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Personalized Management of Palbociclib and Ribociclib Using TDM, Pharmacogenetics, and Drug–Drug Interaction Assessment: A Clinical Case Series

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ABSTRACT

A substantial person-to-person variability in clinical outcomes with cyclin-dependent kinase 4 and 6 inhibitors (CDKis) has been documented. Here, we describe a series of five individuals receiving palbociclib or ribociclib who were evaluated through our clinical pharmacology consultation service, which included therapeutic drug monitoring (TDM), pharmacogenetic assessment, and drug–drug interaction review to assist physicians in optimizing CDKi therapy for metastatic breast cancer. Plasma samples used for TDM were obtained at steady state and quantified via an LC-MS/MS procedure to determine minimum plasma concentrations (Cmin). Drug underexposure or overexposure was assessed in relation to mean Cmin values reported in population pharmacokinetic investigations. Genetic variants in selected ADME-related genes (CYP3A4, CYP3A5, ABCB1, SLCO1B1, and ABCG2) were examined. Three of the five patients showed CDKi levels exceeding population means and were evaluated for toxicity. One carried a reduced-function ABCB1 haplotype (ABCB1-rs1128503, rs1045642, and rs2032582), which may explain enhanced oral absorption and elevated drug concentrations. Two subjects demonstrated subtherapeutic exposure, and one of these experienced early disease progression. In another case, a CYP3A5*1/*3 genotype was identified as a possible driver of increased metabolic activity and reduced plasma drug levels. This more detailed pharmacologic strategy in a real-world setting appears to help treating oncologists refine drug and dose selection and may ultimately improve both the safety and therapeutic performance of CDKi regimens.

Keywords: Personalized medicine, TDM, Polymorphisms, Pharmacological counselling, Preast cancer, CDK4/6 inhibitors

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Introduction

Cyclin-dependent kinase 4 and 6 inhibitors (CDKis), when used together with endocrine treatment, constitute the preferred first- or second-line option for hormone receptor (HR)-positive, HER2-negative metastatic breast cancer (MBC) [1, 2]. Although clear benefits have been demonstrated for progression-free survival (PFS) and overall survival (OS), marked variability in individual therapeutic outcomes has been observed [3]. Some patients develop pronounced or unexpected toxicities requiring dose modification, interruptions, or discontinuation, while others obtain differing degrees of clinical benefit.

Variations in patient-specific plasma exposure to these agents likely contribute to this heterogeneity. All three CDKis in clinical practice—abemaciclib, palbociclib, and ribociclib—show notable between-person differences in exposure, with coefficients of variation for minimum plasma concentration (Cmin) spanning 40 to 95% [3]. Although links between CDKi exposure and treatment efficacy remain insufficiently characterized, the association between systemic exposure and toxicity is increasingly recognized [3]. Elevated palbociclib exposure (evaluated through AUC) has been tied to a higher likelihood of neutropenia and thrombocytopenia [4-6]. For ribociclib, cardiac adverse effects have been correlated with steady-state maximum concentration (Cmax) [7]. A phase I trial

reported a relationship between increased ribociclib Cmin and hematologic toxicities, including neutropenia and thrombocytopenia [8], with later investigations confirming this pattern [3]. Increased exposure to abemaciclib has also been associated with a greater risk of neutropenia [9]. Yet, findings regarding exposure–efficacy for palbociclib and ribociclib have been inconsistent [7]. In the PALOMA-1 study, individuals whose average palbociclib concentration exceeded the population median (61 ng/ml) tended to show longer PFS [10]. Conversely, analyses from MONARCH 3 indicated that higher abemaciclib levels correlated with greater tumor reduction and a reduced hazard of disease progression [9]. Numerous internal and external contributors—including genetic variability and concomitant interacting therapies—may alter CDKi exposure by influencing absorption, distribution, metabolism, and excretion (ADME) **(Figure 1)**.

