Case Reports in Oncology

Case Rep Oncol 2023;16:1362–1369
DOI: 10.1159/000534595
Received: September 24, 2023
Accepted: October 11, 2023
Published online: November 9, 2023

Interference of Herbal Medicine with Axitinib in Metastatic Renal Cell Cancer Treatment: A Case Study

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Keywords

Advanced metastatic renal cell cancer · Axitinib · Checkpoint inhibitors · Herbal medicine · Electronic patient-reported outcome · Pharmaco-oncology

Abstract

Introduction: The awareness and the clinical relevance of the potential interactions between standard and complementary medicine are increasing in medical oncology. Nonetheless, the research and experience of the efficacy, safety, and toxicity of herbal substances are poorly documented. ***Case Presentation:*** Here, we report the case of a 68-year-old female patient who had been diagnosed with advanced renal cell cancer with metastasis in the liver and pancreas and had undergone surgical resection with hemi-hepatectomy and resection of metastasis in the pancreas in November 2021. Thereafter, chemotherapy was immediately initiated with three-weekly infusions of pembrolizumab and daily intake of the tyrosine kinase inhibitor axitinib. Surprisingly, 3 months after initiation of systemic treatment, the patient developed early progression and metastasis in the liver, which was then treated with selective internal radiotherapy. Despite continued axitinib and pembrolizumab treatment, a short-term follow-up in November 2022 revealed another metastatic lesion in her pancreas. Due to the presumed lack of response to treatment, the plasma concentration of axitinib was measured and found to demonstrate subtherapeutic levels of exposure. Upon extended anamnesis, the patient reported regular intake of herbal substances prescribed by her oncology acupuncturist for gastrointestinal complaints associated with the primary operation. ***Conclusion:*** Further clinical-pharmacological workup strikingly demonstrated a reduction of the therapeutic concentration of axitinib of about 90%, likely caused by herbal drugs such as Dang gui and Bai zhu.

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Introduction

Unintended impairment of efficacy in oncological treatments and in particular in targeted drugs may arise in patients seeking amelioration of potential side effects and toxicities by using complementary medicine. Some of these compounds harbor to varying degrees the potential for interactions with standard oncological treatments.

Renal cell carcinoma (RCC) accounts for 3% of all cancers. In approximately one-third of these patients, RCC develops metastatic spread with infiltration in the lung, bone, brain, liver and adrenal gland, and pancreas [1]. Even though surgery remains the most important curative approach in localized disease and selected advanced RCC, the prognosis of metastatic disease has also been improved significantly by inhibiting the interaction of the programmed death 1 receptor with its ligand (checkpoint inhibitors) and drugs such as tyrosine kinase inhibitors (TKIs) targeting the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin pathways [1].

A meta-analysis showed that complete remission can be achieved with immune checkpoint treatment [2]. It was shown that a combination of immunotherapeutic compounds was more effective than monotherapy [2]; the combination of nivolumab and ipilimumab led to an ORR of 42% in intermediate and high-risk renal cell cancer, and a significant and relevant increase in progression-free survival and overall survival [3]. This demonstrates clearly the promise and importance of further research on immunotherapeutic compounds and their combinations.

There is hope for more opportunities to improve the prognosis and prediction of therapeutic methods through new biomarkers in the future. For example, one can interpret the expression level of programmed death 1 receptor with its ligand as a negative prognostic factor with an unclear prognosis for the response to immune checkpoint inhibitors in patients with RCC. However, so far, no such specific biomarkers that can predict which patients would respond particularly well to immunotherapy or reveal which therapeutic method would be most successful for each patient are known [4].

The TKI axitinib is one of the most active VEGF-R inhibitors and has demonstrated a significant role in angiogenesis and tumor progression of RCC. Axitinib binds to intracellular tyrosine kinase domains of VEGFR and blocks downstream signaling pathways, inhibits endothelial cell proliferation, tube formation, and vascular permeability. Axitinib is metabolized and inactivated by the important cytochrome P450 (CYP) enzyme CYP3A4, both in the liver and in the intestinal endothelium, and to a lesser degree by CYP2C19. In addition, axitinib is a substrate of the UGT1A1 enzyme [5]. Ketoconazole, which inhibits CYP3A4 activity, or rifampicin, which induces many of the CYP enzymes, are classic examples of drugs that could potentially affect the metabolism of axitinib [5]. Thus, measurement of the axitinib serum concentration and consequent assessment of the potential interaction gains importance with increasingly complex cancer treatments, in particular with suspicion of a presumably poor response to the intended therapeutics. In addition, an increasing number and combination of medications and substances need to be considered for potential alterations of different CYP enzyme activities which are crucial for the proper metabolism of drugs such as axitinib [5]. Besides interactions, genetic variants may cause an unexpectedly low or high enzyme activity. However, limited data are available for the use of complementary medicine compounds, their efficacy, toxicity, and potential interaction with oncological standard therapy.

