Effect of Concomitant Drug Use on the Onset and Exacerbation of Diabetes Mellitus in Everolimus-Treated Cancer

Katsuhiro Ohyama[1], Hiroyuki Tanaka[2], Yusuke Hori[1]

[1]Center for Experiential Pharmacy Practice, School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, Hachioji, Tokyo, Japan; [2]Department of Practical Pharmacy, Faculty of Pharmaceutical Sciences, Toho University, Funabashi, Chiba, Japan

Corresponding Author: Katsuhiro Ohyama, Center for Experiential Pharmacy Practice, School of Pharmacy, Tokyo University of Pharmacy and Life Sciences; 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan; TEL: (+81) 42-676-6873 ; Fax: (+81) 42-676-6873 ; email: ohyamakt@toyaku.ac.jp

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ABSTRACT -- Purpose: Everolimus-induced diabetes mellitus (DM) outcomes include everolimus-resistant tumors and poor hyperglycemia outcomes, which lead to various other negative clinical outcomes. This study aimed to evaluate the effect of associations between concomitant drug treatment and time to DM event occurrence (onset or exacerbation) on the outcomes of everolimus-induced DM in patients with cancer. **Methods:** Data from the Japanese Adverse Drug Event Report database (JADER) were used, and patient drug use, time of DM event occurrence, and DM outcomes were determined from patient records. Associations between concomitant drug groups with everolimus and DM event occurrence were then evaluated for patients with both good and poor DM outcomes. **Results:** Top ten groups used concomitantly were drugs for the treatment of hypertension (HT), controlled DM, constipation, hypothyroidism, kidney disease, insomnia, hyperlipidemia, hyperuricemia, anemia, and gastritis. Among them, only HT, controlled DM, and hyperlipidemia were associated with DM event occurrence. These three drug groups were examined by the outcome of everolimus concomitant usage and revealed a significantly shorter time to DM event occurrence for patients with poor outcomes than for those with good outcomes ($p = 0.015$) among patients without a concomitant drug for DM. Each of these three drug groups was analyzed on patients who were concomitantly administered with one of each drug group with everolimus and revealed a significantly shorter time to DM event occurrence for patients with poor outcomes than for those with good outcomes in patients who received concomitant HT drugs ($p = 0.006$). Moreover, among the four HT drug categories, calcium channel blockers were significantly associated with poor outcomes (odds ratio, 2.18 [1.09–4.34], $p = 0.028$). **Conclusion:** To prevent everolimus-induced poor DM outcomes, early DM detection and treatment are necessary, and the effect of the concomitant drug should be considered before initiating everolimus treatment.

INTRODUCTION

Patients with cancer often exhibit comorbid conditions. Previous studies have reported that older patients receiving chemotherapy for cancer treatment have a mean of three comorbidities and have been prescribed a mean of nine medications (1). However, risks of drug-drug interactions and unwanted adverse drug reactions increase with the number of additionally prescribed drugs (2). In fact, hospitalized patients who take more than six drugs experience more overall adverse events (AEs) than patients taking five or less (3), and the risks of both hospitalization and death increase with the number of daily medications (4). Furthermore, in patients with cancer, multiple concomitant drug therapies have been associated with postoperative complications and treatment-related toxicity (5).

The mammalian target of rapamycin, mTOR, is a serine/threonine kinase that affects downstream signaling of the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway through its distinct protein complexes (complex 1 [C1]) and complex 2) (6, 7). Since the mTOR pathway regulates cellular growth, proliferation, angiogenesis, and survival, it is logical that genes in the mTOR pathway are among the most frequently mutated genes in cancers (8). In fact, the dysregulation of mTOR signaling has been implicated in a variety of human diseases and reported to play a role in more than 70% of cancers (9).