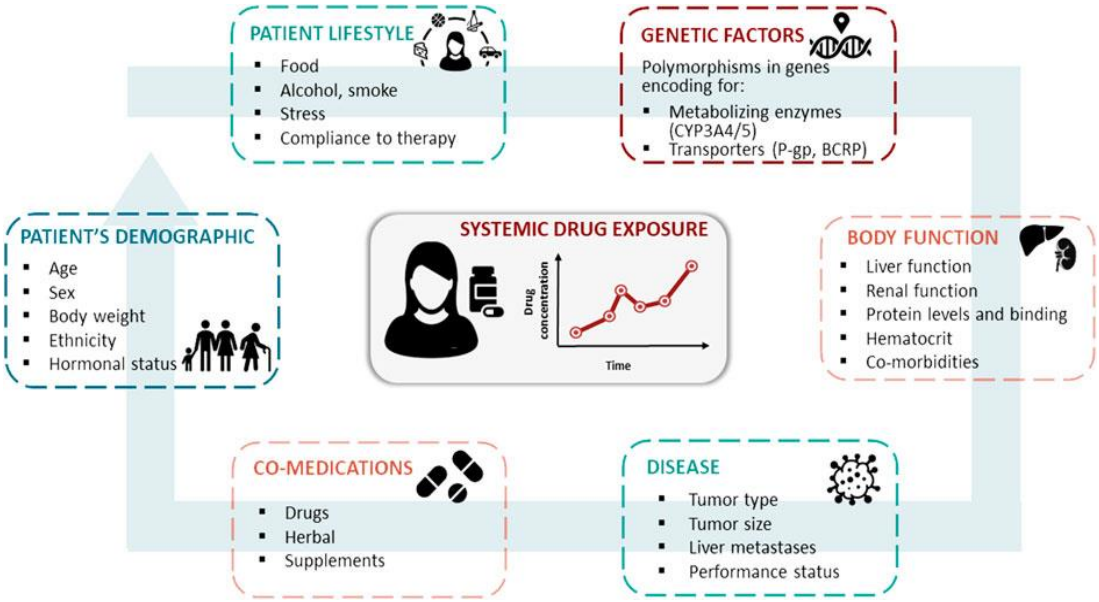

Figure 1. Patient-specific traits, co-medications, lifestyle, genotype, physiological status, and disease factors constitute principal drivers of both between- and within-patient pharmacokinetic variability for oral targeted agents such as CDK4/6 inhibitors.

Following rapid uptake and distribution, all three CDKis are metabolized predominantly by CYP3A. Besides CYP3A involvement, palbociclib also undergoes hepatic biotransformation via SULT2A1. Palbociclib and ribociclib participate in phase-II glucuronidation through UGT enzymes. Palbociclib and abemaciclib act as substrates for the efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), which can influence oral bioavailability and tissue distribution. Ribociclib is likewise transported by P-gp but demonstrates minimal movement through BCRP.

Genetic variants that impact the amount or functional activity of enzymes responsible for hepatic oxidative metabolism or intracellular transport may serve as indicators of CDKi systemic exposure [11]. Although CDKis were incorporated into routine oncology practice only in recent years, evidence on how pharmacogenetics might guide their optimal use is still sparse. Insights from well-established genotype–drug relationships—such as DPYD-fluoropyrimidines, CYP2D6-tamoxifen, TPMT/NUDT15-thiopurines, and UGT1A1-irinotecan [12] — have demonstrated that inherited differences in ADME genes can predict circulating drug concentrations and therapeutic response. Comparable exploratory findings have also been reported for several oral kinase inhibitors (KIs), including imatinib [13], gefitinib [14], sunitinib [15], and the selective estrogen receptor modulator tamoxifen [16]. These observations raise the possibility that similar variability may influence CDKi performance, though targeted investigations remain necessary. Drug–drug interactions (DDIs) have already been shown to markedly modify CDKi pharmacokinetics, thereby shaping both benefit and risk profiles [17, 18]. The AMBORA trial further demonstrated the value of structured pharmacological support in improving medication safety and patient-reported outcomes in those treated with palbociclib or ribociclib [19].

Recently, the Experimental and Clinical Pharmacology Unit at the National Cancer Institute CRO Aviano launched a pharmacological counselling program. This service incorporates therapeutic drug monitoring (TDM), genetic characterization, and evaluation of concomitant therapies for a wide range of medications. It includes

compounds with validated exposure–response relationships and established Cmin targets, such as imatinib and sunitinib—where TDM is recommended—or agents like letrozole, for which monitoring may provide added value [20]. The service also evaluates TKIs with uncertain exposure–outcome relationships, including CDK4/6 inhibitors and PARP inhibitors, for which TDM remains exploratory.

Within breast cancer management, the usefulness of a more detailed pharmacologic strategy becomes evident, considering how TDM, pharmacogenetics, and DDIs can influence CDKi-related results. Hematologic toxicities constitute the predominant dose-limiting adverse effects of CDK4/6 inhibition, contributing to treatment interruption in roughly 70% of individuals and prompting early dose reduction in 40–50% [21]. Abemaciclib is associated with fewer hematologic problems than palbociclib or ribociclib, with diarrhea representing the typical reason for a dose change. This type of evaluation may be valuable in a reactive context—when unexpected toxicity or lack of efficacy suggests altered exposure—or in a pre-treatment setting to adapt therapy and limit DDIs or drug–gene interactions (DGIs). This report outlines the outcomes of the counselling program recently adopted at the National Cancer Institute CRO Aviano, Italy, as a support tool for optimizing CDKi use in MBC.

Materials and Methods

Patients

In September 2020, the Clinical Pharmacology Unit at the National Cancer Institute CRO Aviano initiated pharmacological counselling to assist oncologists in selecting first- or second-line CDKis (palbociclib, abemaciclib, ribociclib) and endocrine therapy (letrozole) for HR-positive/HER2-negative MBC. The service had previously been available for other oncology KIs such as imatinib, sorafenib, regorafenib, sunitinib, and lenvatinib, as well as three PARP inhibitors: olaparib, niraparib, and rucaparib. Written consent was obtained for both pharmacogenetic and TDM evaluations, and for the publication of these anonymized cases. Information regarding age, diagnosis, stage, molecular classification, therapeutic regimen, dosage, adverse events, and concomitant treatments was extracted from electronic health records based on clinicians' documentation. Toxicities were retrospectively collected through chart review and scored using CTCAE Version 5.0.