In light of patients' increasing desire for self-empowerment and active participation in treatment decisions, the importance of a thorough anamnesis on expanded medication including over-the-counter drugs and complementary treatments becomes evident. Here, we report of a female patient with advanced RCC who experienced multiple recurrences of metastases due to the metabolic interaction of her herbal medication with the TKI inhibitor axitinib. 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/10.1159/000534595).

Case Presentation

We report the case of a 68-year-old white female patient who was diagnosed with metastatic RCC in 2021 (shown in Fig. 1) as an incidental finding since a CT scan was performed during post-COVID surveillance due to unexplained coughing and increased inflammatory blood parameters. The patient was an ex-smoker (20 packyears), who neither drank alcohol nor reported any regular drug intake. Despite the advanced tumor stage, with tumor spread into the liver and pancreas, she underwent surgery with left-sided nephrectomy and splenectomy. Subsequently, adjuvant therapy with 5 mg axitinib orally twice daily and pembrolizumab 200 mg intravenously every 3 weeks was started [1]. A few weeks after the initiation of systemic treatment, the patient mentioned that she was exploring oncology acupuncture because of gastrointestinal side effects related to previous surgery [6]. She also reported mild redness, swelling, and sometimes pain in her hands and feet, possible symptoms of the hand-foot syndrome recognized as a common side effect of the TKI axitinib [7]. Furthermore, the patient was motivated to report side effects and her well-being by using the medidux™ application, wherein she indicated a moderate (grade 1–2) hand-foot syndrome and some bowel irritation, known frequent side effects during axitinib therapy (shown in Fig. 2). Various studies have shown that the use of electronic patient-reported outcomes has proven to be effective [8, 9] since the recording of symptoms and functional status assessment in a dynamic structured and standardized manner allow oncologists to monitor their patients' journeys. Shared monitoring and symptom reviews can further improve patient self-empowerment, understanding and management of side effects and optimize patient care through helpful tips and recommendations for the amelioration of specific symptoms through self-care [8]. Hence, it can be inferred that electronic patient-reported outcomes are efficacious not only in the context of personalized medicine based on our example but also in conjunction with targeted drugs.

Only a few months later, at the end of March 2022, one new metastasis in the liver demonstrated progression and a presumably ineffective systemic treatment. According to the patient's explicit wish, the lesion was removed surgically straight-away. Since a significant proportion of patients will eventually develop metastasis after nephrectomy due to altered signal transduction, next-generation sequencing (NGS) of the tumor tissue was performed. Although a TSC1 W750 pathogenic mutation was demonstrated, potentially related to tumor suppressor function of the mammalian target of rapamycin signaling pathway according to the Memorial Sloan Kettering Cancer Center Data Base, no impact with respect to the outcome of the first-line therapy or specific restriction in therapy was indicated. After an MR-scan had identified another novel lesion in the liver in October 2022, selective internal radiation therapy was performed. Finally, this rapid and unexpected dynamic tumor growth prompted the pharmacological assessment of axitinib serum concentrations in December 2022. This analysis revealed a serum concentration of 2 ng/mL 6 h after the intake of 5 mg axitinib in the morning. This axitinib concentration was unexpected and significantly lower than the threshold associated with a good response to therapy. Peak serum concentrations should be at least 12 ng/mL (at T_{max} = after 2.5–4 h after intake), or trough concentrations should exceed 2.5–5 ng/mL (Table 1).

To exclude a pharmacogenetic reason for the test results, genotyping of CYP2C19, CYP2C9, CYP2D6, CYP3A5, and UGT1A1 was carried out. The patient harbored genotypes which lead to reduced functions of CYP2C9, CYP2D6, and UGT1A1 (intermediate metabolizer), while no activity-changing variant in CYP2C19 was detected (CYP2C19*1/*1). As in most Europeans, the CYP3A5 genotype indicated a CYP3A5 non-expressor status.

