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Case Report

Blood Concentration of Cabazitaxel in a Patient Whose General Condition Worsened with Concomitant Use of Clarithromycin

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Keywords
Cytochrome P450 · Drug-drug interaction · Cabazitaxel · Clarithromycin · Blood concentration

Abstract
We encountered a case in which the general condition of a patient receiving cabazitaxel worsened with concomitant use of clarithromycin. Cabazitaxel is metabolized mainly by CYP3A4, and the frequency of adverse events is known to increase with increasing exposure. Although these drugs are not often quantified in daily practice, we quantified them because we considered it possible that the blood concentration of cabazitaxel had increased due to CYP3A4 inhibition of clarithromycin and that cabazitaxel-related adverse events had occurred. However, the concentration of cabazitaxel was not increased and we attributed the patient's deterioration to decreased tolerability of cabazitaxel. At least at a trough concentration of 70 ng/mL, which is the trough concentration when a normal dose of clarithromycin is administered, clarithromycin does not appear to have a significant effect on the blood concentration of cabazitaxel. This case suggests that the administration of the normal dose of clarithromycin might be relatively safe in patients receiving cabazitaxel.

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Introduction

Castration-resistant prostate cancer (CRPC) is a malignancy that progresses despite medical or surgical castration and is treated with a combination of docetaxel and prednisolone as first-line therapy. In recent years, several drugs have been developed to treat CRPC, including androgen receptor signal blockers (apalutamide, darolutamide, and enzalutamide), a cytochrome P450 (CYP) 17A inhibitor (abiraterone), and a second-generation tubulin-binding taxane (cabazitaxel). These treatment options have dramatically improved the clinical outcome of CPRC.

Cabazitaxel is one of the few drugs with demonstrated activity in patients with docetaxel-resistant CPRC, as shown in the phase III TROPIC trial, and has become an essential drug in the treatment of CRPC together with docetaxel [1]. Cabazitaxel and docetaxel are metabolized mainly by CYP3A4 [2, 3], so concomitant use of either of these agents with a drug that affects CYP3A4 activity requires caution. Concomitant use of clarithromycin, which inhibits CYP3A4, with docetaxel has been reported to increase the plasma concentration of docetaxel and the risk of neutropenia [4]. Moreover, coadministration of ketoconazole, another strong CYP3A4 inhibitor, with cabazitaxel was reported to increase the area under the curve of cabazitaxel by around 25% [5]. However, there are few reports on drug-drug interactions between taxanes and CYP3A4 inhibitors, especially in the case of cabazitaxel. The prescribing information for cabazitaxel lists CYP3A4 inhibitors that may increase its plasma concentration (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole), but no formal drug interaction studies have been conducted. There are no reports of interactions of cabazitaxel with other drugs that affect CYP3A4, such as clarithromycin, and the details of such interactions are not known. Drug-drug interactions are known to be caused by multiple factors, including genetic, food, sex, and environmental factors, and clinicians must carefully consider potential interactions when treating patients. This requires actual drug-drug interactions to be analyzed and reported in detail. However, given that recommendations have been made about providing too many details on drug-drug interactions so as to avoid alert fatigue [6], reporting on cases in clinical practice is important to accumulate knowledge.

To avoid possible CYP3A4-mediated drug-drug interactions, administration of drugs that affect CYP3A4 activity tends to be avoided in patients receiving taxanes in the clinical setting. However, there are some situations where concomitant use of a CYP3A4 modulator and a taxane is necessary, and more information on drug-drug interactions between the taxanes and CYP3A4 inhibitors is needed. We encountered a case in which the general condition of a patient worsened the day after cabazitaxel administration during concomitant clarithromycin therapy. The patient had been started on clarithromycin for medication-related osteonecrosis of the jaw that developed during cabazitaxel therapy for CRPC. However, he developed general malaise and anorexia after concomitant administration of cabazitaxel and clarithromycin. Therefore, we measured the blood concentrations of cabazitaxel and clarithromycin to determine if his deteriorating condition was the result of a drug-drug interaction.

Case Presentation

The patient was a 75-year-old man who was admitted to hospital with a diagnosis of grade 3 leukopenia following complaints of loss of appetite and general malaise during treatment with cabazitaxel for CRPC. He had previously received combined androgen blockade for prostate cancer that recurred after total prostatectomy. His treatment was switched to intensity-modulated radiotherapy because of an elevated prostate serum antigen level and

recurrence in a right internal iliac lymph node. We confirmed relapse despite administration of bicalutamide and a luteinizing hormone-releasing hormone (LH-RH) analog, docetaxel, abiraterone, and enzalutamide in that order. Therefore, the patient was started on cabazitaxel (22.5mg/m^2, intravenously administered once every 3 weeks) in the outpatient department. Continuation of cabazitaxel therapy was planned until disease progression. At this time, his height was 165.5 cm, body weight was 53.5 kg, body surface area was 1.58 m^2, and there were no other physical findings of note. There were no abnormal findings on clinical examination and both renal function and liver function were within the normal range. His past medical history included sigmoid colon cancer, right inguinal hernia, and a right adrenal tumor. No drug therapy had been administered for any of these conditions at the start of chemotherapy for prostate cancer. There was no history of drug-induced allergy other than to iodinated contrast.