The pharmacology laboratory is currently progressing through UNI EN ISO-15189 accreditation and participates in EMQN (www.emqn.org) and SKML (www.skml.nl) external proficiency programs for routine pharmacogenetic and TDM analyses.

Pharmacogenetic analysis

Genes of interest were chosen following a PubMed-MEDLINE review, prioritizing those encoding proteins relevant to the ADME profile of CDK inhibitors [11]. Since CDKis are frequently co-prescribed with letrozole, genotyping for SLCO1B1*5/*15/*17 was also performed [22]. Genotype assessment included CYP3A4 (*1B, rs2740574; *1G, rs2242480; *3, rs4986910; *20, rs67666821; *22, rs35599367; *26, rs1381053638); CYP3A5 (*3, rs776746; *6, rs10264272; *7, rs41303343); SLCO1B1 *5/*15/*17 (rs4149056); ABCB1 (1236C > T, rs1128503; 3435C > T, rs1045642; 2677G > T/A, rs2032582); and ABCG2 (421C > A, rs2231142). SNP detection was carried out using the SNPline PCR Genotyping System with KASP chemistry (LGC Genomics, Hoddesdon, United Kingdom) following the manufacturer's protocol [23]. The tri-allelic call for ABCB1 2677G > T/A was completed by PyroMark Q48 (Qiagen, Hilden, Germany). Primer information and further genotyping specifications can be supplied on request. Each run included appropriate positive and negative controls.

Therapeutic drug monitoring

Plasma samples were produced by centrifuging whole-blood EDTA tubes at 2,450 g for 10 min at 4°C, then stored at −80°C. Concentrations were determined with a newly validated LC-MS/MS assay as described previously [24]. Sampling at predefined intervals permitted estimation of steady-state C_{min} or C_{max}. Patients were instructed to take their last dose either 24 h before sampling (C_{min}) or 1–4 h prior (C_{max} for ribociclib). Times of administration (self-reported) and of sampling were documented. Based on prior data [6], the published average exposure for the approved dose was considered the "target C_{min}." Concentrations were compared to the population mean C_{min} of 61 ng/ml for palbociclib at 125 mg/day [25] and 732 ng/ml for ribociclib at 600 mg/day [7]. The reported mean steady-state C_{max} for ribociclib is 2,237 ng/ml. For letrozole, a target C_{min} of 85.6 ng/ml has been established [26].

Drug–drug interaction analysis

Possible interactions were screened through Lexicomp [27], the Drugs.com interaction checker [28], the Flockhart table [29], summaries of product characteristics [30, 31], and Medscape [32]. All flagged interactions were examined and categorized as moderate (requiring monitoring) or severe (to be avoided).

Statistical analysis section

Standard descriptive methods were applied to summarize TDM findings. The literature-reported mean C_{min} for patients receiving the usual dose was used as the reference, and ±20% ranges were computed according to accepted variability limits for incurred sample reanalysis [33, 34]. Values outside these limits were interpreted as potential under- or overexposure. Thus, palbociclib concentrations between 49–73 ng/ml and ribociclib C_{min} values between 586–878 ng/ml were deemed within the acceptable interval, independent of the dose given.

Case series

At the time of writing, over 80 individuals had participated in the reinforced pharmacology program. Five were chosen for detailed description due to the particular pharmacological considerations they presented and the illustrative value for clinical decision-making. Key demographics, clinical outcomes, treatment duration, principal adverse drug reactions (ADRs), and metastatic involvement at baseline are summarized in **(Table 1)**; temporal events are shown in **(Figure 2).**

Table 1. Baseline and clinical data for included subjects. Toxicities follow NCI-CTCAE v5.0.

Parameter	Case I	Case II	Case III	Case IV	Case V
Age (years)	72	71	75	50	60
Body mass index (kg/m²)	27.6	30.1	30	22.8	24.9
Baseline absolute neutrophil count	3.03 × 10³/mm³	3.14 × 10³/mm³	N.A.	7.21 × 10³/mm³	2.39 × 10³/mm³
CDK4/6 inhibitor (dose)	Palbociclib 125 mg/day + fulvestrant 500 mg q28d	Palbociclib 125 → 100 mg/day + letrozole 2.5 mg/day	Ribociclib 200 mg/day + fulvestrant 500 mg q28d	Ribociclib 600 mg/day + letrozole 2.5 mg/day	Palbociclib 125 → 100 mg/day + letrozole 2.5 mg/day
Main concomitant medications	Codeine/paracetamol prn, desvenlafaxine 30 mg/day, venlafaxine 75 mg/day, vitamin D	Aspirin 100 mg, atorvastatin 20 mg, bisoprolol 2.5 mg, perindopril 5 mg, cetirizine 10 mg, hydrochlorothiazide 12.5 mg, vitamin D	Aspirin 100 mg, atenolol 100 mg, atorvastatin 40 mg, levothyroxine 75 µg, omeprazole 20 mg	Pantoprazole 20 mg/day	Zoledronic acid 4 mg/12 weeks
Line of therapy	2nd line	2nd line	2nd line	1st line	1st line
Metastatic sites	Bone, lymph nodes	Lung, bone, lymph nodes	Lung, bone, lymph nodes	Lung, bone, lymph nodes	Liver, bone, lymph nodes
Reason for pharmacological consultation	Suspected progression + DDI with antidepressants	Recurrent G3–4 neutropenia	Persistent cutaneous toxicity >1 year	Recurrent haematological & cutaneous toxicity	Neutropenia
Worst toxicity recorded	Neutropenia G3, palpitations G3	Neutropenia G4	Cutaneous rash G3	Neutropenia G3, rash G1	Neutropenia G3
CYP3A4 phenotype	NM (*1/*1)	NM (*1/*1)	NM (*1/*1)	NM (*1/*1)	NM (*1/*1)
CYP3A5 phenotype	PM (*3/*3)	PM (*3/*3)	PM (*3/*3)	PM (*3/*3)	IM (*1/*3)
ABCB1 haplotype (rs1128503–rs1045642–rs2032582)	1236CT–3435CC–2677CG	1236TT–3435TT–2677TT	1236CT–3435CT–2677GT	1236CT–3435CT–2677GT	1236CT–3435CT–2677GT

