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Abemaciclib-associated kidney injuries: A retrospective analysis of the United States Food and Drug Administration adverse events reporting system

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Abstract

Background: Abemaciclib, an oral kinase inhibitor, is used to treat hormone receptor–positive and HER2-negative breast cancer patients. However, there has been a decrease in studies reporting adverse reactions to abemaciclib-related kidney injuries. Thus, this study was aimed at assessing its safety profile using a large-scale pharmacovigilance database.

Methods: Abemaciclib-related adverse drug reaction reports from the Food and Drug Administration Adverse Event Reporting System were obtained and scrutinized, and adverse drug reactions were selected using reporting odds ratio, the proportional reporting ratio methods, empirical Bayes geometric mean and UK Medicines and Healthcare products Regulatory Agency methods.

Results: We selected 10,757 matched reports associated with abemaciclib, among which we found eight adverse reactions about kidney injuries correlated with abeamciclib, such as increased

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blood creatinine, renal disorder, decreased glomerular filtration rate, increased blood urea, hydronephrosis, abnormal renal function test, increased creatinine renal clearance and increased cystatin C. A demographic analysis of reported cases of abemaciclib-associated renal injury revealed that the majority were female, aged $\geq$46 years and had taken the drug $\geq$30 days.
Conclusion: This study highlights the characteristics of adverse reactions with abemaciclib and those associated with renal damage, which are crucial for safety studies on the clinical use of this drug.

Plain language summary
Objective: Abemaciclib is an oral kinase inhibitor commonly used to treat hormone receptor–positive and HER2-negative breast cancer. Although it has shown efficacy in treating breast cancer, there have been concerns about its potential to cause kidney injuries. Despite this, studies addressing the adverse effects of abemaciclib on kidney function have been limited. This study aimed to assess the safety profile of abemaciclib, focusing on its association with kidney-related adverse events.
Methods: We conducted a retrospective analysis of adverse drug reactions (ADRs) related to abemaciclib using the Food and Drug Administration Adverse Event Reporting System (FAERS). The study focused on ADRs associated with kidney injuries, and we employed several disproportionality analysis methods to identify potential signals of kidney-related adverse reactions. These methods included the reporting odds ratio (ROR), proportional reporting ratio (PRR), empirical Bayes geometric mean (EBGM), and UK Medicines and Healthcare products Regulatory Agency (MHRA) methods.
Results: Our analysis identified a total of 10,757 reports associated with abemaciclib. Among these, we found eight distinct kidney-related adverse reactions, including increased blood creatinine, renal disorders, decreased glomerular filtration rate, increased blood urea, and abnormal renal function tests. A demographic analysis revealed that the majority of the affected patients were female, over 46 years of age, and had been taking abemaciclib for more than 30 days.
Conclusion: This study provides valuable insights into the kidney-related adverse effects of abemaciclib. The findings suggest that kidney injuries may be an underreported side effect of this medication, particularly among women and those on prolonged treatment regimens. Further research is needed to better understand the renal safety of abemaciclib and to develop guidelines for managing potential kidney-related risks in patients undergoing treatment.

Keywords
Food and Drug Administration Adverse Event Reporting System, abemaciclib, kidney injuries, adverse reactions

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Objective

Abemaciclib, approved by the Food and Drug Administration (FDA) in 2017 in the United States, is an oral kinase inhibitor (kinase inhibitor indicated) currently used as a single agent or in combination with other agents for the treatment of hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative breast cancer patients.[1]

Breast cancer is a common type of cancer in women, accounting for 32% of new cancers diagnosed in women in the United States in 2024 alone, and is a significant cause of cancer-related deaths in women; according to a 2021 statistic, for women, breast cancer causes the second highest number of cancer-related deaths after lung cancer. As for men, although the incidence of breast cancer is not as high as for women (approximately 1% of all breast cancer cases), it is still a cancer that should not be ignored as the incidence of breast cancer in men is increasing with the aging of the population.[2] Meanwhile, in breast cancer, aberrant cell cycle regulation has been identified as an important mechanism for breast cancer progression and has been used as a potential therapeutic target.[3]

Abemaciclib, a new generation cyclin-dependent kinases (CDK) inhibitor, selectively inhibits CDK4/6 in targeting breast cancer, targeting the cyclin-CDK-retinoblastoma (Rb) pathway, and inducing cell cycle arrest to achieve therapeutic effect.[4]

The use of selective CDK inhibitors such as abemaciclib is an effective strategy for the treatment of breast cancer, and in a randomised, double-blind, phase III study comparing abemaciclib plus NSAI (anastrozole or letrozole) versus placebo plus NSAI in postmenopausal women with HR+, HER2- ABC without prior systemic therapy in the advanced setting.[5] The final results showed numerical improvement in chemotherapy-free survival with the addition of abemaciclib.

However, the use of abemaciclib is accompanied by a variety of adverse effects, and the known adverse effects are diarrhoea, neutropenia, interstitial lung disease or pneumonitis, hepatotoxicity, venous thromboembolism, etc.[6] Regarding the effect on the kidney, the specification only mentions that it may lead to a transient increase in blood creatinine, but in clinical use, we have found that patients treated with abemaciclib may develop renal damage, manifested as increased blood creatinine, decreased glomerular filtration rate, increased blood urea, and increased cystatin C.[1]

Therefore, we extracted and screened the reports related to abemaciclib in the FDA Adverse Event Reporting System (FAERS) from 2017q3 to 2024q2 and analysed the reports of adverse reactions that may be related to abemaciclib, aiming to investigate the relationship between abemaciclib and adverse reactions of renal damage.

