Effect of dasatinib on blood concentrations of sunitinib and adverse events in a patient with metastatic renal cell carcinoma treated with sunitinib: A case report

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Abstract. The combined use of sunitinib and other tyrosine kinase inhibitors (TKIs) is discouraged because of the increased risk of adverse events (AEs). Furthermore, plasma sunitinib levels are affected by drugs that affect CYP3A4 activity; therefore, caution should be exercised when using CYP3A4 inhibitors. In the present study, a 59-year-old Japanese man with metastatic renal cell carcinoma (RCC) was diagnosed with chronic myeloid leukemia (CML) while on sunitinib treatment and was simultaneously treated with sunitinib and dasatinib, a multi-TKI used for CML with moderate CYP3A4 inhibitory activity. The trough levels of sunitinib and *N*-desethyl sunitinib were 63.7 and 13.7 ng/ml, respectively, with sunitinib 50 mg/day alone. While grade 2 hand-foot skin reactions and grade 2 diarrhea were observed after starting dasatinib, the trough levels of sunitinib and *N*-desethyl sunitinib were stable, and dasatinib levels were lower than the reference range. Because of the risk of severe AEs, the doses of sunitinib and dasatinib were temporarily reduced or suspended. Ultimately, they were maintained at 87.5 and 83.3% of their initial doses, respectively, with no severe AEs observed. The patient achieved a complete cytogenetic response for CML on day 154 after starting dasatinib treatment; however, RCC metastasis was observed on day 186, leading to a switch from sunitinib to axitinib. This suggests that dasatinib did not significantly affect the plasma levels of sunitinib. A dose reduction at the start of combination therapy is advisable, increasing the dose while monitoring AEs may safely provide sufficient therapeutic intensity.

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Abbreviations: TKI, tyrosine kinase inhibitor; AEs, adverse events; mRCC, metastatic renal cell carcinoma; CML, chronic myeloid leukemia; WBC, white blood cell; PLT, platelet counts; TDM, therapeutic drug monitoring; eGFR, estimated glomerular filtration rate; HFSR, hand-foot skin reaction; VEGF, vascular endothelial growth factor; PDGFR, platelet-derived growth factor receptor

Key words: sunitinib, *N*-desethyl sunitinib, dasatinib, therapeutic drug monitoring, adverse events, metastatic renal cell carcinoma, chronic myeloid leukemia

Introduction

Sunitinib is an oral multi-tyrosine kinase inhibitor (TKI) used as a first-line treatment of metastatic renal cell carcinoma (mRCC). It is primarily metabolized by CYP3A4 to an active metabolite, *N*-desethyl sunitinib, which has kinase inhibitory activity similar to that of sunitinib. Sunitinib and *N*-desetyl sunitinib contribute to therapeutic efficacy and the occurrence of adverse events (AEs) (1-6). Therefore, in clinical practice, the target trough concentration for sunitinib treatment planning is set at 50-100 ng/ml as the total sunitinib concentration, which is the sum of sunitinib and *N*-desethyl sunitinib concentrations (7,8). Given that CYP3A4 is also involved in the metabolism of sunitinib to its inactive metabolites, a combination of drugs that affect CYP3A4 activity should be considered with caution. On the other hand, although, a study on drug-drug interactions in rats reported that the combination of ketoconazole, a CYP3A4 inhibitor, and sunitinib significantly increased the concentration of sunitinib (9), the effects of drug combinations with moderate or weak CYP3A4 inhibitors remain unclear. Furthermore, while the combination of TKIs may be highly effective, their efficacy and safety are unexplored and therefore not recommended. We report the case of a patient undergoing sunitinib therapy for mRCC who was diagnosed with chronic myeloid leukemia (CML), and was simultaneously treated with sunitinib and dasatinib, a multi-TKI with moderate CYP3A4 inhibition (10,11) for CML.

Case report

A 55-year-old Japanese man visited the Department of Urology at Gunma University Hospital as an outpatient for treatment of mRCC. The patient had undergone right nephrectomy for RCC at another hospital 19 years prior to the outpatient visit, and the pathology results at that time showed clear cell RCC of the right kidney, G1>G2. The International mRCC Database Consortium risk classification at the time of diagnosis indicated a favorable risk. After nephrectomy, the patient was treated with postoperative interferon therapy for RCC according to the RCC guidelines in Japan at that time; however, metastases in the lymph nodes, pancreas, and liver were observed. Therefore, sunitinib treatment was initiated four years prior to the outpatient visit. Sunitinib at the Japanese standard dose of 37.5 mg/day for mRCC. Due to progressive metastatic growth, the sunitinib dose was increased to 50 mg/day, thus achieving disease control. Sunitinib was administered in 14-day on/7 day-off cycles. His medical history included mRCC, diabetes mellitus, Graves' disease, hypertension, and hyperlipidemia, all of which were controlled with drug therapy (sitagliptin phosphate hydrate, miglitol, azilsartan, amlodipine besylate, and atorvastatin calcium hydrate).