ABCG2 c.421C>A	CC	CT	CT	CT	CC
SLCO1B1 phenotype	*1/*5 (decreased)	*5/*5 (poor)	*1/*1 (normal)	*1/*5 (decreased)	*1/*1 (normal)
TDM result – C_{min} at steady state	Palbociclib 27.3 ng/mL (on 75 mg/day)	Palbociclib 20.8 ng/mL (125 mg), 62.3 ng/mL (100 mg); letrozole 93.1 ng/mL	Ribociclib 110.9 ng/mL (600 mg); letrozole 70.3 ng/mL	Ribociclib 171.6 ng/mL (600 mg); letrozole 181.9 ng/mL	Palbociclib 36.2 ng/mL (125 mg); letrozole 31.4 ng/mL
Key pharmacological interpretation	No relevant DDI; progression unrelated to exposure	Severe neutropenia linked to overexposure + risk factors	Persistent rash likely due to ribociclib overexposure	Haematological/cutaneous toxicity due to marked overexposure	Neutropenia despite underexposure (CYP3A5 IM + other risk factors)
Recommendation	Continue antidepressants; consider alternative anticancer therapy	Safe to reduce palbociclib dose	Safe and recommended to reduce ribociclib dose	Safe to reduce ribociclib dose; toxicity ultimately tolerated at full dose	Dose reduction unlikely to resolve neutropenia; consider treatment switch
Final clinical outcome	Disease progression → treatment discontinued	Neutropenia persisted despite dose reduction	Dose reduced after >1 year; eventual treatment failure	Toxicity managed; full dose maintained	Neutropenia persisted after dose reduction

ANC = absolute neutrophil count.

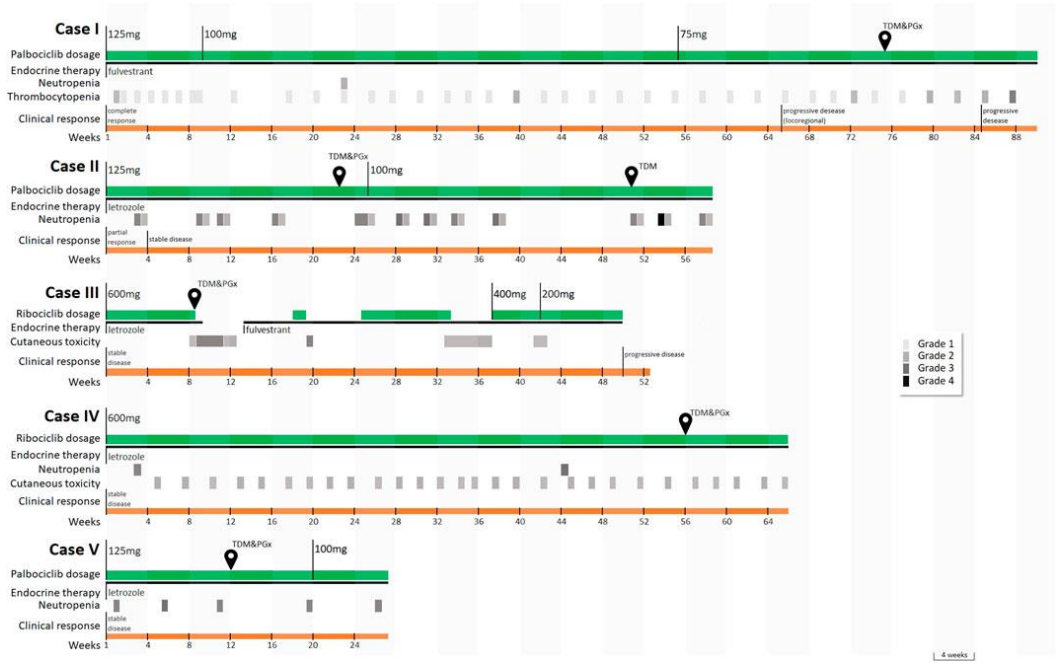

Figure 2. Chronology of major clinical events and sample acquisition for the case series. Planned treatment delays related to drug-label toxicity guidance are not shown. CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease; TDM = therapeutic drug monitoring; PGx = pharmacogenetic analysis. Toxicity grading followed CTCAE v5.0.