Metabolic disorders commonly occur in patients treated with mTOR inhibitors (10), which appear to induce hyperglycemia by reducing insulin secretion through direct effects on pancreatic beta cells, accelerating the breakdown of glycogen in the liver, and increasing insulin resistance through reduced insulin signaling (11-13). Indeed, hyperglycemia is one of the main side effects experienced by everolimus-treated patients, and according to drug labels in Japan, the probabilities that everolimus-treated patients will experience hyperglycemia and either the onset or exacerbation of diabetes mellitus (DM) are 8.6 and 2.7%, respectively. The occurrence of treatment-induced hyperglycemia and DM is significant since such conditions can induce drug resistance. For example, recent preclinical studies in hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer cells and mouse models have demonstrated that PI3K inhibitor-induced increases in serum insulin levels of patients with cancer can reactivate the PI3K/AKT/mTORC1 pathway, thereby inducing resistance to PI3K inhibition (14). Furthermore, everolimus-induced hyperglycemia has been reported to increase the resistance of cancer cells to everolimus by reactivating the PI3K/AKT/mTORC1 pathway and stimulating the mitogen-activated protein kinase pathway (15-17), and studies of everolimus-treated patients have also reported correlations between hyperglycemia and worse progression-free survival (18).

There is little information on the onset time of AEs for concomitant medications in treatment with everolimus. Clinical practitioners would benefit from the ability to recognize the effect of concomitant medications on the timing or outcomes of everolimus-induced diabetic events, especially when the AEs may exacerbate the disorder of interest. Therefore, the aim of the present study was to use information in the Japanese Adverse Drug Event Report database (JADER) to evaluate the associations between concomitant drug with everolimus and DM event timing on the outcomes of everolimus-induced DM in cancer.

METHODS

Study data

Figure 1 shows the flowchart for patient selection. JADER records, which were downloaded from the Pharmaceuticals and Medical Devices Agency website (https://www.pmda.go.jp), included four types of information: patient demographics (DEMO), drug treatments (DRUG), AEs (REAC), and primary disease information (HIST). Reports with incomplete/vague age or sex data were excluded. The REAC data involved preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA). The standardized MedDRA Query (SMQ) index is a group of MedDRA terms from one or more "System Organ Class" related to the desired medical state or region of interest. Only records with time to DM event data were analyzed.

Records of ≥30-year-old patients who received everolimus and experienced DM-related AEs were included in the study (Table 1, Figure 1).

Table 1. Characteristics of the everolimus-treated patient population.

	Number of cases	%
Total	2304	100.0
Sex		
Male	1201	52.2
Female	1103	47.8
Age (years)		
30–39	66	2.9
40–49	149	6.5
50–59	430	18.7
60–69	838	36.4
70–79	682	29.6
80–89	136	5.9
90–99	3	0.1
Indication[1]		
Renal cell carcinoma	1312	56.9
Breast cancer	591	25.7
Neuroendocrine tumors	318	13.8
Others/Unknown	90	3.9
Concomitant corticosteroid		
Dexamethasone	65	2.8
Prednisolone	68	3.0
Methylprednisolone	10	0.04
Comorbid Condition		
Hypertension	484	21.0
Diabetes mellitus	291	12.6
Constipation	120	5.2
Hypothyroidism	110	4.8
Kidney disease	107	4.6
Insomnia	104	4.5
Hyperlipidemia	104	4.5
Hyperuricemia	98	4.3
Anemia	97	4.2
Gastritis	68	3.0

[1]One patient presented with both breast cancer and neuroendocrine tumors.

