

EVEROLIMUS THERAPEUTIC DRUG MONITORING IN A CANCER RENAL CANCER PATIENT WHEN DOUBLE DRUG-DRUG INTERACTION IS DETECTED AND A REVIEW OF THE LITERATURE

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Abstract

Everolimus is an inhibitor of mammalian target of rapamycin (mTOR) widely used as an immunosuppressant in transplant patients. In transplantation setting, several recommendations for therapeutic drug monitoring are available, due to potential drug-drug interactions with chronic medication, which can affect everolimus pharmacokinetic profile. Everolimus is also used in breast, neuroendocrine and renal cancer, at higher doses than in transplantation and without systematic drug monitoring requirement. We present a case-report of a 72years-old woman with epilepsy history to whom everolimus 10mg/daily was prescribed as third line of treatment for renal cell carcinoma. The patient's chronic medication was checked by the outpatient hospital pharmacist before initiating treatment. As a result, two major interactions with inducers of CYP3A4 metabolism as carbamazepine and phenytoin were detected. Since trough plasma concentration of everolimus could be affected, by these pharmacokinetic interactions, a therapeutic drug monitoring of everolimus was proposed. Based on the literature, C_{min} plasma concentration (C_{minss}) of everolimus over 10ng/ml is associated with better response to treatment and progression free survival. During the oncologist follow-up visit and according to pharmaceutical recommendations, everolimus dosage was increased to 10mg every 12 hours. In the following determinations of trough plasma everolimus concentration, C_{min} grew up from 3.7ng/ml to 10.8ng/mL. Depending on the CYP3A4 induction capacity and potency of the drug/s administered concomitant to everolimus and how many of them can potentially interact with it, therapeutic everolimus monitoring would be advisable in order to adjust dosage if required to prevent underexposure.

INTRODUCTION

Everolimus is an orally administered rapamycin derivate inhibiting the mammalian target of rapamycin (mTOR). This is a key signalling molecule in the phosphatidylinositol 3-kinase (PI3K)/Akt pathway which is involved in the regulation, growth, proliferation, metabolism, survival and angiogenesis of cells that is often dysregulated in cancer (Figure I). Nowadays is used as cancer treatment at a fixed dose of 10mg/daily for metastatic renal cell cancer and in neuroendocrine tumours, and in combination with exemestane for advanced hormone receptor positive (HR+), negative human epidermal growth factor-2 (HER2-) breast cancer.^{1-3.}

Everolimus is also used in transplant patients as immunosuppressant. Due to its narrow therapeutic index and pharmacokinetic inter-individual variability, routine therapeutic drug monitoring (TDM) is recommended to

maintain a Cminss between 3-8 ng/ml⁴⁻⁵. In cancer patients, Cminss below 10ng/ml have been associated with worse response to treatment while Cminss higher than 26.3ng/ml has been related to higher incidence of adverse events. However, in cancer setting, TDM is not currently performed. Variability in everolimus blood exposure may be influenced by several factors, including age, sex, body composition, genetic factors and drug-drug interactions which could affect its hepatic metabolism by cytochrome CYP3A4⁷⁻⁹. We present a case report of a 72 years-old woman treated with everolimus for renal cell cancer and a double drug-drug interaction with carbamazepine and phenytoin.

CASE DESCRIPTION

A 72-year-old woman with smoking and epilepsy history was diagnosed from a stage pT3a renal carcinoma in December 2015. Radical right nephrectomy was performed in February 2016 and oncological follow-up was performed every 3 months. In September 2018, a right lung segmentectomy was practiced due to lepidic adenocarcinoma growth. Post-surgical changes included right atelectasis, pleural effusion and a right hilar adenopathy of 16 x 13 ml was detected. Two and a half years later, on February 2021 progression was detected with right adrenal massive bleeding, hilar adenopathy and left renal adrenal metastasis. In May 2021, treatment with nivolumab for intermediate-risk clear-cell renal carcinoma was initiated achieving stabilization of the tumour. Treatment was well-tolerated, despite dry mouth, grade II anorexia and grade I astheny, without immune-mediated toxicities found. However, a new progression was detected and oral treatment with cabozantinib 60 mg daily was initiated as second line treatment in December 2021. Secondary to treatment, patient had grade I hypertension, and also referred nausea and grade I diarrhoea, so treatment with enalapril 5mg c/24h was prescribed, but no reduction in cabozantinib dose was needed. A new progression of cancer was detected and third line treatment with everolimus at 10 mg/daily in fasted conditions (1 hour before breakfast) was started in the 21st of March, 2022.