Case I

Case I age 54, was diagnosed with breast cancer and received neoadjuvant chemotherapy, followed by radical mastectomy, then 5 years of tamoxifen and an additional year of letrozole. Five years later, nodal relapse prompted re-initiation of letrozole as first-line therapy. After 2 more years, bone and nodal progression led to second-line fulvestrant plus palbociclib. More recently, the patient began venlafaxine for moderate depressive symptoms

while still on duloxetine for a pre-existing mood disorder, and mild bone PD was detected on PET imaging. She was referred for pharmacological review to evaluate whether palbociclib–venlafaxine interactions might influence CDKi treatment outcomes. When the consultation occurred, palbociclib had already been lowered to 75 mg/day (from 125 mg/day), administered 3 weeks on/1 week off, because of repeated hematologic toxicities (neutropenia and thrombocytopenia).

A steady-state blood draw was obtained to determine palbociclib plasma levels 24 h after the most recent dose (C_{min}). As previously noted, the patient was taking 75 mg daily when the sample was collected. The literature reports an average Cmin of 61 ng/ml in individuals receiving the full 125 mg/day dose. The measured C_{min} of 27.3 ng/ml aligned with expectations for the reduced 75 mg/day regimen. From a pharmacogenomic standpoint, no loss-of-function variants influencing palbociclib disposition were identified within CYP3A4, CYP3A5, ABCB1, or ABCG2.

Assessment of drug–drug interactions identified only a heightened likelihood of serotonin toxicity/serotonin syndrome because of simultaneous use of two serotonin–norepinephrine reuptake inhibitors. Although this was not central to the counselling request, it represented a potentially harmful interaction and reinforced the relevance of enhanced pharmacology follow-up.

A sustained period of insufficient drug exposure, combined with disease-related contributors, might have reduced treatment benefit. The patient's adverse effects were unlikely to stem from excessive palbociclib levels; instead, they may reflect an individual predisposition to the drug's hematologic effects. Her baseline absolute neutrophil count (ANC) was $3.03 \times 10^3/mm^3$, a value previously associated with elevated neutropenia risk [35]. Based on these considerations, transitioning to abemaciclib—which shows a lower frequency of neutropenia [36] —could have been an option.

The skeletal lesion prompting evaluation was managed with localized radiotherapy, and fulvestrant plus palbociclib were continued. Five months later, PET imaging again indicated mild bone PD, leading to another course of local radiotherapy, after which therapy proceeded unchanged. One month later, systemic PD was confirmed, and capecitabine was initiated as second-line therapy. No further samples were obtained for C_{min} assessment of palbociclib or letrozole.

Key takeaway: The analysis ruled out a meaningful interaction between venlafaxine or duloxetine and palbociclib, so modifications to antidepressant therapy were unnecessary. Counselling also excluded pharmacogenetic defects and drug overexposure as explanations for hematologic toxicity, instead highlighting that a baseline ANC below $3.60 \times 10^3/mm^3$ increases risk. Reducing the palbociclib dose consequently placed the patient at risk of insufficient exposure. Switching to abemaciclib, a CDKi with less marrow suppression, might have been advantageous; however, at that time, inter-CDKi switching remained off-label.

Case II

Case II received a breast cancer diagnosis at age 60 and underwent breast-conserving surgery, followed by five years of adjuvant letrozole. A recent CT scan revealed distant disease involving the lungs, lymph nodes, and bone. First-line treatment was initiated with palbociclib 125 mg/day (3 weeks on, 1 week off) plus letrozole 2.5 mg/day. Recurrent grade 3 neutropenia prompted a dose reduction to 100 mg/day and referral for pharmacological review. Steady-state plasma levels of both drugs were measured 22 h after the last intake. The evaluation showed:

1. palbociclib at 85.2 ng/ml for the 125 mg/day dose—about 30% above the reference mean C_{min} of 61 ng/ml;
2. letrozole at 93.1 ng/ml—consistent with the target C_{min} of 85.6 ng/ml.

Pharmacogenetic testing revealed an ABCB1 haplotype consisting of homozygous rs1128503, rs1045642, and rs2032582, associated with reduced P-gp function [37], potentially explaining the elevated exposure. This pattern was further supported by heterozygosity for ABCG2 421C > A [38]. The patient also carried the SLCO1B1*5/*5 genotype, linked with decreased transporter activity [39].

No additional predisposing conditions were identified, and the recommendation was to continue therapy at the reduced dose with ongoing monitoring. This guidance was followed, and at 100 mg/day, the palbociclib C_{min} was 62.3 ng/ml—within the target range. Despite this, the patient again developed up to grade 4 neutropenia. Her baseline ANC was $3.14 \times 10^3/mm^3$.

Key takeaway: Three independent contributors to neutropenia were identified:

1. elevated palbociclib exposure at 125 mg/day;
2. a baseline ANC below 3.60 × 10^3/mm^3;
3. a low-function ABCB1 genotype.