The day after administration of cabazitaxel, pegfilgrastim 3.6 mg was administered subcutaneously to prevent adverse drug reactions (ADRs) such as febrile neutropenia. During cycle 7 of cabazitaxel therapy, bone scintigraphy showed an accumulation in the left lower jaw. The oral and maxillofacial surgery department diagnosed medication-related osteonecrosis of the jaw (stage II), and clarithromycin 400 mg/day was started on the same day, which was planned to continue for at least several months until his symptoms disappeared. Grade 1 anorexia appeared the day after dose 8 of cabazitaxel, after which the patient's general condition deteriorated and drinking became difficult. Nine days after dose 8 of cabazitaxel (day 10 after starting cycle 8 of cabazitaxel therapy, C8d10), the patient was hospitalized (day 0). No febrile neutropenia was seen on admission. There were no significant changes in laboratory parameters or concomitant use of drugs known to interact with cabazitaxel or clarithromycin.

On admission (day 0), although the first examination revealed pancytopenia, liver and renal function tests were within the normal range (hemoglobin 9.2 g/dL, white blood cells 1.4×10^3/μL, neutrophils 1.0×10^3/μL, platelets 8.9×10^4/μL, total bilirubin 0.9 mg/dL, aspartate aminotransferase 34 U/L, alanine aminotransferase 13 U/L, blood urea nitrogen 17 mg/dL, and serum creatinine 0.77 mg/dL). Given that the only change in drug therapy in the month after starting cycle 8 of cabazitaxel therapy was initiation of clarithromycin, the patient's symptoms were attributed to an ADR resulting from an interaction between clarithromycin and cabazitaxel and an increased blood cabazitaxel level. Clarithromycin was discontinued on the same day. The patient's general condition improved gradually and oral intake became possible on continuous fluid replacement for dehydration and anorexia. He was discharged from hospital on day 10 (C8d20).

After discharge, treatment with cabazitaxel was resumed on day 18 (C9d1). However, on day 19 (C9d2), dehydration and anorexia reappeared, and the patient was hospitalized again on day 23 (C9d16). His general condition gradually improved on fluid replacement, and he was discharged from hospital on day 32 (C9d25).

Dose 10 of cabazitaxel was administered on day 75 (C10d1) at 12.5 mg/m^2. However, his symptoms recurred, and cabazitaxel was discontinued. Thereafter, the patient was treated with an LH-RH agonist and enzalutamide; however, progression occurred on both (Fig. 1).

The patient's symptoms were thought to be an ADR stemming from an inhibitory effect of clarithromycin on CYP3A4 and an increased blood cabazitaxel level. Liquid chromatography with tandem mass spectrometry revealed cabazitaxel and clarithromycin concentrations of 1.0 ng/mL and 69.7 ng/mL, respectively, on day 0 and 1.2 ng/mL and below the limit of lower detection (<20 ng/mL) on day 28 (Fig. 2). Blood levels were taken around 9:00 a.m. and were trough concentrations. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000530547).