Before any oral cancer treatment initiation, patient chronic medication plan is reviewed by the hospital pharmacist as part of pharmaceutical care provided. On this occasion, treatment included Carbamazepine 400mg every 12hours, Phenytoin 100mg every 12 hours and Acetaminophen 650mg plus Tramadol 75mg every 8 hours. Drug interaction checking was performed, using two databases (Lexicomp and Drugs). As a result, a joined interaction of everolimus with both antiepileptic drugs was detected. Carbamazepine and Phenytoin are classified as strong CYP3A4 inducers and could lead to decreased everolimus Cminss and diminish its efficacy. According to this finding, after multidisciplinary discussion within the oncologist and the pharmacist, a TDM was suggested and planned, and blood samples were obtained immediately before everolimus administration in 20th April. Method used for analysis was ultra-high-performance liquid chromatography coupled to tandem mass spectrometry. TDM result showed a Cminss of 3.7ng/ml which was considered as an underexposure to everolimus .

Adherence to treatment was reinforced to patient and, since patient didn't have any relevant toxicities, pharmacist suggested an everolimus dose increase from 10 mg to 15 mg daily (administered 10 mg, 1-hour before breakfast and 5 mg, 1-hour before dinner) which was agreed with patient's oncologist. A second TDM was scheduled in 16th of May and showed that Cminss had increased from 3.7 to 6.4 ng/ml, without relevant toxicities. A second dose adjustment was made, and dose was increased once again until 10mg every 12 hours, administered before meals. Two-weeks and a month later, new TDM were planned and Cminss observed were 10.6ng/ml and 8.7ng/ml, respectively (Figure I). During everolimus treatment, stable disease was achieved, and no relevant toxicities were observed. Unfortunately, everolimus treatment was stopped on July 2022, due to lung progression, pleural effusion, and respiratory insufficiency, and finally patient died one week later.

DISCUSSION

Everolimus is an oral mTOR inhibitor that binds with high affinity to the FK506 binding protein-12 (FKBP-12), and activation of mTOR is inhibited by this complex. Due to several factors could affect its pharmacokinetic profile, TDM is routinely established when everolimus is used in transplant patients to achieve the optimal Cmins, whereas in cancer patients is not established¹⁰.

According to product label, in oncology, everolimus is prescribed as an standard fixed oral dose of 10 mg,

administered once daily. It is absorbed rapidly and peak concentration is reached after 1.3–1.8 hours. The systemic availability of a single oral 10 mg dose of everolimus is significantly reduced by coadministration with a meal compared with fasting conditions. Maximum concentration (C_{max}) and area under the concentration-curve time (AUC) were reduced by 42% and 22% after low-fat meals; this reduction is increased until 54% and 33% after a high-fat meal¹¹. To avoid this variability in absorption we recommended our patient to take everolimus every day in fasting conditions, at least 1-hour before breakfast. Everolimus steady (SS) state is reached within 7-14 days, and steady-state peak and trough concentrations, and AUC are proportional to dosage.

Five studies with 945 patients treated with everolimus (lung, renal and neuroendocrine tumors) were included in a meta-analysis by Ravaud et al where the mean everolimus C_{minss} was 15.65ng/ml (90%CI 14,79-16.55ng/ml)⁶. Better response and major reduction in tumour size were observed with a two-fold increase in C_{minss}. In conclusion, C_{minss} [?] 10 ng/mL could be used as target value for optimal response, while C_{minss} > 26.3 ng/mL was associated with a 4-fold increased risk of toxicity compared to C_{minss} < 26.3 ng/mL. Only 45% of patients with neuroendocrine tumors achieved optimal everolimus plasmatic concentrations (10-30ng/ml), while in lung and renal cancer were 55.2% and 62.9%, respectively. Administering everolimus with strong CYP3A4 inhibitors increased everolimus C_{ss} by 10%. On the other hand, a 7% decrease was observed upon coadministration of CYP3A4 inducers. In another study by Hirabatake et al. median PFS was 13.7 months (1.7-55.8 months) and fifty per cent of breast cancer patients treated with everolimus showed C_{ss} below 10ng/ml. PFS was significantly longer in the 10-20ng/ml group (p=0.0078) and the median of C_{minss} in patients with dose-limiting toxicities was 19ng/ml (11.3-64.6ng/ml)¹².

One of the reasons of the interindividual pharmacokinetic variability of everolimus can be explained by different activities of the drug efflux pump P-glycoprotein and of metabolism by cytochrome P450 (CYP) 3A4, 3A5 and 2C8⁸. The critical role of the CYP3A4 system for everolimus biotransformation leads to drug-drug interactions with other drugs metabolised by this cytochrome system and could affect its efficacy or toxicity.