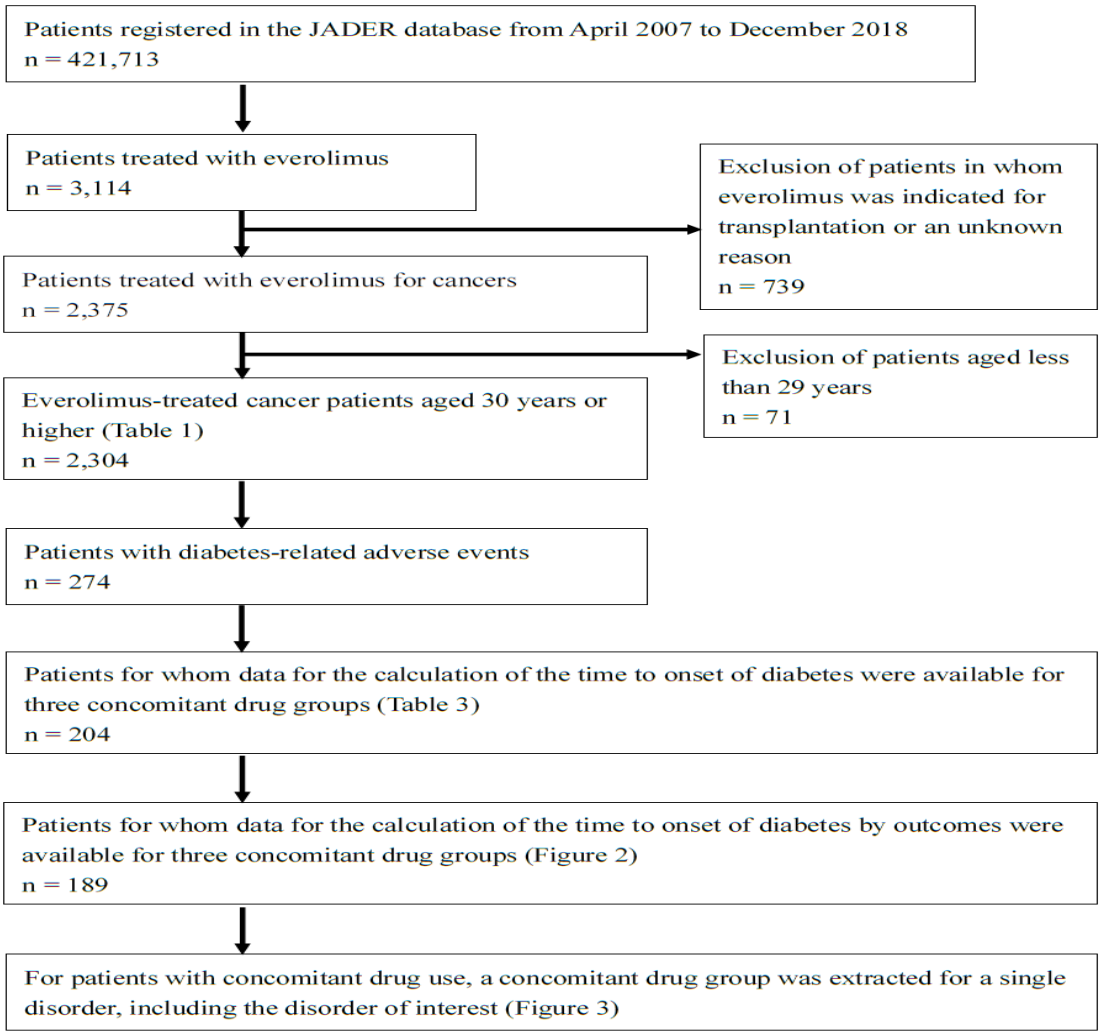

Figure 1. Selection process for the JADER records included in the present study.

Definition of everolimus

Based on the brand name or the "reason for use", the cases where everolimus had been used for cancer treatment were extracted from the DRUG data. Cases in which everolimus had been indicated for transplantation were excluded. (Table 1, Figure 1).

Definition of DM

In the present study, DM was defined as a condition associated with several Medical Dictionary for Regulatory Activities (MedDRA/J ver. 22.1) preferred terms, including increased blood glucose (PT 10005557), DM (PT 10012601), impaired glucose tolerance (PT 10018429), hyperglycemia (PT 10020635), and type 2 DM (PT 10067585).