During a routine follow-up blood test, an increase in white blood cell (WBC) and platelet counts (PLT) was observed (WBC $17.3x10^3/\mu l$ and PLT $601x10^3/\mu l$). Cytogenetic analysis identified a 46, XY, t (9; 22) (q34; q11.2) karyotype (Fig. 1), and genetic testing using real-time PCR conducted by SRL (Fukuoka, Japan), an external laboratory with clinical laboratory accreditation, detected major BCR-ABL fusion mRNA. Fluorescence *in situ* hybridization showed 98.0% positivity for the BCR-ABL1 fusion signal (Fig. 2). Based on these finding, the patient was diagnosed with chronic-phase CML. Treatment with dasatinib was initiated to prevent progression to the acute phase due to rising blast counts. In addition, it was difficult to reduce or discontinue sunitinib because the disease had previously progressed with administration of low-dose sunitinib. At that time, pembrolizumab had not yet been approved, and while nivolumab had been approved as an alternative, the clinical team preferred to reserve nivolumab for potential future use in case sunitinib became ineffective. Given the demonstrated efficacy of sunitinib at the increased dose, it was decided to continue sunitinib as the primary treatment for mRCC. After multidisciplinary discussions between the urology and hematology teams, it was decided to implement concurrent therapy with sunitinib and dasatinib. Sunitinib and dasatinib share similar mechanisms of action, raising concerns about the potential risk of overlapping toxicities. Furthermore, the moderate CYP3A4 inhibitory effect of dasatinib posed an additional risk of pharmacokinetic interactions between the two drugs. Considering these points, the attending physician and medical staff determined that the risks could be effectively managed by closely monitoring the patient's clinical condition and implementing therapeutic drug monitoring (TDM) of sunitinib, a recognized TDM target drug in Japan, to ensure safe and effective administration.

At the start of dasatinib administration (day 1), his height and weight were 172 cm and 68.2 kg, respectively, and laboratory data were serum creatinine level 1.11 mg/dl, estimated glomerular filtration rate (eGFR) level 53.7 ml/min/1.73 m^2, aspartate aminotransferase level 17 U/IL, alanine aminotransferase level 15 U/IL, and total bilirubin level 0.4 mg/dl, without detectable abnormalities in renal and hepatic function. The combination drugs included sunitinib (50 mg/day, 14 days on/7 days off), bifidobacteria powder, heparinoid cream, sitagliptin phosphate hydrate, miglitol, azilsartan, amlodipine besylate, atorvastatin calcium hydrate, and esomeprazole magnesium hydrate, and no change in medications taken in the past month. A hand-foot skin reaction (HFSR) and diarrhea (both CTCAE grade 1) occurred on day -30 and were controlled using heparinoid cream and bifidobacterial powder. No other AEs were detected. The total sunitinib trough serum concentration immediately before starting dasatinib treatment was 77.4 ng/ml (sunitinib: 63.7 ng/ml, *N*-desethyl sunitinib: 13.7 ng/ml, Fig. 3).

The initial dose of dasatinib was set at 60 mg/day (60% dose) at the hematologist's discretion, considering the risk of worsening of comorbidities such as diabetes mellitus and abdominal aortic aneurysm, and drug-drug interactions between sunitinib and dasatinib. After starting dasatinib treatment, the HFSR worsened to CTCAE grade 2 on day 7, and treatment with betamethasone butyrate propionate ointment was initiated. Sunitinib and *N*-desethyl sunitinib concentrations were measured on day 7, considering the risk of drug-drug interactions between sunitinib and dasatinib. The total sunitinib trough serum concentration was 77.1 ng/ml (sunitinib: 64.9 ng/ml, *N*-desethyl sunitinib: 12.2 ng/ml), and no change in sunitinib serum concentration was observed after starting the dasatinib combination therapy (Fig. 3). CTCAE grade 2 vomiting and grade 2 diarrhea occurred on day 8 and dasatinib treatment was paused on day 9.