As axitinib is metabolized by CYP3A4 and CYP2C19, the tested genetic influences could not explain the low serum concentrations of axitinib. Further extensive anamnestic workup then revealed that the patient took in a mixture of ten herbal medications twice daily (shown

Case Rep Oncol 2023;16:1362–1369
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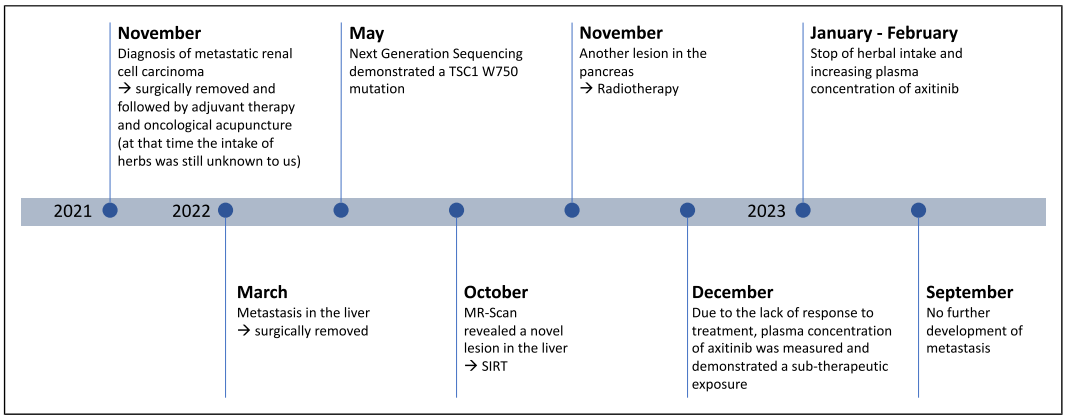

Fig. 1. This timeline presents a chronological overview of the main events in our patient's medical history from the diagnosis of metastatic renal cell carcinoma.

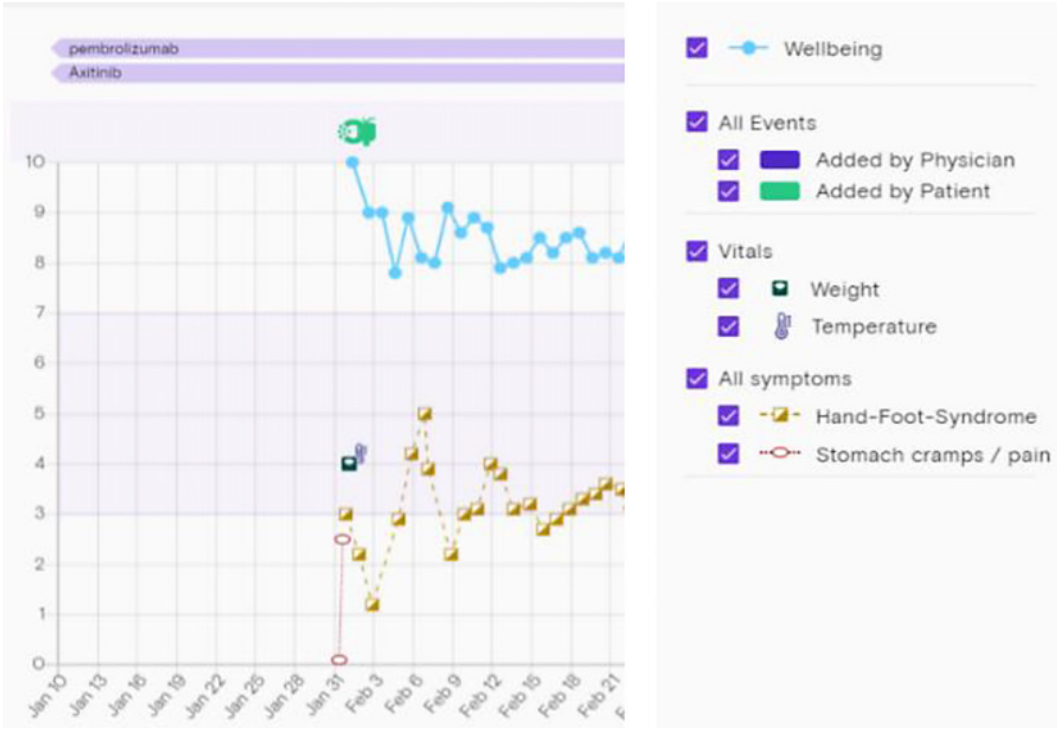

Fig. 2. History chart of ePROs as reported by the patient on her mobile device during axitinib and pembrolizumab treatment. Blue, well-being; yellow, hand-foot syndrome; red, stomach cramps/pain. ePROs, electronic patient-reported outcomes.

in Table 2), 4 h before and after the intake of axitinib, respectively, in order to relieve her gastrointestinal pain and other side effects of the systemic treatment such as her hand-foot syndrome (shown in Fig. 2). She also indicated that she had already started to take the ten-herb mixture in the beginning of her antineoplastic therapy in December 2021. The patient denied the intake of further phytopharmaceuticals or food supplements and the consumption of grapefruit or St. John's wort [10]. Upon our recommendation, the patient then stopped the intake of all herbal substances (Table 2).