Definition of DM outcomes

The outcomes of DM were separated into two groups according to the six outcome descriptors used in the REAC data of the JADER records: recovery, remission, no recovery, aftereffects, death, and unknown. JADER records with "recovery" or "remission" outcome descriptions were classified as "good outcome" and those with "no recovery", "aftereffects", or "death" outcome descriptions were classified as "poor outcome". Those with "unknown" outcome were excluded from analysis.

Concomitant corticosteroids and drug groups for frequently reported disorders

Concomitant corticosteroids, including dexamethasone, prednisolone, and methylprednisolone were extracted, except for topical use. Concomitant drug groups were established by reviewing the "reason for use" section of DRUG data using the frequently reported disorders, excluding indications for cancer (Table 1, Supplemental Table 1).

Data analysis

Based on drug efficacy, the association between the concomitant drug group and DM-related AEs were examined using the chi-square test. The concomitant drug groups showing significance were examined using logistic regression analysis using ratios with 95% confidence intervals (CIs), with aged over 60 y.o. and sex as confounders. Next, the time to onset of DM-related AEs was examined in patients with and without concomitant drug treatment. Time to DM event occurrence was calculated from the JADER data by adding 1 day to the number of days between the first day of treatment and first day of AE occurrence, median time (no. d) to DM event occurrence was calculated, and the Wilcoxon rank-sum test was used for comparison. Cumulative incidences were plotted using the Kaplan-Meier method, and log-rank tests were used to examine the association between concomitant drug groups and time to DM event occurrence by outcomes. In the concomitant drug use groups, the Wilcoxon rank-sum tests were used to examine the association between concomitant drug groups and time to DM event occurrence by outcomes. Among the group showing significance, associations between individual mechanism of action categories and poor DM outcome were evaluated through logistic regression analysis using sex and age as confounding factors.

All statistical analyses and data visualizations were performed using JMP Pro ver. 13.2.1 (SAS Institute, Cary, NC, USA), and *p*-values <0.05 of the Chi-square test, the Wilcoxon rank-sum test, and log-rank test, and the lower limit of the 95% CI >1 of odds ratio were considered to be significant.

RESULTS

Study data

A total of 421713 records, from April 2007 to December 2018, were obtained from the JADER. Based on the "reason for use" section of DRUG data (Supplementary Table S1), indications and comorbid conditions were examined. Of the 2304 patients that experienced adverse reactions in response to everolimus treatment, 274 (11.9%) developed DM (Table 1), and DM onset rates of 13.5% (177/1312), 15.1% (48/318), and 8.4 % (50/591) were observed for patients with renal cell carcinoma, neuroendocrine tumors, and breast cancer, respectively. For comorbid conditions, the number of cases of drug groups was 484 for hypertension (HT), 291 for DM, 120 for constipation, 110 for hypothyroidism, 107 for kidney disease, 104 for insomnia, 104 for hyperlipidemia (HL), 98 for hyperuricemia, 97 for anemia, and 68 for gastritis (Table 1).

DM-associated concomitant drug groups

Based on the comorbid conditions described in Table 1, associations of concomitant drugs with onset and exacerbation of DM were evaluated. Among 10 drug groups evaluated, the HT, DM, and HL groups were associated with DM events (Table 2).

Effect of concomitant drug group

Among the drug groups, time (median no. d [interquartile range, IQR]) to DM event occurrence was significantly affected by concomitant DM drug treatment (25.5 d [15–57 d] vs. 40.5 d [23.5–74.5 d]; $p = 0.008$) but not by concomitant treatment with either HT (36 d [21.5–68.5 d] vs. 32 d [18.5–57.5 d]; $p = 0.439$) or HL (37.5 d [16–57 d] vs. 33 d [20–64 d]; $p = 0.600$) drug groups (Table 3).

Table 3. Effect of "with-or-without" concomitant drug group use on the median day in causing diabetes mellitus in everolimus-treated cancer.