Although vomiting and diarrhea were subsequently controlled, due to the risk of severe AEs occurring with the combination of sunitinib and dasatinib, the sunitinib dose was changed to 37.5 mg/day (one dose reduction level, 14 days on/7 days off) on day 18 in accordance with the Japanese package insert of sunitinib. As vomiting and diarrhea were resolved, dasatinib was resumed on day 28 with a dose reduction of 50 mg/day (80% dose) according to the National Comprehensive Cancer Network guidelines for CML. The total sunitinib trough serum concentration on day 32 was 33.3 ng/ml (sunitinib: 28.6 ng/ml, *N*-desethyl sunitinib: 4.7 ng/ml, Fig. 3). Although the total sunitinib trough serum concentration was below the target serum concentration (Fig. 3), with the risk of AEs due to the combination of sunitinib and dasatinib, we decided to continue 37.5 mg/day. On day 57, CTCAE grade 3 neutrophil count decreased [absolute neutrophil count (ANC): $0.9x10^3/\mu l$] and CTCAE grade 1 PLT decreased (PLT: $78x10^3/\mu l$) were observed, so dasatinib was again paused. On day 70, both the ANC and PLT levels returned to the normal range, and dasatinib treatment was resumed at 50 mg/day. The total sunitinib trough serum concentration on day 70.0 was 36.6 ng/ml (sunitinib: 27.5 ng/ml, *N*-desethyl sunitinib: 9.1 ng/ml, Fig. 3). As no worsening of AEs was subsequently observed, the sunitinib dose was changed to 50.0 and 37.5 mg/day alternately (14 days on/7 days off) on day 81. The total sunitinib trough serum concentration on day 84 was 46.1 ng/ml (sunitinib: 38.7 ng/ml, *N*-desethyl sunitinib: 7.4 ng/ml, Fig. 3), and no