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Table 1. Analysis of axitinib intake in different time intervals

Date of intake	December 21, 2022	January 19, 2023	January 31, 2023	February 01, 2023
Hours after the last intake, h	6	3.5	10	3.5
Expected concentration	2 h post-peak	Peak	Approx. trough	Peak
Herbal co-medication	Yes	No	No	No
Measured value, ng/mL	2	9	2	13

The measured drug concentrations refer to an intake of 5 mg axitinib twice a day; differentiation of herbal co-medication presence; reference drug levels: 12 ng/mL as C_{max} (peak) after 2.5–4 h or 2.5–5 ng/mL as the trough concentration.

Complementary and alternative traditional Chinese medicine is using the herbal substance Dang gui [(9) in Table 2] for the treatment of menstrual cramps and menopausal disorders. An in vitro study by Yu et al. [11] indicated that the use of Dang gui can induce CYP3A4 by activating the pregnane X receptor (PXR). The PXR is a transcription factor that regulates the expression of a variety of genes involved in the biotransformation and transport of endogenous substances, natural products, drugs, and xenobiotics. PXR affects the activities of different cytochrome P450 enzymes. PXR is present mainly in the liver but also in other tissues and plays a key role in the regulation of drug metabolism, transport, and presumably other physiological processes [12].

Additionally, the study showed a weak induction of CYP3A4 by the herbal substance Bai zhu. The herbal substance named Bai zhu [(1) in Table 2] is used for the treatment of spleen infections and gastrointestinal disorders. In Chinese language literature, which is unfortunately only available as an abstract via Pubmed, more publications about the CYP3A4-inducing effect of the two above mentioned herbal substances seem to exist [13]. Induction of CYP3A4 can decrease the serum concentrations of drugs that are metabolized by this enzyme, such as axitinib. Although we did not identify any known inductor of CYP3A4 or CYP2C19 among the remaining medicinal herbs she was taking, we cannot exclude the possibility of further interactions given the scant availability of relevant literature. Therefore, it was recommended that the patient stop the intake of the medicinal herbs for 10 days and also pause any calcium, magnesium, or antacid drugs intake, which could be in conflict with the intake of axitinib. Since the solubility of axitinib depends on the gastric pH, with higher solubility achieved in acidic pH, potential effects of acid-suppressing agents had also to be excluded [5]. As expected, the axitinib serum concentration increased during the abstinence of the medicinal herbs (9 ng/mL) in January 2023 and (13 ng/mL) in February 2023 (shown in Table 1).

To confirm the possibility of potential acceleration of the metabolism of axitinib by the Chinese herbs, we ensured that the patient was not taking any additional medication that could have triggered further interaction. Unfortunately, the patient did not agree to take in the herbs again for a limited number of days for re-exposure purposes.

The patient finally continued the standard therapy for metastatic renal cell cancer with axitinib 2 × 5 mg daily and pembrolizumab every 3 weeks. Importantly, according to a recent CT scan performed in September 2023, she has not developed further metastases.

Discussion

The pharmacokinetics of axitinib have been well-examined, indicating that there is a risk of interaction between axitinib and strong inducers or inhibitors of CYP3A4. Therefore, a variety of co-medications are not recommended [5]. As the therapy response with axitinib in

Table 2. List of herbs that our patient took in addition to cancer therapy: the botanical Latin name (right) corresponds to the Chinese term (left)

(1) Bai zhu	Atractylodis macrocephalae Rh
(2) Shan yao	Dioscoreae Rh
(3) Tai zi shen	Pseudostellariae Rx
(4) Sang ji sheng	Taxilli Hb
(5) Ji xue teng	Spatholobi Cl
(6) Long yan rou	Longan Arillus
(7) Nü zhen zi	Ligustri Lucidi Fr
(8) Ci wu jia	Acanthopanacis Senticosi Rx et Rh
(9) Dang gui	Angelicae Sinensis Rx
(10) Lian zi	Nelumbinis Sm

our patient was poor, further evaluation led to the discovery of an interaction between axitinib and Chinese herbs, which probably induced CYP3A4 and thereby enhanced axitinib elimination, preventing sufficient serum concentrations, and, thereby, therapeutic efficacy. As hypothesized, stopping the herbal compounds led to a rise of serum concentrations into the therapeutic range. Since our patient did not take any other medication or substances that might be known to affect the CYP enzymes or axitinib exposure, we strongly assume that an interaction between the Chinese herbs and axitinib led to the poor therapy response.