Concomitant drug group	Use (+/-)	Number of cases	Median Day (IQR)	*p*
Hypertension	+	72	36 (21.5–68.5)	0.439
	-	132	32 (18.5–57.5)	
Diabetes mellitus[1]	+	84	25.5 (15–57)	0.004*
	-	120	40.5 (23.5–74.5)	
Hyperlipidemia	+	22	37.5 (16–57)	0.600
	-	182	33 (20-64)	

[1]Controlled diabetes mellitus; *$p < 0.05$; Abbreviations: IQR, interquartile range

Effect of DM outcomes

A total of 132 of 157 good outcomes (74 "recovery", 83 "remission") and 57 of 62 poor outcomes (61 "no recovery", one "aftereffects") were calculable as some of the outcomes lacked data for the initiation or occurrence of AE, thus used for analysis. Time to DM event occurrence was significantly shorter in patients with poor DM outcomes (29 d [15–50 d]) than in those with good DM outcomes (43 d [25.5–95.5 d]; $p = 0.015$; Figure 2).

Table 2. Association of concomitant drugs with onset and exacerbation of diabetes mellitus in everolimus-treated cancer patients.

Risk factor	Number of cases	*p*	Adjusted OR[1] (95% CI)	*p*
Sex (female)	111	0.009*		
Age (≥60 years)	211	0.049*		
Concomitant corticosteroid	21	0.175		
Target of concomitant drug				
Hypertension	81	<0.001*	1.57 (1.18–2.10)	0.002*
Diabetes mellitus	102	<0.001*	5.58 (4.17–7.45)	<0.001*
Constipation	12	0.511		
Hypothyroidism	14	0.782		
Kidney disease	9	0.255		
Insomnia	11	0.672		
Hyperlipidemia	21	0.003*	1.97 (1.20–3.21)	0.007*
Hyperuricemia	12	0.912		
Anemia	13	0.639		
Gastritis	18	0.268		

[1]ORs were adjusted by sex and age; *$p < 0.05$; Abbreviations: CI, confidence interval; OR, odds ratio

Effect of concomitant drug group for a single disorder

Similarly, median time to DM event occurrence for drug group for a single disorder was evaluated by outcomes. In patients treated only with HT group drugs and everolimus, time to DM event occurrence was significantly shorter in patients with poor DM outcomes (21.5 d [14–40 d]) than in those with good DM outcomes (72 d [29.5–191 d], $p = 0.008$; Figure 3).

Effect of HT drugs on poor DM outcomes

Since there was a significant difference in the group taking only the concomitant drug for HT, the data were also examined to evaluate associations between drug category and poor outcomes. Of the four mechanism-of-action categories of the HT group, only calcium channel blocker (CaB) drugs were significantly associated with poor DM outcomes (OR: 2.18 [1.09–4.34], $p = 0.028$; Table 4).

DISCUSSION

The findings suggested that concomitant HT, DM, and HL drugs were associated with DM onset or exacerbation during everolimus use. The time to DM event occurrence was significantly shorter for patients with poor outcomes than that for patients with good outcomes. However, when patients receiving multiple concomitant drug treatments were excluded from the analysis, the time to DM event occurrence in patients with good and poor outcomes was only affected significantly by concomitant HT drug treatment. Moreover, of the four mechanism-of-action categories in this group, only CaB drugs were associated with poor DM outcomes.

Limited information about hyperglycemia is provided on the drug label for everolimus in Japan. In fact, the drug label only states that "fasting blood glucose level should be measured before and after the initiation of everolimus, and the blood glucose level should be appropriately controlled before initiating everolimus because of the possible occurrence of hyperglycemia." The drug label used for everolimus in the United States also states that dosage modification (reduction by 50% of the current dose) is required for patients that experience grade 3 AEs and that, if the modified dose is lower than the lowest available dose, drug administration on alternate days is recommended. The US label also states that the drug should be permanently discontinued in patients that experience grade 4 AEs. Therefore, the results of the present study may provide useful information that can help patients prepare for AEs.