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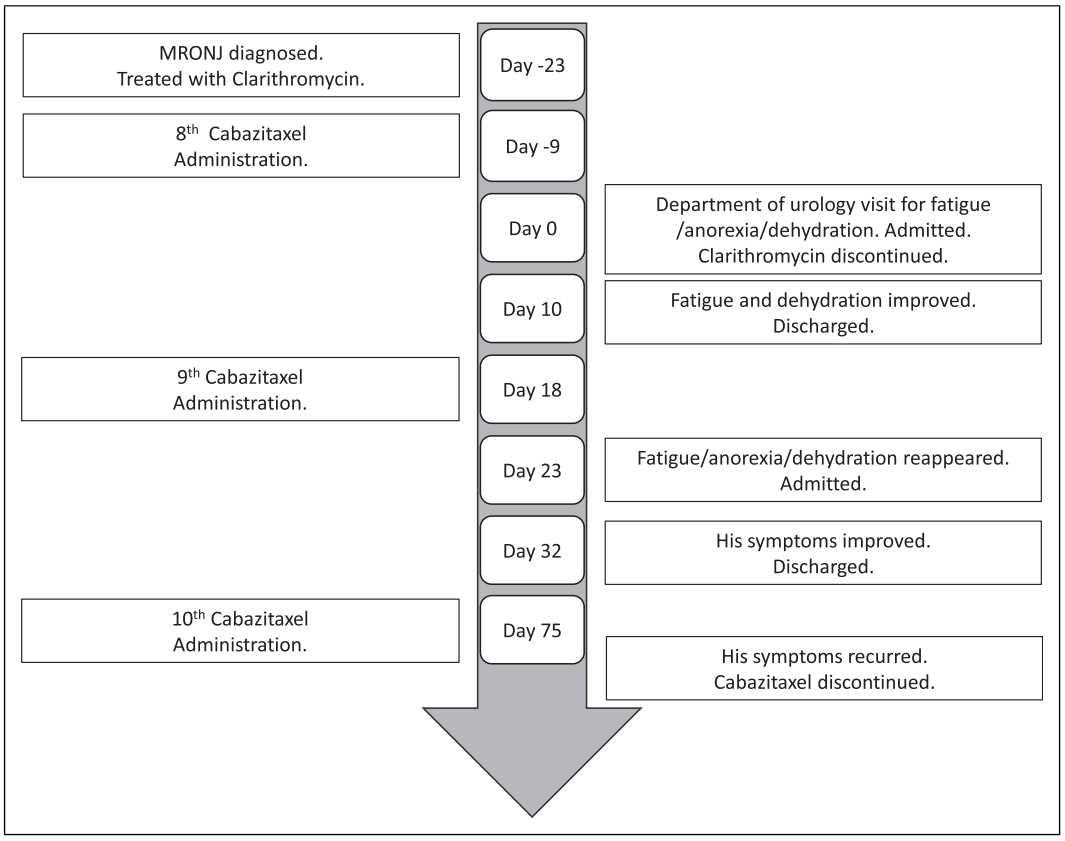

Fig. 1. Timeline for the patient.

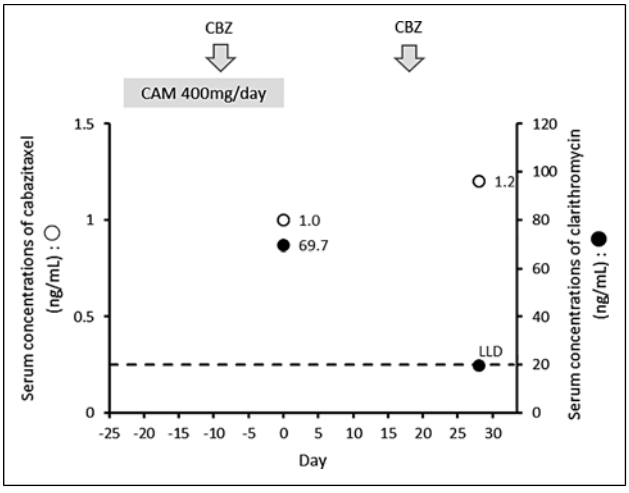

Fig. 2. The dynamics of serum concentrations of cabazitaxel (CBZ) and clarithromycin (CAM). The horizontal axis shows the day the patient was first admitted was set as day 0. The vertical axis shows CBZ or CAM concentrations. White dots (○) and black dots (●) are shown for CBZ and CAM, respectively. LLD, limit of lower detection.

Discussion

In this case, the general condition of the patient worsened the day after cabazitaxel administration while he was receiving clarithromycin. Suspecting that this deterioration was an ADR resulting from an interaction between cabazitaxel and clarithromycin, we measured

the blood concentrations of both drugs. However, we found that the blood cabazitaxel level was not significantly different after concomitant use of clarithromycin or from previously reported levels [7]. Furthermore, our patient continued to experience anorexia after clarithromycin was discontinued and the cabazitaxel dose was reduced by 50%. Therefore, we attributed the deterioration and poor appetite to accumulated damage caused by chemotherapy and loss of tolerability.

More than 90% of the total metabolic clearance of cabazitaxel (30 L/h/m^2) is reported to be due to hepatic metabolism [8], which means that the hepatic clearance of cabazitaxel is about 50% of hepatic blood flow. Therefore, the total metabolic clearance of cabazitaxel could be affected to some extent by fluctuation of hepatic intrinsic clearance. Assuming that the metabolic clearance of cabazitaxel does not fluctuate except due to fluctuations in hepatic clearance, hepatic blood flow is 1.5 L/min, and 90% of CLtot of cabazitaxel is hepatic clearance, then the product of the protein nonbinding type ratio and hepatic intrinsic clearance (fB * CLint) is approximately 1.35 L/min. Asha et al. [9] investigated the CYP3A4 inhibitory activity of clarithromycin using midazolam and reported that the magnitude of the maximal inhibition of CYP3A4 by clarithromycin 250 mg twice daily was about 60%. According to the prescribing information for cabazitaxel, the contribution of CYP3A to the hepatic metabolism of cabazitaxel is 80–90%. Assuming that the contribution of CYP3A4 to the hepatic metabolism of cabazitaxel is 85% and that clarithromycin inhibits CYP3A4 metabolism by 60%, then we would expect CLint of cabazitaxel, hepatic clearance, and CLtot to be reduced by about 50%, 35%, and 33%, respectively, using equations 1 and 2 as follows:

$$\mathrm{CLtot} = \mathrm{CLh} + \mathrm{CLother} \quad (1)$$

$$\mathrm{CLh} = \frac{\mathrm{Qh} \times \mathrm{fB} \times \mathrm{CLint}}{(\mathrm{Qh} + \mathrm{fB} \times \mathrm{CLint})} \quad (2)$$