Method

Data for this study were obtained from the FAERS database. FAERS supports post-market safety monitoring of marketed drugs and therapeutic biologics and contains reports of adverse reactions received by the FDA from manufacturers, as well as from consumers and professionals involved in the healthcare business. Since our data are derived from a public database (FAERS), any identifiable patient information has already been removed. Additionally, we will recheck the data to ensure that no patient-identifiable information is present, safeguarding patient privacy. In this study, data from 2017q3 to 2024q2 were obtained from the FAERS database and were screened for data on adverse event reports related to abemaciclib in the kidney. Our screening method was to de-emphasise the data according to the FDA-recommended method and to identify the role played by the drug in the adverse events as primary suspect drug (PS). We determined the PS by four calculation methods (reporting odds ratio [ROR], proportional reporting ratio [PRR], Medicines and Healthcare Products Regulatory Agency [MHRA] and Empirical Bayes Geometric Mean [EBGM]) to calculate the signal intensity of each preferred term (PT, level medical terminology describing the

event, using the Medical Dictionary for Regulatory Activities [MedDRA]). The study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013, and the reporting of this study conformed to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[7]

Data extraction and identification

The data for this study were obtained from the ASCII data packages in the FAERS database (updated quarterly), and we chose the data for a total of 28 quarters from 2017q3 to 2024q2. The data package in each quarter includes seven types of data files: DEMO contains patient demographic and administrative information, a single record for each event report; DRUG contains drug/biologic information for as many medications as were reported for the event (1 or more per event); REAC contains all terms coded for the adverse event (1 or more). For more information on MedDRA, please contact the MSSO Help Desk at msso-help@meddra.org (www.meddra.org); OUTC contains patient outcomes for the event; RPSR contains report sources for the event; THER contains drug therapy start dates and end dates for the reported drugs. In the current study, we used the following: DEMOyyQq, DRUGyyQq, THERyyQq, and REACyyQq data files; we imported the above three data files for 28 quarters into a MySQL database program (version 8.0), linked the data and de-duplicated them according to the recommended methods in the ASC_NTS.DOC instruction document in the data package given by the FDA. Subsequently, we identified eight adverse reactions related to renal function, including increased cystatin C, increased creatinine renal clearance, increased blood creatinine, an abnormal renal function test, hydronephrosis, increased blood urea, decreased glomerular filtration rate, renal disorder, and were included in our principle of matching data. The reports and their corresponding PTs were screened according to the matching principle that the active ingredient of the drug was abemaciclib (pro_ai = abemaciclib), the drug was reported as the first suspect (role_cod = PS), and the PTs were the renal-related adverse reactions that we had identified in the eight (PT = "above") (Figure 1).

Statistical analysis

In view of the constraints inherent in the FAERS database, which encompasses spontaneous reports and is deficient in comprehensive real-world adverse drug reaction data, it is not feasible to directly calculate the incidence of adverse drug reaction events. Nevertheless, disproportionality analysis is an effective method for identifying signals of adverse drug reaction events in retrospective pharmacological studies. In order to overcome the limitations of single algorithms and to enhance the reliability and accuracy of the resulting data mining, multiple algorithms were employed for the analysis of the data.[8] Consequently, the identification of adverse event signals was performed using disproportionality analysis (DPA) with the ROR,[9] the PRR methods, EBGM based on disproportionality analysis and UK MHRA methods.

The ROR method employs a two-sided test with a 95% confidence interval (CI), wherein a lower limit exceeding one signifies a signal, contingent on the number of reports (N) being equal to or greater than three. In order for the PRR method to generate a signal, the following criteria must be met: a minimum number of reports (N) of three, a PRR value of two or higher, and a variance (χ^2) of four or higher. The EBGM method, although less sensitive, permits stratified analysis of population factors. In comparison to the ROR and PRR methods, the Bayesian method exhibits several

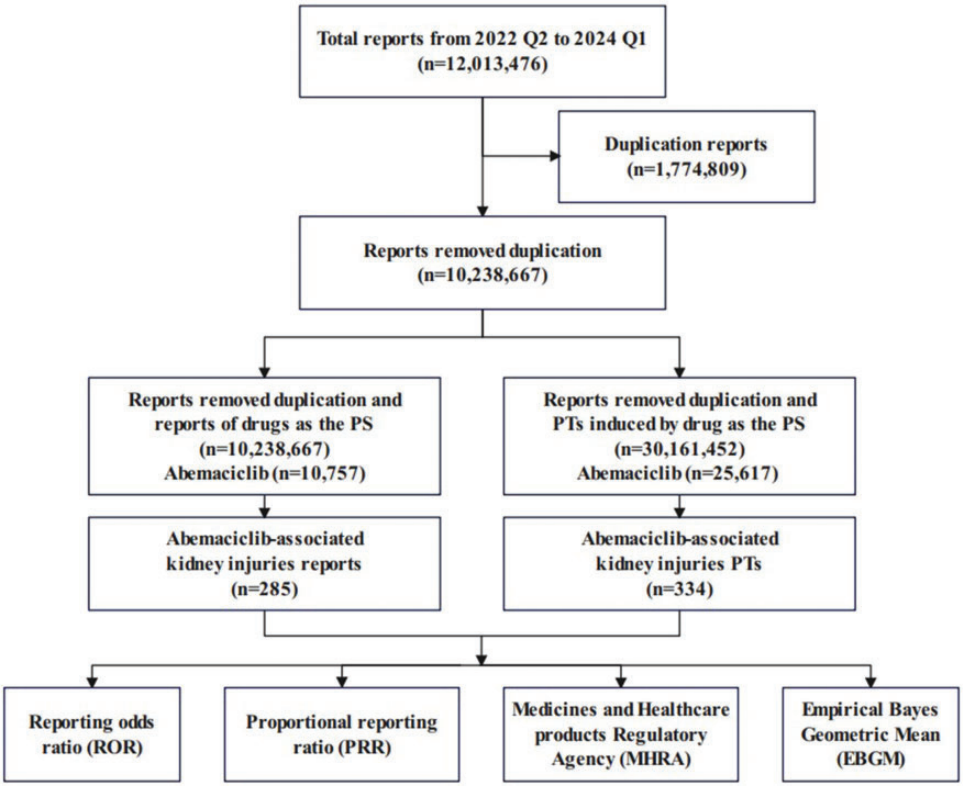

Figure 1. Flow chart.