The assessment further emphasized the value of TDM in clarifying that ongoing neutropenia was not linked to excessive drug levels, as toxicity persisted even when C_{min} at 100 mg/day matched the expected therapeutic range.

Case III

Case III received a breast cancer diagnosis at age 57 and was treated with breast-conserving surgery, followed by adjuvant chemotherapy and then tamoxifen. Sixteen years afterward, pulmonary metastases were identified, leading to initiation of first-line endocrine therapy consisting of ribociclib (600 mg/day on a 3-weeks-on/1-week-off schedule) plus letrozole 2.5 mg/day. The regimen was initially manageable, but a persistent grade 2 dermatologic reaction developed after 2 months. Over the following year, full-dose therapy was intermittently stopped multiple times (up to 2 months of interruption), after which the patient was sent for pharmacology consultation.

Two steady-state blood samples were obtained—one at 24 h and another 1.5 h after the latest dose—to quantify plasma exposure to ribociclib and letrozole. These measurements provided reliable C_{min} values and an approximate estimation of ribociclib C_{max}, which is typically achieved within 1–4 h post-dose. Ribociclib C_{min} measured 1,100 ng/ml and letrozole 70.3 ng/ml, while the corresponding estimated C_{max} values were 2,020 ng/ml and 94.1 ng/ml, respectively. The ribociclib level at 24 h was notably above the reference population C_{min} of 732 ng/ml [9], indicating that excess exposure might have contributed to the skin toxicity. Letrozole C_{min}, on the other hand, was slightly below the 85.6 ng/ml expected target.

Neither the PGx evaluation—screening for reduced-function variants in CYP3A4, CYP3A5, SLCO1B1, ABCB1, and ABCG2—nor the DDI assessment accounted for this elevated ribociclib level. Because the prescribing information provides no specific management strategy for dermatologic toxicity, ribociclib therapy was maintained, but letrozole was exchanged for fulvestrant; later, the ribociclib dose was tapered from 600 mg to 400 mg and subsequently to 200 mg, which resulted in milder skin events. After 4 months of reduced dosing, CT imaging demonstrated progression, and capecitabine was initiated as the next-line therapy.

Within the counselling context, TDM might have supported an earlier adjustment to a more tolerable dose, potentially maintaining adequate drug exposure while limiting treatment interruptions that may have influenced effectiveness.

Key takeaway: The review identified excessive ribociclib exposure at the standard 600 mg/day dose as a plausible contributor to cutaneous toxicity and excluded PGx abnormalities as the cause. Earlier TDM-based down-titration could have optimized tolerability and exposure. However, the referral occurred after more than a year of recurrent toxicity episodes, limiting the opportunity for earlier intervention.

Case IV

Case IV involves a 38-year-old woman treated for early breast cancer who, after neoadjuvant chemotherapy, underwent radical mastectomy and subsequently received 5 years of tamoxifen plus a Luteinizing Hormone-Releasing Hormone analogue (LHRHa). Seven years later, nodal metastatic recurrence was confirmed, and first-line treatment with letrozole and ribociclib was initiated. She was referred for pharmacological assessment because of repeated episodes of persistent xerosis, rash, and mild dysphagia—symptoms consistent with a low-grade hypersensitivity reaction likely linked to ribociclib. Over the treatment period, two instances of grade 3 neutropenia were documented despite a comparatively high baseline ANC of 7.21 × 10^3/mm^3. During the last 14 months, she had been maintained on ribociclib 600 mg/day (3-weeks-on/1-week-off) plus letrozole 2.5 mg/day.

To examine steady-state levels of both agents, a plasma sample was collected roughly 23.5 h after the previous dose. The resulting C_{min} values were 1,717.6 ng/ml for ribociclib and 181.9 ng/ml for letrozole—both substantially above their respective population C_{min} targets of 732 ng/ml and 85.6 ng/ml.

Neither the PGx panel—which detected no damaging variants in CYP3A4, CYP2C9, ABCB1 (T allele present heterozygously at all three loci), nor ABCG2—nor the DDI analysis clarified the reason for this degree of overexposure. The patient also had an SLCO1B1*1/*5 genotype, compatible with reduced transporter function.

A reduction in ribociclib dosing could have been a reasonable strategy, accompanied by TDM surveillance to guide exposure and enhance safety and adherence.

Key takeaway: The counselling identified markedly elevated exposure to 600 mg/day ribociclib as a factor likely contributing to neutropenia and ruled out PGx defects as explanatory. A proactive, TDM-directed dose adjustment might have allowed a more tolerable regimen, but referral occurred only after multiple toxicity-related events.

Case V

Case V presented with luminal MBC accompanied by lymph node and skeletal metastases, leading to initiation of first-line treatment with palbociclib (125 mg/day, 3-weeks-on/1-week-off) plus letrozole (2.5 mg/day). Three months after starting therapy, a pharmacological consultation was requested to oversee treatment due to emerging neutropenia. A blood sample was obtained to determine palbociclib concentration 23 h after the most recent dose (C_{min}) under steady-state conditions. Typical mean C_{min} values for standard dosing are 61 ng/ml for palbociclib and 85.6 ng/ml for letrozole. In Case V, palbociclib measured 36.2 ng/ml and letrozole 31.4 ng/ml, indicating both were below their expected C_{min} thresholds.

