in our patient DAS was markedly eliminated by HD, while BOS was scarcely eliminated. Thus, in CML patients with renal and hepatic impairment it is necessary to measure TKI concentrations in order to optimize such drug treatment.

**Author's disclosure of potential Conflicts of Interest (COI).**

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