advantages, including high specificity, a stable signal, and a low probability of misclassification.[10] Consequently, it can be considered a more prudent method. In regard to the MHRA method, adverse events with a lower limit of the 95% CI greater than one and reported in at least three cases using the ROR method, and with PRR > 2, C2 > 4, and reported in at least three cases using the MHRA method, were defined as adverse drug event signals.[11] The FAERS data employed in this study and analysis process were collected and conducted using the RStudio software, version 4.3.1 (Table 1).

Meanwhile, we further selected five adverse reactions of abemaciclib-associated renal injury that were not mentioned in the specification, on top of the eight previously identified adverse reactions related to renal function (decreased glomerular filtration rate, increased cystatin C, renal disorder, abnormal renal function test, increased blood urea), the data in their DEMOyyQq and THERyyQq were extracted and organised into a table, where the columns 'time_of_onset_group' were calculated to categorise the results into groups after calculation ('event_dt' - 'start_dt') (event_dt:date the adverse event occurred or began, start_dt:date the therapy was started), in which, the data that does not satisfy the format of YYYY/MM/DD will be discarded, and 'start_dt' if there is more than one, then the earliest reported time will be selected (Table 2).

Table 1. Formulas and threshold values of ROR, PRR, MHRA and EBGM.

Methods	Formula	Threshold value
ROR	$ROR = \frac{ad}{bc}$	a ≥ 3; A signal is generated if the lower limit of 95% CI of ROR > 1
PRR	$PRR = \frac{a(c+d)}{c(a+b)}$	a ≥ 3; PRR ≥ 2, $X^2 \geq 4$, a signal is generated
MHRA	$PRR = \frac{[a/(a+b)]}{[c/(c+d)]}$	When a ≥ 3, PRR > 2 and c2 > 4, 1 ADE signal is generated
EBGM (MGPS)	$EBGM = \frac{a(a+b+c+d)}{(a+c)/(b+d)}$	EBGM05 ≥ 2 N > 0

ADE: adverse drug event; CI: confidence interval; EBGM: Empirical Bayes Geometric Mean; MGPS: multi-item gamma poisson shrinker; MHRA: Medicines and Healthcare products Regulatory Agency; PRR: proportional reporting ratio; PT: preferred term; ROR: reporting odds ratio.

Results

We screened 10,757 matched reports (25,617 by PTs) from FAERS. Overall, the top 30 adverse reactions for abemaciclib included diarrhoea, fatigue, nausea, vomiting, malignant neoplasm progression, decreased appetite, white blood cell count decreased, dehydration, anaemia, neutropenia, and so on. Among these, the most frequent PT was diarrhoea (a = 3136, 12.24%, ROR = 12.82 [95% CI, 12.34–13.31], EBGM = 10.79), which accounted for 12.24% of all reported PTs, followed by fatigue (a = 962, 3.76%, ROR = 2.86 [95% CI, 2.68–3.05], EBGM = 2.77), and then nausea (a = 932, 3.64%, ROR = 3.07 [95% CI, 2.87–3.28], EBGM = 2.96; Table 3).

Based on disproportionate signalling analysis, the top 30 adverse reactions associated with abemaciclib included pseudocirrhosis, cystatin C increased, tumour marker abnormal, creatinine renal clearance increased, cell marker increased, dairy intolerance, asymptomatic coronavirus disease 2019, radiation pneumonitis, embolism venous, lymphangiosis carcinomatosa, and so on. Of these, the signal intensities of the top four adverse reactions showed a substantial lead in signal intensity compared with the others (ROR > 40, EBGM > 30; Table 4).

Among these reports, there were 285 reports of renal adverse reactions, with a total of 334 PTs reported, ranging from our selected eight renal function-related adverse reactions (increased blood creatinine, renal disorder, decreased glomerular filtration rate, increased blood urea, hydronephrosis, abnormal renal function test, increased creatinine renal clearance and increased cystatin C), the number of reported adverse reactions for blood creatinine increased were faultily reported relative to other abemaciclib-related renal function-related adverse reactions (a = 210, 62.87%, ROR = 7.92 [95% CI, 6.90–9.10], EBGM = 7.60), accounting for 62.87% of all renal function-related adverse reactions, while second was renal disorder (a = 47, 14.07%, ROR = 2.89 [95% CI, 2.16–3.85], EBGM = 2.86). According to the results of signal intensity analysis, cystatin C increased (a = 3, 0.90%, ROR = 41.71 [95% CI, 11.98–145.14], EBGM = 34.52), creatinine renal clearance increased (a = 6, 1.80%, ROR = 40.27 [95% CI, 16.72–97.01], EBGM = 33.53) were in TOP1, TOP2. The third was blood creatinine increased (a = 210, 62.87%, ROR = 7.92 [95% CI, 6.90–9.10], EBGM = 7.60). Kidney injuries associated clinical adverse reactions of abemaciclib ranked by ROR, the first and the second PTs signal intensities were higher (ROR > 40, EBGM > 30) (Table 5, Table 6).