Pharmacogenetic screening showed no reduced-function variants in CYP3A4, CYP2C9, SLCO1B1, ABCB1 (T allele heterozygous at all three sites analyzed), or ABCG2, except for a CYP3A5*3/*1 heterozygous genotype. This intermediate CYP3A5 metabolic phenotype may contribute to faster palbociclib clearance, potentially explaining the decreased plasma exposure. Evaluation of comedications identified no relevant DDIs. It was also confirmed that dosing occurred with food, ruling out this known source of variability for palbociclib absorption [40].

After 5 months, persistent grade 3 neutropenia required decreasing palbociclib to 100 mg/day, even though circulating drug levels were relatively low. Additional non-pharmacokinetic factors may have contributed to the neutropenia. Importantly, the patient started therapy with an ANC of 2.39 × 10^3/mm^3, which may have facilitated hematologic toxicity [35]. Another episode of grade 3 neutropenia occurred. No further blood samples were drawn for palbociclib or letrozole C_{min} assessments. A hypersensitive hematologic response to treatment—independent of palbociclib disposition—was suspected. A switch to abemaciclib was considered because it is associated with fewer hematologic adverse effects, especially neutropenia [36].

Key takeaway: The pharmacology review excluded excessive exposure as the cause of neutropenia and emphasized that a baseline ANC lower than 3.60 × 10^3/mm^3 increases risk. Counselling also revealed subtherapeutic exposure at 125 mg/day and identified the CYP3A5*1 allele as a possible contributor. The dose decrease introduced the possibility of inadequate therapeutic levels. An alternative approach—such as switching to a CDKi with reduced marrow-suppressive potential, like abemaciclib—might be more suitable for recurrent hematologic toxicity.

Results and Discussion

This series summarizes five referrals to the CRO-Aviano pharmacology service during CDKi therapy to explore precision-medicine-based approaches combining TDM, pharmacogenetic analysis, and co-medication assessment to inform treatment decisions.

Initially, the expanded counselling program focused on oral anticancer KIs, where TDM is already well established (e.g., imatinib, sunitinib). CDKis were only recently added, as they meet the main criteria for TDM applicability: narrow therapeutic index, large inter-patient variability in exposure, and documented exposure–response relationships. Moreover, hematologic toxicities frequently limit CDKi dosing and cause interruptions. In routine practice, dose modification relies solely on individual tolerability.

The objective of this collection of cases is to provide insight into the potential advantages of implementing a more structured pharmacologic support pathway for CDKi therapy.

The multidisciplinary team delivering this service comprises three clinical pharmacologists, a pharmacist, an LC-MS/MS analytical chemist, a biologist specializing in pharmacogenomic variants, and a technician conducting the genetic testing.

Referrals are made by oncologists to the Experimental and Clinical Pharmacology Unit of CRO-Aviano in a non-systematic, mostly reactive fashion—generally triggered by clinical concerns such as new co-prescriptions, unexpected AEs, or disease progression. After receiving a request, the laboratory performs pharmacogenetic

assays and TDM, and a full report is returned within 1 month of blood collection. Patients can be monitored over time, especially when treatment adjustments occur (dose, schedule, or new concomitant drugs) or when unresolved clinical problems persist. Additional reports are issued if required. The service is provided at no cost to patients and is reimbursed by the Italian national health system.

In this series, two of five individuals (Cases I and V) had CDKi C_{min} values below the target range for standard dosing, whereas three (Cases II, III, IV) had C_{min} values above it. In this pilot context, TDM proved valuable in distinguishing patients whose toxicity stemmed from pharmacokinetic overexposure—successfully managed with dose reductions—from those who exhibited intolerance despite therapeutic or low exposure. In cases where toxicity emerged in patients with normal or low C_{min}, dose reduction did not alleviate adverse effects and instead risked producing subtherapeutic concentrations of CDKis.

TDM can offer meaningful guidance for individuals receiving a standard dose who experience insufficient therapeutic benefit. In such situations, assessing plasma drug levels helps determine whether reduced efficacy is linked to inadequate exposure. When underexposure is confirmed, adherence, genetic variations, and clinically significant drug–drug interactions should also be explored. In Case I, ruling out a harmful DDI enabled clinicians to maintain the antidepressant therapy that had been suspected of contributing to the lack of response.

Because pronounced toxicities were observed in patients with elevated exposure, an early dose adjustment informed by TDM could have mitigated adverse events while preserving therapeutic levels and avoiding treatment interruptions. Within this series, TDM was especially valuable in a reactive setting, offering clear justification for dose reductions when toxicity coincided with above-target drug concentrations.

The series also reinforced the relevance of baseline ANC. A combination of high C_{min} values and reduced ANC appeared in cases with marked hematologic toxicity [35, 41]. Individuals with both high baseline ANC and elevated C_{min} —such as Case IV—may still face neutropenia risk and could benefit from dose lowering accompanied by TDM. Conversely, subjects with simultaneously low C_{min} and low baseline ANC, exemplified by Cases I and V, may be better managed by switching agents rather than reducing the current dose, since their hematologic events were unlikely due to palbociclib overexposure. In such contexts, switching to abemaciclib, which has a more favorable hematologic safety profile, is a rational alternative.