Where CLtot is total clearance, CLh is hepatic clearance, CLother is extrahepatic clearance, Qh is hepatic blood flow, fB is protein nonbinding ratio, and CLint is intrinsic clearance.

In addition, Sarantopoulos et al. reported a 20% reduction in the clearance of cabazitaxel after repeated administration of ketoconazole, a potent CYP3A4 inhibitor [5], at a dosage of 400 mg/day, which means that the hepatic clearance, CLint, and CYP3A4 inhibition rate were reduced by about 22%, 37%, and 43%, respectively.

The CYP3A4 inhibitory activity of clarithromycin, a macrolide antimicrobial agent, is generally considered to be weaker than that of azole antifungal agents. However, based on the inhibition rate predicted from in vitro data, the CYP3A4 inhibitory activity of clarithromycin is comparable to that of ketoconazole [10]. Moreover, clarithromycin is known to cause mechanism-based inhibition of CYP3A4 activity, which is an irreversible metabolism-dependent inhibitory effect that decreases CYP3A4 activity by 42% [11]. Although the strength of the CYP3A4 inhibitory activity of clarithromycin is controversial, it is known to be at least as good as that of azole antifungal agents. Therefore, the inhibitory effect of clarithromycin on the metabolism of cabazitaxel is thought to be approximately 40% or less, at least when used in circumstances where the trough concentration of clarithromycin is about 70 ng/mL [12]. In the present study, because we took the maximum inhibition rate for clarithromycin to be 60% and the inhibition rate for ketoconazole was calculated from actual measurements, these are not generally comparable. On the other hand, taking into account the maximum inhibition rate reported in previous studies in our calculation, even at maximum inhibitory activity, the variation in total clearance would have been about 30%, which would have resulted in a maximum increase in AUC of about 43%. In fact, because the inhibition rate of clarithromycin is estimated to be about 40%, the fluctuation in total clearance would be about 20% and the fluctuation in the AUC would be about 25%. This appears reasonable even with respect to actual clinical practice. This means that the rate of decrease in CLtot was ≤20%

and that concomitant use of clarithromycin did not significantly affect the concentration of cabazitaxel in blood.

The limitation of this case report is that blood concentration measurements of cabazitaxel and clarithromycin were not evaluated at multiple points. Although the clearance of docetaxel has been found to be slower in patients who receive docetaxel in combination with ketoconazole than in those who receive docetaxel alone [13], another report has suggested that ketoconazole does not affect the pharmacokinetics of docetaxel [14]. However, with increasing attention being paid to drug-drug-gene interactions, drug-drug interactions, and drug-gene-interactions in recent years [15] and the paucity of information available on potential interactions, we should not conclude on the basis of this case alone that concomitant use of clarithromycin and cabazitaxel will not be problematic. More cases need to be accumulated.

One of the factors that can affect the blood concentration of cabazitaxel is induction of CYP3A by prednisolone, which is widely known to be an inducer of CYP3A. However, some reports have shown that prednisolone does not affect the clearance of cabazitaxel. Furthermore, in our case, there was no difference in the prednisolone dose used with and without clarithromycin. Therefore, we can rule out that clarithromycin affected the disposition of cabazitaxel by the administration of prednisolone. The patient was not receiving other concomitant medications, such as 3A4 inhibitors or inducers, that could have affected the pharmacokinetics of cabazitaxel, and dietary or environmental factors were largely unchanged.

In conclusion, although more cases need to be accumulated, our experience suggests that clarithromycin does not have a significant effect on the blood concentration of cabazitaxel, at least when used in doses such that the trough concentration of clarithromycin is about 70 ng/mL. Normal doses of clarithromycin appear to be relatively safe in patients receiving cabazitaxel.

Statement of Ethics

This case was managed in compliance with the ethical standards set out in the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of the details of their medical case. The Institutional Review Board of Gunma University does not require Ethics Committee approval for reporting individual cases.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S.K., T.A., and H.Y. designed and performed the experiments. S.K. and T.A. analyzed the data and wrote the paper. K.S. and Y.M. were in charge of the patient and decided the

treatment. K.Y., T.A., K.S., and Y.M. revised the paper. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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