For the five specifications we selected (including increased blood urea, increased

Table 2. Features of abemaciclib-associated kidney injuries adverse reactions cases not mentioned by drug instructions.

Variable	Level	Increased blood urea	Increased cystatin C	Decreased glomerular filtration rate	Renal disorder	Abnormal renal function test	p value
n		20	3	27	47	10	
age_group	0–18 y	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	19–45 y	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	46–64 y	2 (16.7)	0 (0.0)	3 (17.6)	5 (26.3)	3 (42.9)	
	65+ y	10 (83.3)	2 (100.0)	14 (82.4)	14 (73.7)	4 (57.1)	
sex	F	16 (80.0)	2 (66.7)	24 (88.9)	37 (78.7)	10 (100.0)	0.146
	M	3 (15.0)	0 (0.0)	1 (3.7)	1 (2.1)	0 (0.0)	
	NULL	1 (5.0)	1 (33.3)	2 (7.4)	9 (19.1)	0 (0.0)	
occp_cod	CN	10 (50.0)	2 (66.7)	19 (70.4)	25 (53.2)	6 (60.0)	0.563
	HP	3 (15.0)	0 (0.0)	1 (3.7)	10 (21.3)	0 (0.0)	
	MD	3 (15.0)	1 (33.3)	6 (22.2)	3 (6.4)	1 (10.0)	
	NULL	2 (10.0)	0 (0.0)	0 (0.0)	5 (10.6)	2 (20.0)	
	OT	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	
	PH	2 (10.0)	0 (0.0)	1 (3.7)	3 (6.4)	1 (10.0)	
reporter_country	AT	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	1 (10.0)	0.124
	BR	1 (5.0)	1 (33.3)	0 (0.0)	1 (2.1)	0 (0.0)	
	CH	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	0 (0.0)	
	CN	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	1 (10.0)	
	CZ	1 (5.0)	0 (0.0)	1 (3.7)	0 (0.0)	0 (0.0)	
	DE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	
	EG	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	
	ES	1 (5.0)	0 (0.0)	1 (3.7)	0 (0.0)	0 (0.0)	
	FR	0 (0.0)	0 (0.0)	3 (11.1)	0 (0.0)	0 (0.0)	
	GB	1 (5.0)	0 (0.0)	2 (7.4)	0 (0.0)	0 (0.0)	
	HK	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	
	IN	1 (5.0)	0 (0.0)	1 (3.7)	0 (0.0)	0 (0.0)	
	JP	2 (10.0)	0 (0.0)	2 (7.4)	4 (8.5)	0 (0.0)	
	KR	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	0 (0.0)	
	PL	1 (5.0)	0 (0.0)	4 (14.8)	1 (2.1)	0 (0.0)	
	RO	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	US	11 (55.0)	2 (66.7)	10 (37.0)	38 (80.9)	7 (70.0)	
time_of_onset_group	0–7	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)	0 (0.0)	0.792
	8–30	3 (18.8)	0 (0.0)	1 (5.3)	3 (10.7)	0 (0.0)	
	31–180	7 (43.8)	1 (100.0)	8 (42.1)	10 (35.7)	6 (66.7)	
	180+	6 (37.5)	0 (0.0)	10 (52.6)	14 (50.0)	3 (33.3)	

AT: Austria; BR: Brazil; CH: Switzerland; CN: China or consumer; CZ: Czechia; DE: Germany; EG: Egypt; ES: Spain; FR: France; GB: United Kingdom; HK: Hong Kong; HP: PH, pharmacist; IN: India; JP: Japan; KR: Korea, South; MD: physician; OT: other health-professional; PH: pharmacist; PL: Poland; RO: Romania; US: United States.

cystatin C, decreased glomerular filtration rate, renal disorder and abnormal renal function test), there was no mention of abemaciclib. We analysed the demographic data for the five adverse reactions of abemaciclib associated with renal injury that were not mentioned in the specification (including increased blood urea, increased

Table 3. Top 30 clinical adverse reactions of abemaciclib ranked by frequency (N) at the PT's level in FAERS database calculated by disproportionality analysis.