Among possible CDKi-related toxicities, dermatologic events represent an emerging area of concern with incompletely understood mechanisms. Notably, Cases III and IV developed skin toxicities and were also found to have ribociclib overexposure.

A variety of intrinsic and extrinsic determinants can influence CDKi plasma levels **(Figure 1)**, including ADME-related genetic variants and concomitant medications, which may predispose patients either to underexposure and diminished efficacy or to overexposure and increased toxicity.

In this group, one out of three individuals with concentrations above the population target (Case II) carried functional changes in genes encoding P-gp and BCRP transporters. Specifically, Case II possessed the low-function ABCB1 haplotype formed by rs1128503, rs1045642, and rs2032582 [42, 43]. Reduced intestinal P-gp expression may enhance oral drug uptake, leading to higher systemic exposure, consistent with what was observed. Recent analyses in PALOMA-2 and -3 confirmed that the ABCB1-rs1128503 genotype is associated with palbociclib-induced neutropenia risk [35]. Multivariate modeling indicated a protective effect of the ABCB1-rs1128503 CC wild-type genotype; however, no link between ABCB1 variants and palbociclib exposure was detected. Similar patterns have been documented for other oral kinase inhibitors—such as imatinib—where the same low-function ABCB1 haplotype correlated with altered drug levels [44]. The overall impact of P-gp polymorphisms on substrate pharmacokinetics remains debated [45], emphasizing the need for additional studies. Furthermore, ABCG2 421C>A, also carried by the patient, is known to impair ABCG2 transport efficiency and has been implicated in modifying gefitinib pharmacokinetics [14].

In contrast, Case V harbored the CYP3A5*1/*3 genotype, associated with higher CYP3A5 expression and increased metabolic activity, potentially explaining the reduced palbociclib concentrations detected. Comparable observations have been reported for other oral anticancer agents, including imatinib [44].

Cases II, IV, and V also received letrozole. Case V exhibited a low letrozole C_{min}, suggesting that the intermediate CYP3A5 metabolic phenotype may also accelerate letrozole clearance. In comparison, Cases II and IV, who showed elevated letrozole C_{min} values, were carriers of at least one C-allele in SLCO1B15 (T521C), which is associated with diminished OATP1B1 transport function. Supporting data have shown that SLCO1B15 carriers exhibit increased exposure to other aromatase inhibitors such as exemestane [22].

DDIs can substantially modify CDKi pharmacokinetics because concurrent medications or dietary components modulate ADME-relevant pathways, including CYP3A4, CYP3A5, and ABCB1, potentially altering circulating drug levels. Such shifts may translate into unpredictable differences in response or toxicity [46]. None of the patients in this report exhibited DDIs capable of accounting for either the clinical events or the measured CDKi concentrations. A combined approach integrating clinical pharmacology and pharmacogenetics is essential to recognize phenoconversion and minimize discrepancies encountered in drug–gene interaction studies [47, 48]. Although assessment of DDIs remains part of clinical care, its application is often inconsistent [19, 49]. Drug–drug–gene interactions, where DDIs overlap with DGIs, frequently cause shifts from predicted genotypic phenotypes. Drawing on the experience acquired through this pilot counseling service, we recommend expanding such programs to guide dose reductions or CDKi transitions in the future. This strategy also allows DDI effects to be more accurately assessed and helps avoid problematic concomitant therapies.

No individuals in this report were treated with abemaciclib; however, the suggested target C_{min} for this agent is 181 ng/ml, derived from MONARCH 3 participants receiving 132 mg twice daily [25].

This work has several clear constraints, chiefly the limited cohort size, the retrospective acquisition of toxicity information, and the variability in the CDKis administered. These factors prevented us from evaluating meaningful correlations between clinical features, molecular traits, and treatment outcomes. Additionally, it should be emphasized that the strategy applied here—focusing on pharmacokinetic and pharmacogenetic characterization to reach a predefined C_{min} —is grounded in population PK models and does not incorporate patient-specific pharmacodynamic or pharmacogenetic differences [50, 51]. Further investigation into this underexplored dimension of variability is needed, particularly to clarify the mechanistic basis for resistance or hypersensitivity despite apparently appropriate systemic exposure, as observed in several examples within this series.

While dedicated trials are required to confirm the clinical utility of this method, our experience indicates that such a service can support evidence-driven use of CDKis. Pharmacological counselling assisted oncologists in selecting between dose reduction and CDKi substitution when toxicity arose. It also allowed a clearer assessment of the relevance of potential DDIs, helping avoid unnecessary alterations to concurrent therapies when no clinical impact was expected. Beyond guiding individualized dosing, comprehensive pharmacology support may help optimize resource use, particularly for high-cost kinase inhibitors such as CDKis. Value-oriented prescribing for oral anticancer agents alone has been estimated to reduce global expenditure by more than US $12 billion annually [52]. Reconsidering dosing standards thus offers an opportunity to enhance patient safety, improve the precision of drug use, and reduce financial burdens on healthcare systems.

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