Some studies have reported that the risk of everolimus-induced hyperglycemia varies by tumor type (11, 12). For example, it has been reported that the risk of everolimus-induced hyperglycemia is the greatest in patients with renal cell carcinoma among the indications (19, 20). In the present study, although the incidents are the highest in renal cell carcinoma, the reported ratio of DM onset or exacerbation was the highest in patients with neuroendocrine tumors. This difference may be reflected the reporting bias, a characteristics of spontaneous reporting system database.

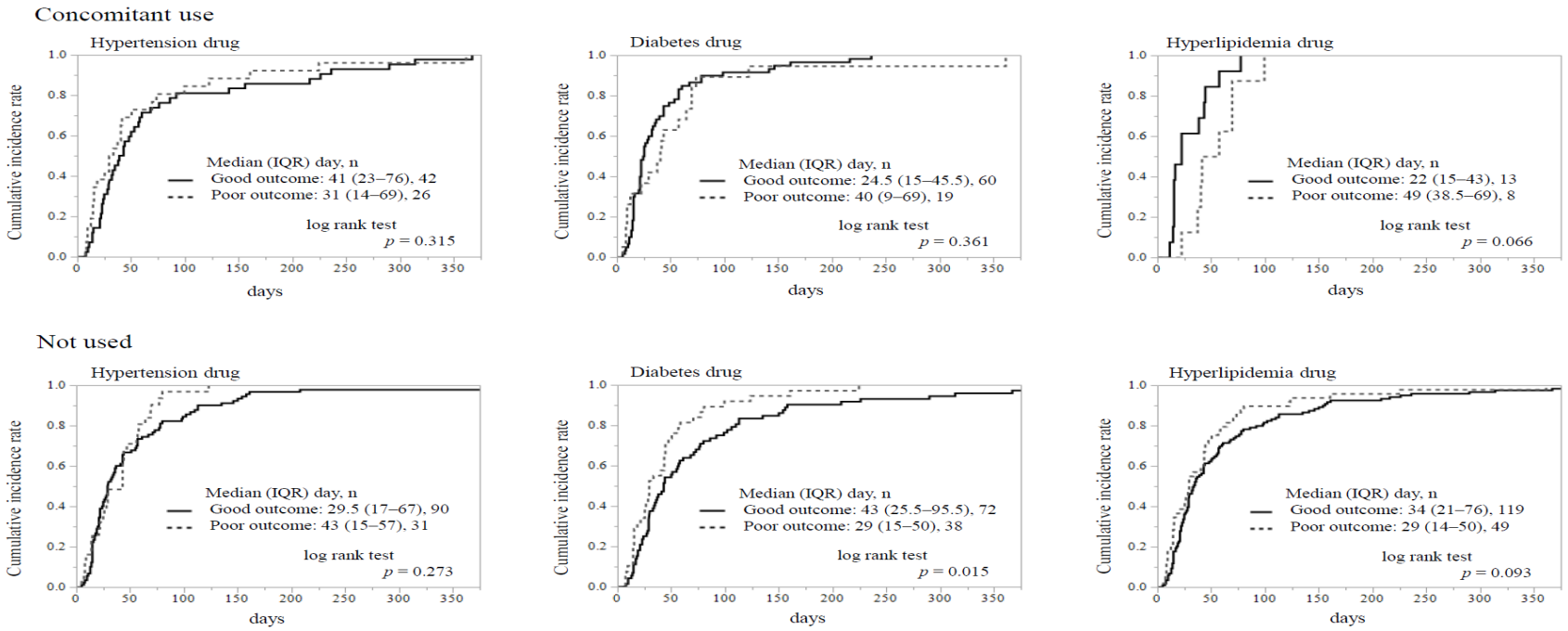

Figure 2. Effect of concomitant drug use on time to diabetes mellitus onset or exacerbation in everolimus-treated cancer and good or poor outcomes.