There are some studies and several reports in the literature with single drug-drug interaction with everolimus.

In a study in 16 healthy subjects reported by Kovarik et al., verapamil (a relatively potent inhibitor of P-glycoprotein, and a moderate inhibitor of CYP3A4) administered as 80mg three times daily, during 6 days, was added to a single 2 mg dose of everolimus¹³. During verapamil co-administration, everolimus C_{max} increased 2.3-fold (90% CI, 1.9,2.7) from 21 ± 8 to 47 ± 18 ng ml⁻¹ and AUC increased 3.5-fold (90% CI, 3.1, 3.9) from 115 ± 45 to 392 ± 142 ng ml⁻¹ h. In a case report by Strobbe et al., interaction with verapamil at 120mg every 12 hours, and everolimus at 7.5mg daily was reported in cancer renal patient¹⁴. The patient developed a grade 3 oral mucositis and everolimus plasma concentration was 52.4 ng/mL. Administration of everolimus was stopped and then was reintroduced to a 5 mg/daily. The efficacy of everolimus was maintained during more than a year, and a partial tumour response to the 5 mg dose was identified and deemed to be generally well tolerated.

In another study by Kovaric et al., erythromycin 500 mg (a CYP3A inhibitor) administered three times daily, for 9 days and a single 2-mg dose of everolimus were co-administered¹⁵. Everolimus C_{max} was risen up 2.0-fold (90% CI, 1.8–2.3) from 20±5 ng/ml to 40±10 ng/ml and AUC was increased 4.4-fold (90% CI, 3.5–5.4) from 116±37 ng h/ml to 524±225 ng h/ml during erythromycin coadministration.

A case of potential interaction in cancer renal patient after three months under everolimus treatment was reported by Miesner et al.¹⁶ when clarithromycin was added to his treatment. *Helicobacter pylori* infection was suspected and amoxicillin, clarithromycin, and omeprazole therapy was started. Then, 12 days after initiation of this regimen, he was admitted with acute kidney injury, proteinuria and an everolimus trough level of 110 ng/mL (20 hours postdose)

Tran et al. reported a case of a 32- year- old female with relapsed Hodgkin's lymphoma who was on everolimus for 5 years and developed nephrotic syndrome and everolimus C_{ss} found was > 40ng/ml, 2 months after initiation of voriconazole for aspergillus pneumonia¹⁷.

Mir et al. described an induction CYP3A4 interaction when fenofibrate was added in a cancer metastatic breast patient who was being treated with everolimus 10mg/daily plus exemestane 25mg/daily¹⁸. Everolimus trough plasma concentration was 10.1 ng/ml before introduction of fenofibrate. Two weeks later, everolimus trough concentration had dropped to 4.2 ng/ml. Hence, fenofibrate was withdrawn. Two weeks later, everolimus trough concentration rose to 11.5 ng/mL.

To our knowledge, this is the first case report in the literature with two major interactions which can affect everolimus metabolism through strong induction of CYP3A4. Everolimus dosing was optimized to achieve optimal C_{ss} by using TDM. Carbamazepine and phenytoin are major CYP3A4 inducers and one month after starting treatment, C_{ss} everolimus detected was 3.7ng/ml. To achieve optimal C_{ss} (10ng/ml) progressive dosage increase from 10mg daily to 15mg daily of everolimus was suggested, and total daily dose was divided into two doses separated 12 hours, 10mg-5mg, in fasting conditions. Pharmacokinetic optimization of everolimus dosing in oncology has been studied, by Verheijen et al., in a crossover trial in 10 patients, that compared everolimus 10 mg once daily with 5 mg twice daily¹⁹. Twice daily dosage regimen showed a significantly decrease in C_{max} from 61.5ng/ml to 40.3ng/ml (p=0.013), and significantly increase in C_{ss} from 9.6ng/ml to 13.7ng/ml (p=0.018), without differences in AUC between them (435ng*h/ml vs 436 ng*h/ml) (p=0.952).

Our patient finally achieved an optimal C_{ss} two months later, after two dose adjustments to increase everolimus dosage to 10mg every 12 hours.

CONCLUSION

Everolimus is a substrate of CYP3A4 and P-glycoprotein whose blood concentrations can be seriously affected by drug interaction at that level, eventually implying underexposure to everolimus. Therefore, TDM should be used whenever potential metabolism drug-drug interactions are detected in cancer patients to monitor drug levels and to contribute to achieve the optimal C_{ss} ultimately associated with better response and a lower toxicity profile.

CONFLICT OF INTERESTS

The authors have no competing interests to declare.

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