pt	N	ROR	ROR_upper	ROR_lower	PRR	x2	MHRA	MHRA_x2	EBGM
Diarrhoea	3136	12.81855932	13.31950701	12.33645232	11.36110741	28321.6132	11.36110741	28321.6132	10.78958077
Fatigue	962	2.862300231	3.054139818	2.682510659	2.791850651	1105.808026	2.791850651	1105.808026	2.76650757
Nausea	932	3.070354545	3.27950936	2.874538839	2.994476824	1234.593805	2.994476824	1234.593805	2.964251582
Vomiting	558	3.067926469	3.338562754	2.819228965	3.022550811	749.1400992	3.022550811	749.1400992	2.991617159
Malignant neoplasm progression	458	8.428618126	9.262483211	7.669822648	8.294827048	2824.486235	8.294827048	2824.486235	7.99660061
Decreased appetite	418	4.231450917	4.66565748	3.837653523	4.178334657	993.3125798	4.178334657	993.3125798	4.111526658
Decreased white blood cell count	344	7.397953817	8.24460475	6.63824675	7.311406585	1809.765232	7.311406585	1809.765232	7.082867231
Dehydration	325	7.366062537	8.234338567	6.589342527	7.284703107	1701.640326	7.284703107	1701.640326	7.057931872
Anaemia	279	3.736354907	4.20894092	3.316831539	3.706333553	542.6677602	3.706333553	542.6677602	3.655752962
Neutropenia	259	4.92340374	5.572967504	4.349550643	4.883444575	781.931226	4.883444575	781.931226	4.788377265
Abdominal pain upper	253	3.033351776	3.436517674	2.677484556	3.013122205	336.2190744	3.013122205	336.2190744	2.982427339
Disease progression	234	4.371181829	4.978724183	3.837776483	4.340161123	589.6615716	4.340161123	589.6615716	4.267291675
Therapy cessation	225	9.227203957	10.55323508	8.067790799	9.154411157	1562.466965	9.154411157	1562.466965	8.788048835
Constipation	218	2.734487647	18.28892199	13.86168334	2.719618661	234.5139086	2.719618661	234.5139086	2.695917778
Myelosuppression	218	15.92216208	3.127356402	2.390972352	15.79424106	2795.800201	15.79424106	2795.800201	14.6836541
Abdominal pain	215	2.40007405	2.74712889	2.096863918	2.38823701	172.0053686	2.38823701	172.0053686	2.371406574
Blood creatinine increased	210	7.922157531	9.099107195	6.897443739	7.86499461	1210.783856	7.86499461	1210.783856	7.598318904
Therapy interrupted	205	5.6771585	6.526446503	4.938388542	5.639454312	761.5175449	5.639454312	761.5175449	5.50879239
Interstitial lung disease	174	8.775724342	10.2202649	7.535356322	8.722520408	1139.560118	8.722520408	1139.560118	8.391228852
Decreased platelet count	172	3.757241636	4.371333776	3.229418168	3.738592578	339.1628744	3.738592578	339.1628744	3.686971983
Decreased haemoglobin	138	3.287831368	3.892010368	2.777442525	3.275416082	214.8888364	3.275416082	214.8888364	3.237751764
Pneumonitis	115	10.02711458	12.09873913	8.310207016	9.986292002	884.9667506	9.986292002	884.9667506	9.547657206
Pulmonary embolism	114	4.520284197	5.444839951	3.752721733	4.504503135	304.0975476	4.504503135	304.0975476	4.425218881
Hospitalisation	113	2.453881181	2.955354452	2.037499375	2.447420757	95.70323525	2.447420757	95.70323525	2.429443339

(continued)

Table 3. Continued.

pt	N	ROR	ROR_upper	ROR_lower	PRR	x2	MHRA	MHRA_x2	EBGM
Abnormal hepatic function	111	7.744033842	9.365295542	6.403434882	7.714596652	624.3378623	7.714596652	624.3378623	7.458560847
Decreased neutrophil count	107	8.513267163	10.33550218	7.012307339	8.481654123	677.0092305	8.481654123	677.0092305	8.169188475
Decreased red blood cell count	97	8.184898023	10.03221771	6.677741411	8.157492002	584.942962	8.157492002	584.942962	7.86952986
Thrombosis	95	4.556720675	5.586780378	3.71657769	4.543433673	256.7607932	4.543433673	256.7607932	4.462591647
Therapy change	79	16.72302316	21.04973607	13.28565368	16.67417853	1072.349792	16.67417853	1072.349792	15.43715545
Hot flush	78	2.861587679	3.57965277	2.287563787	2.855877736	92.81062177	2.855877736	92.81062177	2.829035818

PT: preferred term; FAERS: Food and Drug Administration Adverse Event Reporting System; ROR: reporting odds ratio; PRR: proportional reporting ratio; MHRA: Medicines and Healthcare products Regulatory Agency; EBGM: Empirical Bayes Geometric Mean.

Table 4. Top 30 clinical adverse reactions of abemaciclib ranked by ROR at the PT's level in FAERS database calculated by disproportionality analysis.

pt	N	ROR	ROR_upper	ROR_lower	PRR	x2	MHRA	MHRA_x2	EBGM
Pseudocirrhosis	5	44.23632788	116.8247077	16.75033255	44.22782683	172.1323445	44.22782683	172.1323445	36.22267372
Increased cystatin C	3	41.70532449	145.1342762	11.98430954	41.70052244	98.14322508	41.70052244	98.14322508	34.51807731
Abnormal tumour marker	11	40.40623082	77.36234767	21.10410992	40.38918526	349.9315268	40.38918526	349.9315268	33.61916904
Increased creatinine renal clearance	6	40.27183926	97.0079232	16.71843891	40.26257339	190.3444651	40.26257339	190.3444651	33.53184653
Increased cell marker	3	27.80351033	93.22009511	8.292580969	27.8003483	67.82066478	27.8003483	67.82066478	24.45030476
Dairy intolerance	3	23.3549298	77.35856264	7.050967951	23.35229257	57.30866612	23.35229257	57.30866612	20.95740408
Asymptomatic COVID-19	3	21.62492626	71.28802145	6.55983188	21.62249312	53.10592168	21.62249312	53.10592168	19.56024381
Radiation pneumonitis	11	19.64684403	36.52891113	10.56693092	19.63877815	176.7538282	19.63877815	176.7538282	17.93022349
Embolism venous	29	19.6166145	28.74385001	13.38761385	19.59538439	464.959831	19.59538439	464.959831	17.89422935

(continued)

Table 4. Continued.