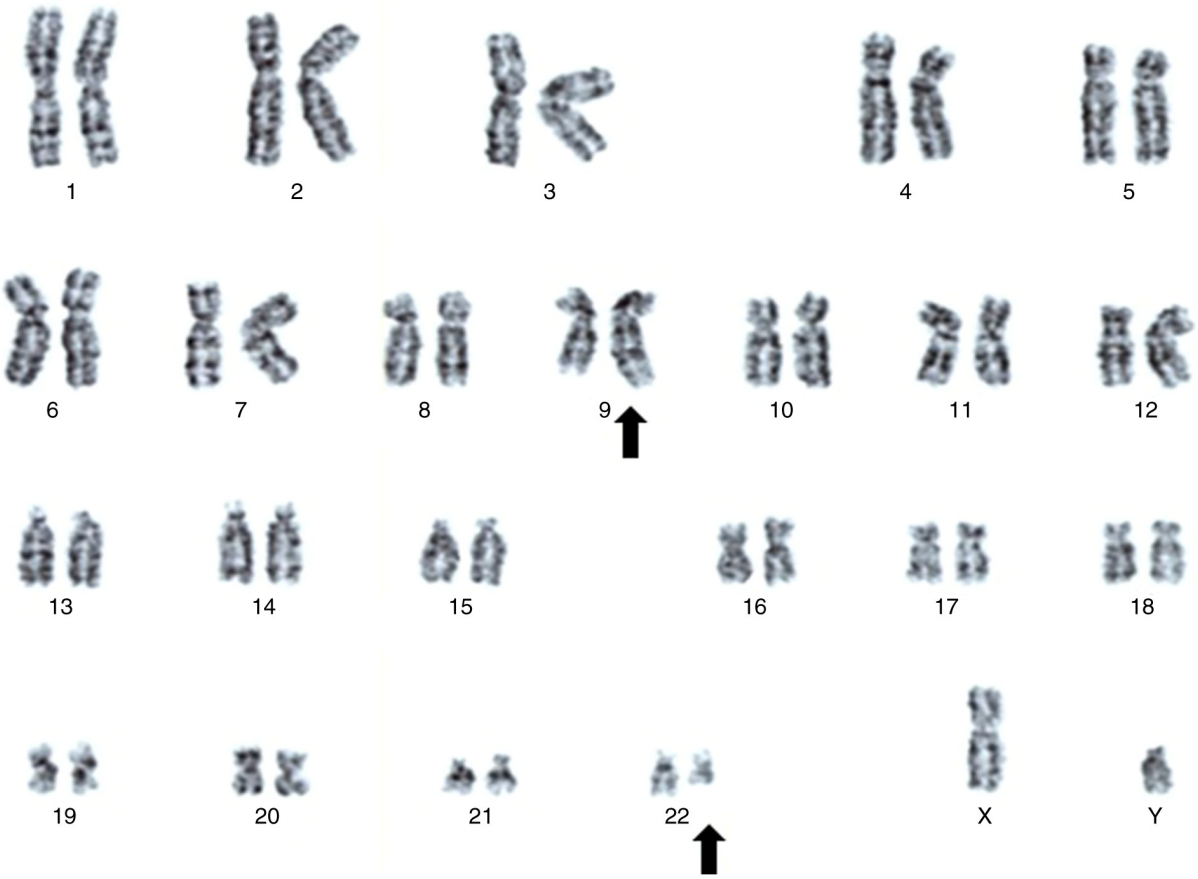

Figure 1. Analysis of the patient chromosomal karyotype.

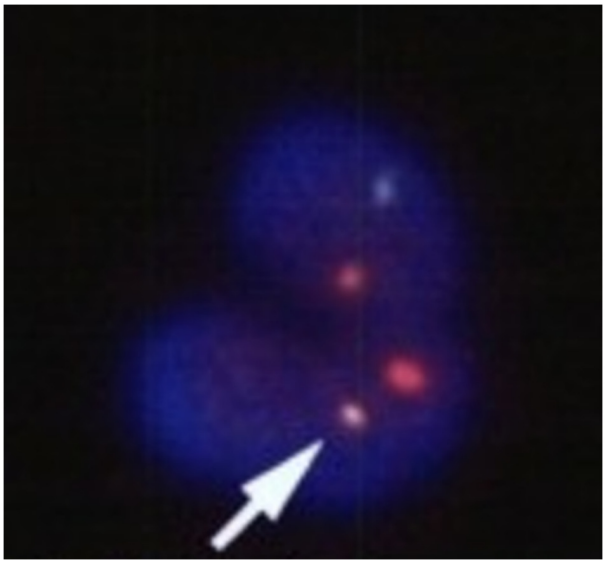

Figure 2. Interphase FISH analysis. Representative image of FISH showing a green (BCR) signal on chromosome 22, an orange (ABL) signal on chromosome 9, and a yellow fusion signal (BCR-ABL) on derivative chromosome 9. The arrows show a yellow dot that is positive for the BCR/ABL infusion gene. FISH, fluorescence *in situ* hybridization.

new AEs occurred. The patient achieved a complete cytogenetic response (BCR::ABL1^{IS}≤1%) for CML on day 154. In contrast, the treatment of the patient's renal cancer was changed from sunitinib to axitinib on day 186 because the pancreatic and left adrenal metastases were enlarged. Thereafter, a combination of axitinib and dasatinib was continued. Thereafter, dasatinib treatment was continued and multiple drugs (nivolumab, pazopanib, and cabozantinib) were administered for mRCC, but the patient died of progression of mRCC 4.4 years after starting dasatinib combination therapy.

To elucidate the reasons for the AEs, dasatinib serum concentration was measured using liquid chromatography-tandem mass spectrometry with the residue sample for sunitinib serum concentration analysis. The dasatinib serum concentrations on days 7, 32, and 84 (8 h after administration) were 1.16 ng/ml, less than the lower limit of quantification (LLOQ: 0.5 ng/ml), and 2.75 ng/ml, respectively. In Japan, sunitinib is subject to TDM, while dasatinib is not. No clear target serum concentration for dasatinib has been specified thus far, which is why it is not routinely measured. Therefore, at the time at which this case was treated, our hospital did not have a system for measuring dasatinib. Therefore, the blood concentration of dasatinib could not be monitored in real time, and analysis was performed at a later date.

Discussion

This is the first case report of the effect of the dasatinib combination on the serum concentrations of sunitinib and the occurrence of AEs in a patient receiving sunitinib. During the treatment period, no significant differences were