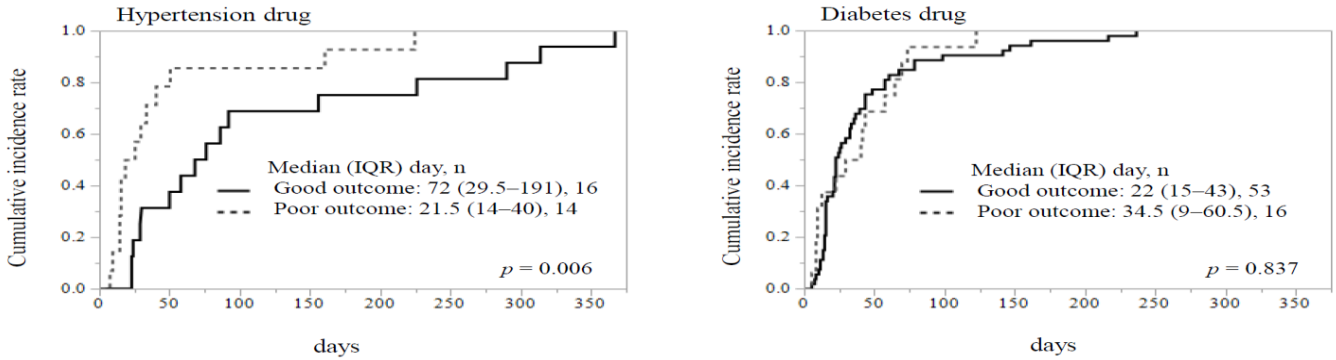

Figure 3. Effect of concomitant drug use for a single disorder on the time to onset or exacerbation of diabetes mellitus in everolimus-treated cancer patients with good or poor outcomes. A figure was not created for the hyperlipidemia drug group, since there was only one case.

Table 4. Association between hypertension drug use and poor outcome of diabetes mellitus in everolimus-treated cancer.

Category	Poor outcome (n)	Good outcome (n)	OR (95% CI)	*p*	Adjusted OR[1] (95% CI)	*p*
β-Blocker	1	6	0.42 (0.05-3.58)	0.676		
Ca channel blocker	21	32	2.07 (1.07-3.98)	0.035*	2.18 (1.09–4.34)	0.028*
RAS inhibitor	14	31	1.22 (0.60-2.50)	0.580		
Thiazide	1	4	0.64 (0.07-5.86)	1.000		

[1] OR was adjusted by sex and age; *$p < 0.05$; Abbreviations: OR, odds ratio; CI, confidence interval; RAS, renin-angiotensin system

Reports of the effects of everolimus on time to DM event occurrence are limited. Tanimura et al. (12) reported the development of hyperglycemia in four patients with cancer after a 3–8-week everolimus treatment. This finding is consistent with the results of the present study (Table 3).

In the present study, time to DM event occurrence was only significantly shorter in patients with poor outcomes and who did not receive concomitant DM treatment (Figure 2). Thus, it is possible that the effects of inter-individual variability and concomitant drug treatment on hyperglycemia are more pronounced in patients who are not taking DM drugs than in patients who are taking them. In fact, Vernieri et al. (21) recently reported that patients who are normoglycemic at baseline and experience treatment-induced DM have lower progression-free survival than patients who are already hyperglycemic at baseline and experience breast cancer treatment-induced DM. Therefore, in the absence of concomitant DM drug treatment, these patterns suggest that patients who develop DM early in treatment may have poor DM outcomes and require prompt treatment, especially considering that everolimus-induced hyperglycemia can also induce drug resistance in cancer cells (14).