pt	N	ROR	ROR_upper	ROR_lower	PRR	x2	MHRA	MHRA_x2	EBGM
Lymphangiosis carcinomatosa	11	18.30344049	33.96499623	9.863564581	18.29595572	164.4045308	18.29595572	164.4045308	16.80958452
Radiation injury	6	17.43096076	40.18789365	7.560445828	17.42708401	85.27187216	17.42708401	85.27187216	16.07691272
Therapy change	79	16.72302316	21.04973607	13.28565368	16.67417853	1072.349792	16.67417853	1072.349792	15.43715545
Loss of therapeutic response	7	16.22105967	35.07430244	7.501867707	16.21686984	92.26298465	16.21686984	92.26298465	15.04634139
Bone marrow infiltration	5	16.21986234	40.392743	6.513148521	16.21686984	65.90178742	16.21686984	65.90178742	15.04634139
Myelosuppression	218	15.92216208	18.28892199	13.86168334	15.79424106	2795.800201	15.79424106	2795.800201	14.6836541
Oophorectomy	3	15.78031971	51.18346594	4.865213512	15.77857606	38.41172884	15.77857606	38.41172884	14.67018285
Recall phenomenon	3	15.78031971	51.18346594	4.865213512	15.77857606	38.41172884	15.77857606	38.41172884	14.67018285
Venous thrombosis limb	9	15.36843555	30.29736141	7.795689134	15.36335037	112.0156137	15.36335037	112.0156137	14.31237352
Diarrhoea	3136	12.81855932	13.31950701	12.33645232	11.36110741	28321.6132	11.36110741	28321.6132	10.78958077
Decreased full blood count	70	11.53420875	14.68348344	9.060382156	11.50521171	634.1276788	11.50521171	634.1276788	10.91879638
Increased tumour marker	30	11.45954145	16.56428629	7.927965507	11.44720224	270.1751923	11.44720224	270.1751923	10.86680211
Mastectomy	3	11.01641399	35.2562891	3.442261799	11.01523234	25.85487143	11.01523234	25.85487143	10.47870204
Osteonecrosis of jaw	28	10.52954332	15.40464602	7.197262592	10.51905071	228.8513897	10.51905071	228.8513897	10.03089426
Lung opacity	14	10.52429412	18.02267844	6.145632969	10.51905071	114.4194144	10.51905071	114.4194144	10.03089426
Pneumonitis	115	10.02711458	12.09873913	8.310207016	9.986292002	884.9667506	9.986292002	884.9667506	9.547657206
Increased carbohydrate antigen 15–3	8	9.324891402	18.95680211	4.586933975	9.322272482	56.72124545	9.322272482	56.72124545	8.94182574
Therapy cessation	225	9.227203957	10.55323508	8.067790799	9.154411157	1562.466965	9.154411157	1562.466965	8.788048835
Interstitial lung disease	174	8.775724342	10.2202649	7.535356322	8.722520408	1139.560118	8.722520408	1139.560118	8.391228852
Decreased neutrophil count	107	8.513267163	10.33550218	7.012307339	8.481654123	677.0092305	8.481654123	677.0092305	8.169188475
Malignant neoplasm progression	458	8.428618126	9.262483211	7.669822648	8.294827048	2824.486235	8.294827048	2824.486235	7.99660061

COVID-19: coronavirus disease 2019; PT: preferred term; FAERS: Food and Drug Administration Adverse Event Reporting System; ROR: reporting odds ratio; PRR: proportional reporting ratio; MHRA: Medicines and Healthcare products Regulatory Agency; EBGM: Empirical Bayes Geometric Mean.

Table 5. Kidney injuries associated with clinical adverse reactions of abemaciclib ranked by frequency (N) at the PT's level in FAERS database calculated by disproportionality analysis.

pt	N	ROR	ROR_upper	ROR_lower	PRR	x2	MHRA	EBGM
Increased blood creatinine	210	7.922157531	9.099107195	6.897443739	7.86499461	1210.783856	7.86499461	7.598318904
Renal disorder	47	2.886940992	3.851517045	2.163933898	2.883453527	57.01486009	2.883453527	2.855953585
Decreased glomerular filtration rate	27	3.353433569	4.906792152	2.291826585	3.350934839	43.79289117	3.350934839	3.31113845
Increased blood urea	20	3.773546397	5.874862554	2.423827329	3.771365079	39.96453075	3.771365079	3.71867753
Hydronephrosis	11	4.451860743	8.094061318	2.448593271	4.450367606	28.77070256	4.450367606	4.373225241
Abnormal renal function test	10	4.794655696	8.980144923	2.559950139	4.793163499	29.29880502	4.793163499	4.701981684
Increased creatinine renal clearance	6	40.27183926	97.0079232	16.71843891	40.26257339	190.3444651	40.26257339	33.53184653
Increased cystatin C	3	41.70532449	145.1342762	11.98430954	41.70052244	98.14322508	41.70052244	34.51807731

PT: preferred term; FAERS: Food and Drug Administration Adverse Event Reporting System; ROR: reporting odds ratio; PRR: proportional reporting ratio; MHRA: Medicines and Healthcare products Regulatory Agency; EBGM: Empirical Bayes Geometric Mean.