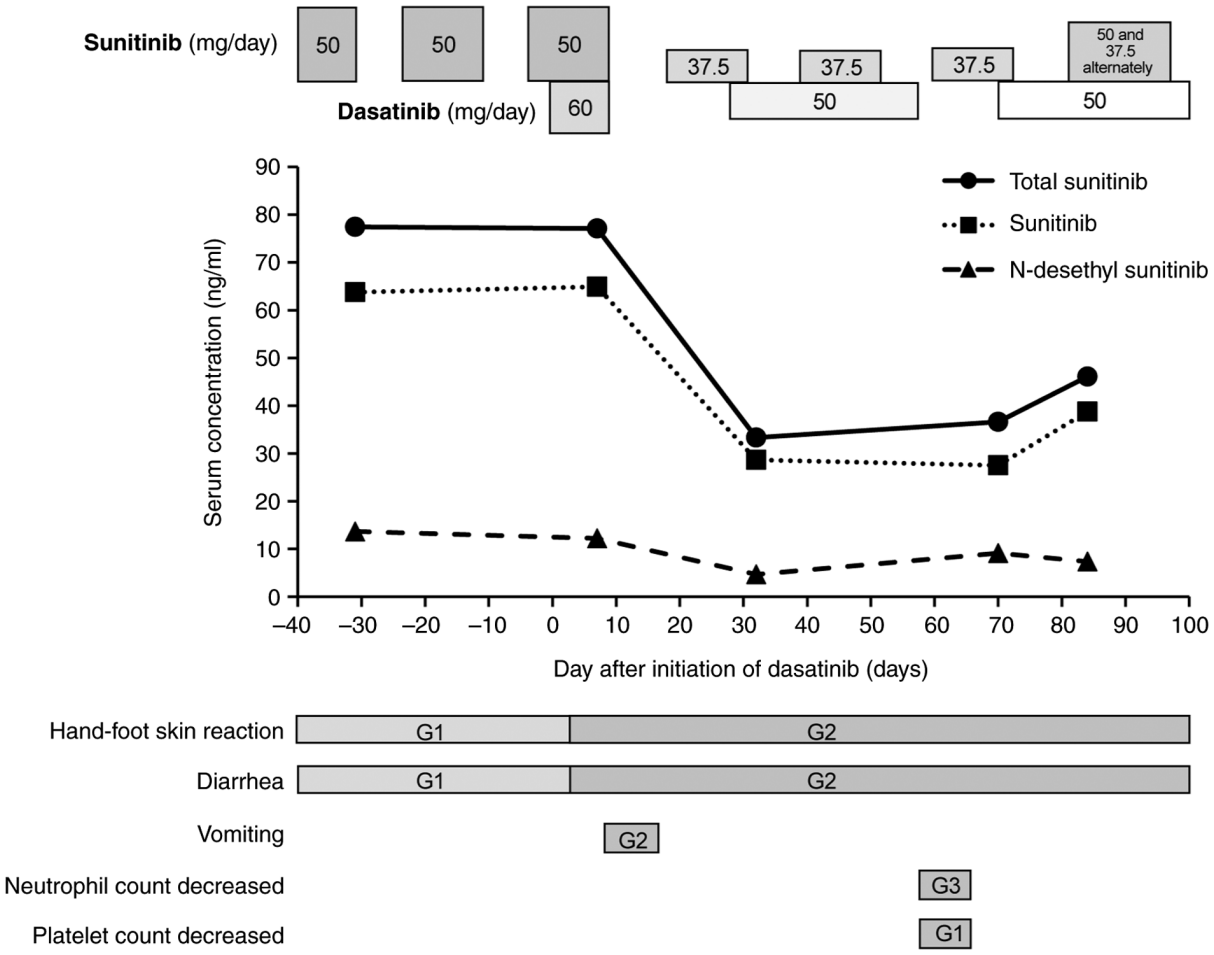

Figure 3. Relationship between adverse events and time course of sunitinib and *N*-desethyl sunitinib concentrations during combination of sunitinib and dasatinib.

observed in the trough levels of total sunitinib, sunitinib, and *N*-desethyl sunitinib between the monotherapy and combination therapy with dasatinib. Dasatinib may have moderate CYP3A4 inhibitory activity (10,11), but this study showed that the administration of dasatinib did not affect the pharmacokinetics of sunitinib, at least under clinical conditions.

Grade 1 HFSR and diarrhea progressed to grade 2 shortly after initiation of sunitinib and dasatinib combination therapy. Although dasatinib achieved sufficient efficacy against CML, its concentration (3 ng/ml, 8 h post-dose) was lower than the typical range (12) and the total sunitinib concentration did not change with the concomitant use of dasatinib. Therefore, the increase of AEs was attributed not to abnormalities of either drug concentrations but to a pharmacodynamic interaction between sunitinib and dasatinib. The lower level of dasatinib maybe due to reduced absorption resulting from the effect of the concomitant medication esomeprazole magnesium. Dasatinib has pH-dependent solubility, and co-administration of proton pump inhibitors, such as omeprazole, can decrease its absorption from the gastrointestinal tract, leading to a reduced area under the curve (13-15).