As the patient provided more information about the motivation of concomitant drug intake, it seems worth mentioning that more than one-third (37%) of cancer patients are using complementary and alternative medicine (CAM) [14], indicating that her situation could not be viewed as exceptional. The most common modality of applying CAM is represented by the intake of herbal substances or supplements, which is associated with a potential risk of a CAM-drug interaction with concomitant cancer therapy [15]. As described here, the consumption of herbs and/or food used as medicine and dietary supplements is common in cancer patients. Since these intakes pose a potential interaction risk to the patient, standardized and structured medical applications may help identify potential cytochrome P450-mediated herb and food-drug interactions in the daily routine [9].

However, the discussion about the likelihood and severity of interactions of CAM supplements with conventional medication will remain controversial due to inconsistent data and a lack of clinical studies [16]. Regarding the utilization of traditional Chinese medicine, another herb mixture called Bu-Shen-Jian-Pi-Fang, which was not employed in our patient's case but also includes the already mentioned Dang gui, is frequently used by patients with RCC. It has been reported to attenuate the tumorigeneses signaling pathway in RCC and supports immunotherapies. These findings should stimulate further clinical investigations into Chinese medicine [17]. Repeated axitinib concentrations taken under the Chinese herb mixture and during abstention, render the described pharmacological mechanism rather likely. Whether the herbal substance induced the metabolism of axitinib via CYP3A4 or whether another unidentified interaction took place, can, however, not be deduced from this case report. In an in vitro study, Dang-gui and Bai zhu have been identified as CYP3A4-inducers [6]. It is, however, not reported whether and to which extent the other herbal compounds of the mixture exert effects on drug metabolism, so that their contribution to the effect remains unknown. Furthermore, it should be noted that the quality and precise make-up of herbal mixtures is not always guaranteed or consistent across the globe. Typically, herbal medicines are available both over-the-counter and as products requiring a prescription. The latter tend to feature higher quality and consistency [18].

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Consequently, the potential interaction risks between conventional cancer therapy and over-the-counter CAM supplements seem frequently underestimated [16] and should potentially promote sequential rather than concomitant compound exposure. Caregivers should address interaction risks, ask explicitly about and document CAM supplement use, and review potential interactions. We must not overlook the significance of distinct effects and responses to gender-specific therapies. Furthermore, there is evidence suggesting that men and women may exhibit different responses to particular immune checkpoint inhibitors, and this aspect should not be underestimated [19]. Additionally, the self-reporting of symptoms in digital diaries may be promoted, allowing for less biased data analytics. However, the use of complementary medicine and food supplements is often not recognized and may therefore be overlooked [20].

Conclusion

Drugs and herbal substances may interfere with standard oncological treatments which may become clinically relevant. This needs to be considered especially in cases of poor response to therapy. Thorough co-medication anamnesis and details about complementary drugs need to be considered in the prescription and monitoring of targeted drugs in oncology.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. We obtained written informed consent from the patient to publish this case report and any associated images.

Conflict of Interest Statement

A.T. is an initiator and stock owner of mobile Health AG, a startup company that operates the medidux smartphone app. He serves as chief medical officer for the startup company. Y.K. is Head of Project Management Mobile Health AG. A.J. has no conflicts of interest to declare.

Funding Sources

The Foundation Swiss Tumor Institute has supported the master's thesis with a restricted grant.

Author Contributions

A.T., A.J., and M.K. are physicians and contributed to the design and conduct of the study and to the writing of the manuscript. F.H. is a medical student and Y.K. is an economist and a former medical student. F.H. and A.T. wrote the manuscript with contributions of A.J. All authors provided final approval of the manuscript. (1) Guarantor of integrity of the entire study: A.T. (2) study concepts and design: F.H., A.T., and A.J. (3) literature research: F.H. and A.T., (4) clinical studies: A.T. and M.K. (5) experimental studies/data analysis: A.T, F.H., and A.J. (6) statistical analyses: na (7) manuscript preparation: F.H., A.T., Y.K., and A.J., and (8) manuscript editing: Y.K. and A.T.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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