Table 6. Kidney injuries associated with clinical adverse reactions of abemaciclib ranked by ROR at the PT's level in FAERS database calculated by disproportionality analysis.

pt	N	ROR	ROR_upper	ROR_lower	PRR	x2	MHRA	EBGM
Increased cystatin C	3	41.70532449	145.1342762	11.98430954	41.70052244	98.14322508	41.70052244	34.51807731
Increased creatinine renal clearance	6	40.27183926	97.0079232	16.71843891	40.26257339	190.3444651	40.26257339	33.53184653
Increased blood creatinine	210	7.922157531	9.099107195	6.897443739	7.86499461	1210.783856	7.86499461	7.598318904
Abnormal renal function test	10	4.794655696	8.980144923	2.559950139	4.793163499	29.29880502	4.793163499	4.701981684
Hydronephrosis	11	4.451860743	8.094061318	2.448593271	4.450367606	28.77070256	4.450367606	4.373225241
Increased blood urea	20	3.773546397	5.874862554	2.423827329	3.771365079	39.96453075	3.771365079	3.71867753
Decreased glomerular filtration rate	27	3.353433569	4.906792152	2.291826585	3.350934839	43.79289117	3.350934839	3.31113845
Renal disorder	47	2.886940992	3.851517045	2.163933898	2.883453527	57.01486009	2.883453527	2.855953585

PT: preferred term; FAERS: Food and Drug Administration Adverse Event Reporting System; ROR: reporting odds ratio; PRR: proportional reporting ratio; MHRA: Medicines and Healthcare products Regulatory Agency; EBGM: Empirical Bayes Geometric Mean.

cystatin C, decreased glomerular filtration rate, renal disorder and abnormal renal function test) by extracting their corresponding DEMO files. For these adverse reactions, we found that the reported PTs were reported by patients concentrated in the 65+ years age group, with all reported reports being 46 years and older. The gender of the reported patients was predominantly female (83.18%), with all of the patients with a PT of abnormal renal function test being female. The most reported patients were consumers (occp_cod = CN), and the country of the reported patients was concentrated in the United States (reporter_country = US).

The column 'time_of_onset_group' is calculated and grouped from the data in DEMO and THER, and represents the grouping of the time of the patient's adverse reaction minus the time of the patient's initiation of the medication, i.e., it can be interpreted as the amount of time after which the patient would have experienced an adverse reaction after the administration of abemaciclib. Overall, the five adverse reactions were more frequently categorised in the groups of 39–180 days (a = 32, 44.4%) and >180 days (a = 33, 45.2%), with only one occurrence of an adverse reaction, renal disorder, being categorised in the 0–7 days group.

Discussion

Diarrhoea was the most frequent adverse reaction in the current study (a = 3136), a phase 2 MONARCH 1 study evaluating the use of abemaciclib monotherapy in the treatment of women with refractory hormone receptor–positive (HR+), HER2- and metastatic breast cancer. Metastatic breast cancer, diarrhoea was the most common adverse reaction (all grades 90.2%, grade 3 19.7%, grade 2 28.8%, grade 1 41.7%) in the phase 2 MONARCH 1 study.[12] This is consistent with the results we obtained. However, it is worth noting that when ranked in terms of signal intensity, the intensity of diarrhoea was in the 19th place, and the intensity value was not high compared with other adverse reactions (a = 3136, ROR = 12.82 [95% CI,12.34–13.31], EBGM = 10.79), probably because diarrhoea is not very specific as an adverse drug reaction, and most of the combined medications can cause diarrhoea.

For all abemaciclib-related adverse reactions, after calculating the signal intensity by four calculations, there were four with higher signal intensity and they were pseudocirrhosis (a = 5, ROR = 44.24 [95% CI, 16.75–116.82], EBGM = 36.22), cystatin C increased (a = 3, ROR = 41.71 [95% CI,11.98–145.13], EBGM = 34.52), tumour marker abnormal (a = 11, ROR = 40.41 [95% CI, 21.10–77.36], EBGM = 33.62), creatinine renal clearance increased (a = 6, ROR = 40.27 [95% CI, 12.72–97.01], EBGM = 33.53). For the adverse reaction pseudocirrhosis, the number of reported PTs was 5, but the signal intensity was high,[12] pseudocirrhosis often occurs after systemic chemotherapy for liver metastases of breast cancer, with a prevalence of 38%–81% in patients with liver metastases of breast cancer,[13] therefore, the pseudocirrhosis, although high in signal, may not be associated with abemaciclib. Given that abemaciclib is a drug primarily used for the treatment of breast cancer, it is possible that it causes Tumour marker abnormalities as a result of normal pharmacological effects or disease factors, which is consistent to the result of a research from Dr Klein, ME.[14]

Cystatin C is a protein that is filtered relatively freely by glomeruli, it is not affected by non-renal factors and is a surrogate marker of renal function.[15] In the present study, the number of reported cases of adverse reaction cystatin C increased was 3, but it had a high signal (ROR = 41.71, EBGM = 34.52), which

suggests that the incidence of this adverse reaction may be low, but its occurrence may be highly correlated with abemaciclib and this PTs is not mentioned in the inserts, so it is recommended for the Healthcare professionals, in the case of cystatin C increased in patients on abemaciclib, can target their suspicion to abemaciclib.

In general, in previous research, increased creatinine renal clearance is a reflection of damage in early diabetic nephropathy.[16] In our study, we found that among the patients using abemaciclib, six cases also reported increased creatinine renal clearance with higher signals, so we suspect that abemaciclib may cause kidney damage similar to diabetic nephropathy. However, due to the small number of reported cases, we do not exclude the possibility that the patients may have comorbid diabetic nephropathy themselves.