Inhibition of the vascular endothelial growth factor (VEGF) and platelet-derived growth factor receptor (PDGFR) is necessary to cause HFSR (16). Imatinib, a PDGFR inhibitor, and bevacizumab, a VEGF inhibitor, which target the inhibition of either one of these receptors alone rarely cause HFSR (17). However, the incidence increased when bevacizumab was combined with sorafenib, which inhibits VEGF and PDGFR (18). Therefore, enhanced inhibition of these related pathways may lead to an increased risk of HFSR. Sunitinib inhibits both PDGFR and VEGFR, whereas dasatinib inhibits PDGFR, suggesting that their combination may have intensified the inhibition of related pathways, potentially leading to the development of HFSR. Diarrhea caused by multi-TKIs is caused by c-Kit, which is expressed in the intestinal cells of Cajal (19). As both sunitinib and dasatinib inhibit c-kit, their combined effects may have contributed to the occurrence of diarrhea. Thus, the pharmacodynamic interaction between sunitinib and dasatinib may play a significant role in the development of HFSR and diarrhea.

Al-Najjar and Jarkowski (20) similarly reported that treatment of CML and mRCC with a combination of everolimus and dasatinib at the same time caused severe pneumonia at a relatively early stage. They pointed out that the combination of multiple molecular-targeted drugs with similar target molecules may cause serious AEs. The case of Al-Najjar and Jarkowski (20) was similar to our patient in

that the patient was a man in his 60s and had comorbidities such as diabetes mellitus. When different molecular-targeted drugs were used in combination, their synergistic effects may have contributed to the occurrence of AEs. Therefore, as in the case of our patient, when using molecular-targeted drugs in combination, caution is required regarding the occurrence of AEs caused by inhibition of those target molecules. These AEs are likely to occur relatively early.

Although the AEs observed after starting the combination therapy of sunitinib and dasatinib were within the tolerable range under supportive care, they were more severe than those observed during sunitinib monotherapy. Following the dose reduction or pause of both drugs, sunitinib and dasatinib were finally maintained at 87.5 and 83.3% of their initial doses, respectively, and no severe AEs were observed.

At the time treatment for this case was started, pembrolizumab had not yet been approved, and there were fewer treatment options available than there are today. However, even now that pembrolizumab is available, molecular-targeted drugs such as sunitinib are key drugs for patients who cannot use immune checkpoint inhibitors due to AEs or who do not achieve sufficient efficacy. The combination of molecular-targeted drugs can be considered an option for cases with multiple tumors. This report shows that in cases in which molecular-targeted drugs with the same target molecule are used in combination, the drug dose should be reduced and the occurrence of AEs should be carefully monitored, especially in the early stages of combination treatment. In addition, our case suggests that it may be possible to maximize therapeutic efficacy by increasing the dose of each drug to the target dose while controlling AEs.

This study has two limitations. First, although the presence of specific gene mutations has been confirmed in multiple tumors, searching for gene mutations using methods such as genome profiling has, to date, not been performed in general clinical practice in urological cancers, including renal cancer, in Japan. Therefore, the causative gene was not searched for this case. However, we cannot rule out the possibility that a specific gene mutation existed and created a situation different from the general case. Second, sunitinib may affect dasatinib plasma levels given the lower dasatinib concentrations observed. More research is needed to assess the effect of sunitinib on the plasma levels of dasatinib when used in combination, and the safety of higher dasatinib concentrations.

In conclusion, although dasatinib concentrations were lower than usual in this case, they were sufficient for CML treatment, and dasatinib did not affect the serum concentration of sunitinib. While HFSR and diarrhea increased after initiating the combination of sunitinib and dasatinib, temporary dose reductions or pauses, and finally maintaining at 87.5 and 83.3% of the initial doses for sunitinib and dasatinib, respectively, allowed for the continuation of therapy without severe AEs. Combination therapy at a reduced dose and escalating it based on AE monitoring may enable safe and effective treatment.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MTS, HY, TA, MN, KS and KY contributed to the conception and design of this study. MTS, HY, TA, and MN collected the data. MN and KS diagnosed and treated the patient. MTS, HY, and TA performed the data analysis. MTS, HY, and TA confirm the authenticity of all the raw data. MTS, HY, TA, MN, KS and KY interpreted the data. MTS wrote the first draft of the manuscript, and all authors commented on previous versions of the manuscript. All the authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Informed written consent was obtained from the patient for publication of this report.

Competing interests

The authors declare that they have no competing interests.

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