Among the three concomitant drug groups associated with DM, only the concomitant HT drug group reduced the median time to DM event occurrence for the poor outcome group (Figure 3), and among concomitant HT drugs, only medications in the CaB category were associated with poor outcomes (Table 4). CaB drugs are the first-line treatment for HT, along with angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and thiazide, according to the Japanese Society of Hypertension Guidelines 2019 (JSH2019).[22] Since CaB drugs do not affect glycemic metabolism, it is unlikely that they directly affect DM outcomes, unlike ACEIs and ARBs, which are also indicated for the treatment of diabetic nephropathy (e.g., microalbuminuria and coexistent proteinuria), or thiazide, which is known to cause glucose intolerance. However, it is also possible that CaB drugs possess unique property that influence everolimus pharmacokinetics. Since everolimus is mainly metabolized by cytochrome P450 (CYP) 3A4 and is simultaneously transported by P-glycoprotein (P-gp) (23), the concomitant use of drugs with such property may alter the pharmacokinetics of everolimus (24, 25). In fact, a case report on the interaction between everolimus and verapamil, which is a CaB drug with a different therapeutic purpose from dihydropyridines, reported that the trough plasma concentration of everolimus in the patient was greatly increased (26), and another study reported that concomitant verapamil treatment in healthy subjects increased the maximum concentration of everolimus by 2.3-fold and the area under the blood concentration-time curve by 3.5-fold (27). Furthermore, doubling the minimum concentration of everolimus increases the risk of grade 3 or more severe adverse metabolic events by 1.3-fold (28). Because inter-individual variation in CYP3A4 and P-gp activity can alter drug effects and AEs, the differential influence of HT group drugs on time to DM in patients with different outcomes may be due to concomitant drug-induced changes in everolimus pharmacokinetics. However, studies have also reported that the coadministration of everolimus and either CYP3A4 or P-gp substrates or weak to moderate CYP3A4 inhibitors fails to affect the minimum concentration of everolimus (28). Therefore, further research is required.

According to several guidelines, everolimus belongs to the low emetic risk class of oral anticancer agents. In the 2016 MASCC/ESMO guidelines, corticosteroids are only recommended for use as single agents, along with 5-HT_3 receptor antagonists and dopamine receptor antagonists (29), and in the 2017 NCCN guidelines, corticosteroids are not listed among the agents recommended for use for antiemetic purposes (29, 30). Therefore, corticosteroids as antiemetic agents are infrequently used concomitantly with everolimus therapy and may have a limited effect on hyperglycemia or DM. In fact, in the present study, the effect of corticosteroids on the development of DM in the

everolimus use group was not significant, and the effect on DM outcomes also did not appear to change. According to drug labels in Japan, treatment with corticosteroids reduces the effect of everolimus, and, therefore, the development of hyperglycemia caused by everolimus itself is also expected to be reduced. However, depending on the dosage and duration of the treatment, corticosteroids can also cause hyperglycemia, and the combination with everolimus is expected to cause hyperglycemia. Further study with a larger sample size for the effect of concomitant use of corticosteroids on the onset time and outcomes of DM is required.

The present study is potentially limited by the characteristics of spontaneous reporting databases. First, there is no certainty that reported AEs are actually the result of treatment with a given drug. Second, not every AE or medication error that occurs with a drug is reported (i.e., reporting bias). Third, in the present study, some data were excluded because of missing data that made it impossible to calculate time to DM event occurrence or because of missing or inadequate data regarding underlying disorders and comorbidities. In addition, as described above, the effect of concomitant corticosteroid use was not considered. However, using a spontaneous reporting system also has many advantages for detecting possible drug-AE associations, including the availability of information on the timing of AEs, patient indications, and medical practices (31).

CONCLUSION

The findings of the present study demonstrate that, depending on concomitant drug treatment, the time to onset or exacerbation of DM may significantly differ in groups with good and poor DM outcomes. Because the everolimus-induced onset and exacerbation of DM can cause tumor resistance to everolimus and are often associated with high tumor aggressiveness, the early detection and treatment of everolimus-induced DM events is important for patient treatment. Further studies are needed to verify our findings to prevent poor DM outcomes in patients receiving everolimus.

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RESEARCH ETHICS AND PATIENT CONSENT. Not applicable.

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