In a multicenter study evaluating the safety of abemaciclib, kidney-related adverse reactions were primarily characterized by increased creatinine levels, which is consistent with our findings.[17] For the eight adverse reactions on the kidney selected in this study, they accounted for approximately 2.65% of all reported reports (in terms of number of reports) and 1.30% of all PTs. It is noteworthy that among these adverse reactions concerning the kidney, only blood creatinine increase was explicitly mentioned in the specification as an adverse reaction after the use of abemaciclib, while the others were not explicitly stated in the specification. Abemaciclib and its major metabolically active agents are known to cause adverse reactions in the kidney through the inhibition of the transporters OCT2 (SLC22A2), MATE1 (SLC47A1), and MATE 2-K (SLC47A2),[18] and inhibit renal tubular secretion of creatinine, which results in the elevation of blood creatinine (SCr) that can be observed with clinical use of abemaciclib (approximately 15%–40%), but which can be reversed with cessation of abemaciclib.[19] Therefore, glomerular filtration rate (GFR) may be high if calculated using SCr in patients on abemaciclib, and this may not be clinically significant for the patient. It may be more appropriate to use other markers (such as blood urea nitrogen [BUN], cystatin C) to assess renal function in patients on abemaciclib.[20] In addition, biomarkers such as kidney injury molecule 1 (KIM-1) may also be appropriate for assessing renal function in patients treated with abemaciclib.[21,22]

For our five selected adverse reactions to abemaciclib-related renal injury that were not mentioned in the specification, we found that the reported patients were over 45 years of age, which we hypothesize is related to abemaciclib's primary indication of breast cancer, which is predominantly clustered in the age range of 60–69 years (ductal carcinoma in situ cases 31%, invasive cases 29%; United States, 2024), with a median age of 62 years.[23] Similarly, reported patients were predominantly female, which may also be related to the gender distribution of breast cancer incidence (men account for approximately 1% of breast cancer cases).[24]

The fact that adverse reactions were most frequently reported by consumers suggests that abemaciclib-associated adverse reactions to renal injury may generally occur in non-healthcare settings, and therefore, physicians and pharmacists should educate patients to be concerned about whether they are experiencing any abnormalities in renal function, concern about the amount of urine they are urinating, the presence of foamy urine, regular checkups of renal function when abemaciclib is given to a patient for use as a treatment. Patients should undergo regular examination of renal function, and if there is any abnormality, they should come to the hospital for timely consultation. It can also be surmised that the higher frequency of discovery by patients is likely to be detected

during non-short-term cycles of drug use, so we turn our discussion to the length of time between drug use and the occurrence of an adverse reaction.

For column 'time_of_onset_group', we note that almost all of these adverse reactions do not occur within a week but mostly in the time period of one month to six months, which suggests that these five adverse reactions may be related to the accumulation of the drug dose, with a certain latency period, and do not appear immediately after the use of the drug, but occur after a period of time of use of the drug or the accumulation of the dose to a certain amount. Therefore, for patients using abemaciclib, more attention should be paid to regular follow-up examinations, as well as the patient's own attention to the condition of their kidneys at home.[25] Specifically, the adverse reactions of increased blood urea and abnormal renal function tests were more concentrated in the group of 31–180 days compared with the other adverse reactions.

Blood urea is an indicator associated with a high-protein diet, so a patient's diet may also affect this indicator, and a high-protein diet may also affect a patient's renal function,[24] so we recommend that patients on abemaciclib control their protein intake at each meal. The renal function test is a comprehensive test that includes urea, blood urea nitrogen (BUN), creatinine and other indicators, which can reflect the basic condition of patients' renal function. The abnormal renal function test adverse reactions are located in the 31–180 group of time_onset_group, which indicates that for patients using abemaciclib, they may have adverse reactions in the 31–180 group. In patients using abemaciclib, renal function impairment may occur more frequently after one month of dosing.[26]

The limitations of this study are that there may be a situation of bias in data analysis because we used study data from the FAERS database, whose adverse event reports were submitted by reporters with different backgrounds; the data content was not fully harmonised, and there is this parts of missing data. Moreover, these reports are past reporting experiences, and we could not extrapolate the current reported patient's. We also observed that in this study, the incidence of adverse reactions in females was higher than that in males. However, due to the relatively small number of reports collected from males, we cannot conclude that abemaciclib-associated adverse reactions are more prevalent in females. Our results are intended as a complementary study to explore post-marketing adverse reactions to this drug.

Conclusion

By analysing the adverse event reports related to abemaciclib in FAERS, the adverse reactions and our selected renal-related adverse reactions and five renal damage-related (including increased blood urea, increased cystatin C, decreased GFR, renal disorder and abnormal renal function test), we can make the following summary of abemaciclib users who experienced renal damage-related adverse reactions: the gender of the reported cases was predominantly female, and all of the reported cases were over 46 years of age. The majority of the reported individuals were from the United States and were of consumer status.

For renal-related adverse reactions, the adverse reaction of increased blood creatinine may be related to the pharmacological effects of abemaciclib itself. We reasoned that increased cystatin C may be an unspecified, potential adverse reaction of abemaciclib. In addition, we found that adverse reactions associated with renal impairment usually reappeared after a period of time on the drug (>31 days), and therefore we urge

healthcare professionals to require long-term follow-up observation of patients using a course of abemaciclib for more than 30 days, with follow-up visits to monitor their renal function, especially cystatin C and blood creatinine.

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Author contributions

Xiangchun Xu and **Xuzheng Guo:** data collection, data analysis and draft editing; **Jinhui Chen:** draft review; **Yuhua Pan** and **Jing Li:** methodology and data duration; **Jing Chen:** conceptualization; **Weihua Lai** and **Lu Lin:** supervision, draft review and conceptualization.

Data availability statement

This study was entirely based on publicly anonymized data made available by the Food and Drug Administration. The raw data can be downloaded at the following link: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html.

Declaration of conflicting interests

The authors declare no conflicts of interest.

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Informed consent statement

Not applicable.

Institutional review board statement

This study used publicly available safety ICSR data that were provided in an anonymous form and were already compliant with ethical standards. Therefore, no further ethical evaluation was necessary.

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